Irish Journal of Medical Science

Quarterly Publication of The Royal Academy of Medicine in Ireland

VOLUME 175 NUMBER 3 JULY, AUGUST, SEPTEMBER 2006

CONTENTS INCLUDE:

ROYAL ACADEMY OF MEDICINE IN IRELAND

150,000 people in Ireland live with severe pain.[1]

Hear their cries. Bring them hope.

A strong opioid for treating severe pain

OxyContin®

Oxycodone HCl prolonged release tablets

Treating severe pain with confidence

NAPP
THE POWER TO CONTROL PAIN

Prescribing Information and Reference

***OxyContin*® prolonged release tablets 5, 10, 20, 40, 80 mg.**

Presentation: Film-coated prolonged release tablets containing oxycodone hydrochloride, marked OC on one side and the tablet strength on the other. Colours: 5 mg - light blue, 10 mg - white, 20 mg - pink, 40 mg - yellow, 80 mg - green. ***Indications:*** For the treatment of severe pain. ***Dosage and administration:*** OxyContin tablets must be swallowed whole, and must not be not broken, chewed or crushed, which may lead to a fatal overdose. *Adults and the elderly:* ***OxyContin*** tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, previous history of analgesic requirements, body weight and sex. The usual starting dose for debilitated elderly patients, opioid naive patients or patients whose pain is uncontrolled with weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be titrated to achieve pain relief. Patients receiving oral morphine before ***OxyContin*** therapy should have the daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. In non-malignant pain, treatment with ***OxyContin*** should be short and intermittent to minimise the risk of dependence. The need for continued treatment should be assessed at regular intervals. Patients should not usually require more than 160 mg per day. *Renal or hepatic impairment:* Dose initiation should follow a conservative approach i.e.one-third to one-half the usual dose. ***OxyContin*** is contra-indicated in acute hepatic disease. *Adults under 20 years and children:* Not recommended. **Contra-indications:** Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, severe obstructive airways disease, severe bronchial asthma, hypercarbia, known sensitivity to oxycodone, morphine or other opioids, acute hepatic disease, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. **Precautions:** Opioid dependent patients, toxic psychosis, raised intracranial pressure, convulsive disorders, delirium tremens, disorders of consciousness, hypotension, hypovolaemia, diseases of the biliary tract, biliary or ureteric colic, pancreatitis, obstructive and inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, hypothyroidism, chronic obstructive airways disease, reduced respiratory reserve, acute alcoholism, chronic renal and hepatic disease, debilitated patients. Do not use where there is a possibility of paralytic ileus occurring. Patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive ***OxyContin*** for 24 hours before surgery. Use with caution following abdominal surgery. Do not use until normal bowel function is assured. Oxycodone has an abuse profile similar to that of other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. Prolonged use may lead to physical dependence. The tablets must not be broken, chewed or crushed, as this may lead to an overdose. **Interactions:** ***OxyContin*** should be used with caution in patients using phenothiazines, tricyclic anti-depressants, anaesthetics, hypnotics, sedatives, alcohol, muscle relaxants, antihypertensives, SSRIs, quinidine, paroxetine, fluoxetine, cimetidine, ketoconazole, erythromycin. **Pregnancy and lactation:** Not recommended. **Side-effects:** The most serious adverse reaction is respiratory depression. Very common adverse drug reactions are nausea, constipation, vomiting, somnolence, dizziness, pruritus. Common adverse drug reactions are oedema, abnormal dreams, anxiety, confusion, depression, insomnia, hallucinations, faintness, asthenia, headache, vasodilation, dyspnoea, bronchospasm, abdominal pain, anorexia, diarrhoea, dry mouth, dyspepsia, flatulence, rash, sweating, urinary disorders, fever. Some side effects which are uncommon but could be serious are hypertonia, paraesthesia syncope, palpitations, gastritis, ileus, biliary spasm, urinary retention, allergic reaction. **Package quantities:** Blister packs of 28 and 56 tablets. **Legal category:** POM. **Product authorisation numbers:** PA 913/22/1-4 and 6. **Product authorisation holder:** Napp Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0GW, UK. **Further information is available from:** Napp Laboratories, 54 Fitzwilliam Square, Dublin 2. Tel: 01-6612115. Member of the Mundipharma Group. **Date of preparation:** January 2006.

® The NAPP device and ***OxyContin*** are Registered Trade Marks.

Reference: 1. http://www.painineurope.com/user_site/index.cfm?item_id=4722689 Ireland

This journal is indexed by Current Contents, Embase and is included in the abstracting and indexing of the Bio Sciences Information Service of Biological Abstracts. It is available in microfilm from University Microfilms Ltd.

All communications to the Editor should be addressed to:
Irish Journal of Medical Science,
2nd Floor, Frederick House,
19 South Frederick Street, Dublin 2
Tel: 00353-1-633 4820 Fax: 00353-1-633 4918
Email: ijms@rami.ie
Website: www.rami.ie www.iformix.com

Annual Subscription:

Ireland and EU Countries	€ 156
Non-EU	€ 192
Single Copy	€ 42

Published by
The Royal Academy of Medicine in Ireland

ISSN 0021-1265

Designed by
Austin Butler
Email: austinbutler@mac.com

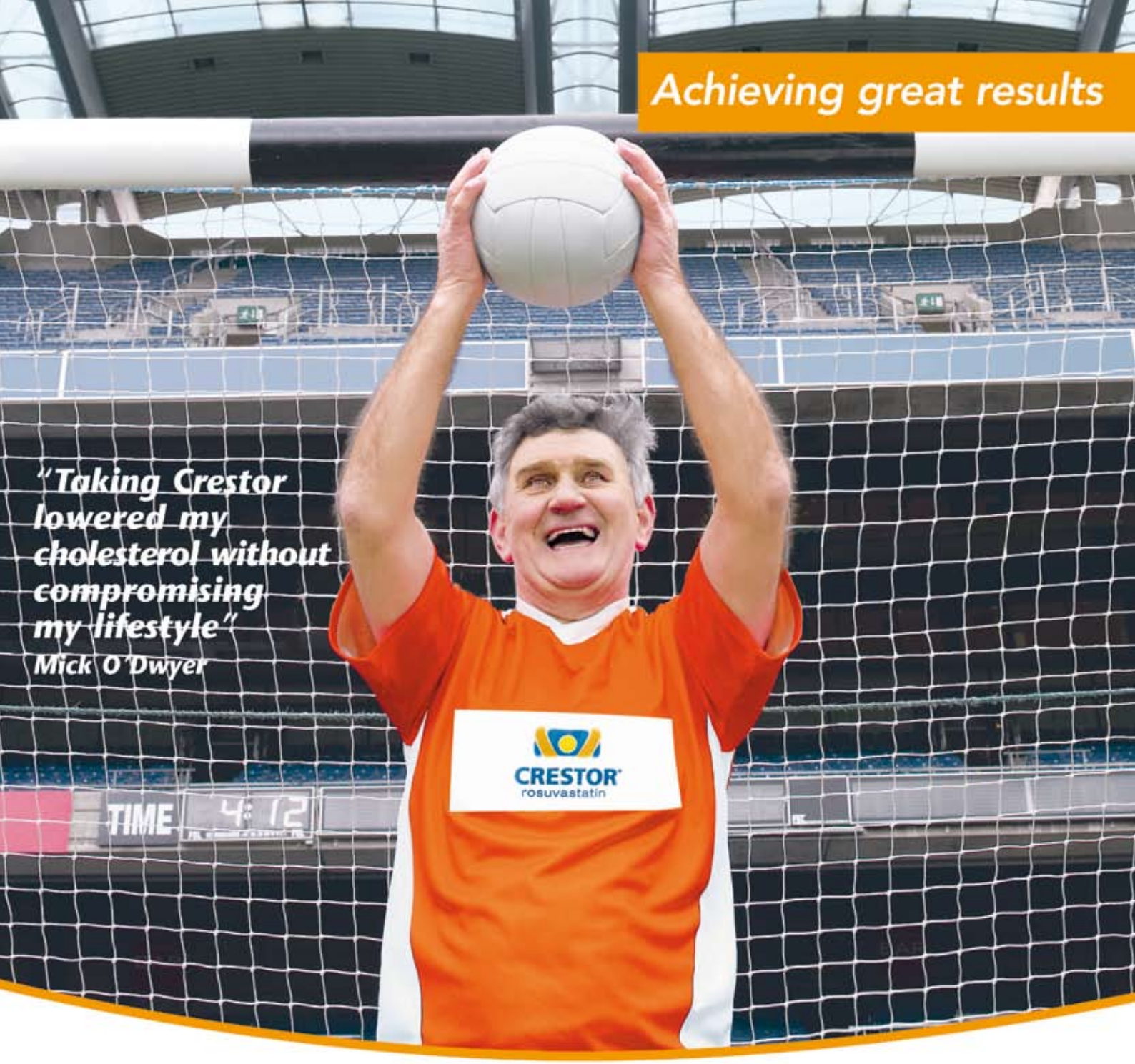
CONTENTS

ORIGINAL PAPERS

GRAND ROUND

LITERARY & HISTORICAL

BOOK REVIEW



CRESTOR — getting your patients to goal

AstraZeneca
CARDIOVASCULAR

CRESTOR®
rosuvastatin

Abbreviated Prescribing Information CRESTOR®
Refer to the full *Summary of Product Characteristics* before prescribing

Presentation: Film-coated tablets containing 5mg,10mg, 20mg, or 40mg of rosuvastatin. **Indications:** In patients unresponsive to diet and other non-pharmacological measures, CRESTOR is indicated for primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), homozygous familial hypercholesterolaemia, or mixed dyslipidaemia. **Dosage:** The recommended start dose is 5 or 10mg daily (including those being switched from other statins). The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4 weeks, if necessary. The maximum daily dose is 40mg. A final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when the 40mg dose is initiated. Doses may be given at any time of the day with or without food. *Elderly:* A start dose of 5mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age. *Dosage in patients with renal insufficiency:* The recommended start dose is 5mg in patients with moderate renal impairment (creatinine clearance <60ml/min). The 40mg dose is contraindicated in patients with moderate renal impairment. The use of Crestor in patients with severe renal impairment is contraindicated for all doses. *Children:* Safety and efficacy have not been established. *Race:* Increased systemic exposure in Asian subjects. Recommended starting dose 5mg. Crestor 40mg is now contraindicated in such patients. *Dosage in patients with pre-disposing factors to myopathy:* The recommended start dose is 5mg in these patients. The 40mg dose is contraindicated in some of these patients (see Contraindications). **Contra-indications:** Hypersensitivity to any of the ingredients; active liver disease or unexplained persistent elevations in serum transaminases; severe renal impairment; myopathy; concomitant cyclosporin; pregnancy and breast-feeding; women of child-bearing potential not using contraception. In addition Crestor 40mg is contraindicated with concomitant fibrates, and in patients with predisposing factors for myopathy/rhabdomyolysis (refer to SPC). **Warnings and precautions:** *Renal effects:* Proteinuria which in most cases decreases or disappears spontaneously on continued therapy – a causal relationship to Crestor has not been established. An assessment of renal function should be considered during routine follow-up of patients treated with CRESTOR 40mg. Haematuria has been observed very rarely. *Muscle effects:* Patients with signs and symptoms of myopathy should have their creatine kinase (CK) levels monitored. CRESTOR should be discontinued if CK levels are markedly elevated or, if muscle symptoms are severe and cause daily discomfort. Risk of myositis and myopathy may increase when administered with certain other drugs, combination of CRESTOR with gemfibrozil is not recommended for this reason. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe and HMG-CoA reductase inhibitors. CRESTOR, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy or rhabdomyolysis. CRESTOR should not be used in patients with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis. Rarely, rhabdomyolysis, occasionally associated with impairment of renal function has been reported with all doses and in particular doses >20mg. *Liver effects:* CRESTOR should be used with caution in patients with a history of liver disease and/or alcoholism. Liver function tests should be carried out, prior to, and 3 months following the initiation of treatment. CRESTOR should be discontinued or the dose reduced if the level of serum transaminases is greater than 3-times the upper limit of normal. The reporting rate of serious hepatic events is higher at the 40mg dose. **Pregnancy and lactation:** CRESTOR is contraindicated in pregnancy and lactation. **Drug interactions:** CRESTOR is neither an inhibitor nor inducer of cytochrome P450 isoenzymes. CRESTOR may potentiate the anticoagulant effect of Vitamin K antagonists (e.g. warfarin). Decrease in CRESTOR levels seen when co-administered with erythromycin or antacids containing aluminium and magnesium hydroxide. Increase in oral contraceptive level and hormone replacement therapy level is seen when co-administered with CRESTOR. Concomitant use of CRESTOR and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax.Concomitant use of Crestor and ezetimibe resulted in no change in AUC or Cmax for either drug; however a pharmacodynamic interaction in terms of adverse events cannot be ruled out. **Undesirable effects:** Side effects most frequently reported: headache, dizziness, constipation, nausea, abdominal pain, myalgia, and asthenia. Uncommon: pruritis, rash and urticaria. Rarely, myopathy, rhabdomyolysis, hypersensitivity reactions including angioedema, increased hepatic transaminases and arthralgia. Very rarely: jaundice, hepatitis and polyneuropathy. Other usually transient side effects: elevation in CK levels, proteinuria. **Legal Category:** POM. **Marketing Authorisation Number(s):** PA 970/57/1-4. **Marketing Authorisation Holder:** AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, UK. Further information is available on request from: AstraZeneca Pharmaceuticals (Ireland) Ltd., College Park House, 20 Nassau Street, Dublin 2 Telephone: (01) 6097100. Updated 04/06 Crestor is a trademark of the AstraZeneca group of companies. Licensed from Shionogi & Co Ltd, Osaka, Japan. URN 06/0140, Date of Preparation: June 2006

Abdominal Aortic Aneurysm neck morphology: Proposed classification system

CO McDonnell, M Halak, A Bartlett, SR Baker*

Dept of Vascular Surgery, Sir Charles Gairdner Hospital, Perth, Western Australia; Zenith Planning Service, Perth, Western Australia*

ABSTRACT

Background While aneurysm neck length, angulation and width have all been previously assessed in endovascular abdominal aortic aneurysm repair (EVAR), aneurysm neck shape has not been considered.

Aims To analyse the influence of aneurysm neck morphology on outcome following EVAR.

Methods Aneurysm neck morphology in 70 patients undergoing EVAR from April 2001 to May 2004 was determined using pre-operative CT scans and graft plans. Necks were classified as flared, parallel, irregular, conical, barrel or hourglass. End-points were death, Type I endoleak and graft migration.

Results Forty-six per cent of necks were flared, 34% parallel, 9% irregular, 6% conical, 3% barrel and 3% hourglass. Mean follow-up was 20.2 months (range 4-35). There was one Type I endoleak and one graft migration. There were no aneurysm related deaths.

Conclusions Assessment of aneurysm neck morphology should be part of the routine preoperative workup for EVAR. A classification system of AAA necks is suggested to facilitate this.

INTRODUCTION

Endovascular aortic aneurysm repair (EVAR) is now an accepted treatment option in the management of abdominal aortic aneurysm (AAA).[1-2] The reduction in surgical insult occurs at the expense of long-term durability and these patients require long-term follow-up indefinitely. Continuing perfusion and pressurisation of the aneurysm sac (Endoleak) is a unique complication associated with EVAR and remains the Achilles heel of the procedure. Of particular importance is the achievement of an adequate seal at the proximal and distal attachment zones in the aorta and iliac vessels. Failure to achieve a seal here results in a Type I endoleak which, if left uncorrected, may eventually result in aneurysm rupture.[3] The anatomy of the aneurysm neck (the portion of normal aorta between renal arteries and aneurysm, which is used as a proximal sealing zone between stent-graft and aortic wall) is therefore a keystone of EVAR. The importance of neck length, neck diameter, and angulation has been well documented by others.[4-6] The actual shape of the proximal sealing zone, and its influence on the planning process, degree of oversizing, and outcome has not previously been examined. Criado and colleagues, when reporting the results of the Talent LPS pivotal clinical trial comment on the fact that the Type I endoleak rate was higher than expected, and speculate that this may reflect difficulties related to unfavourable proximal neck anatomy. Factors that they examined include neck length, width, angulation, and the presence of mural thrombus.[7] As with other studies, however, overall neck morphology was not taken into consideration.

Oversizing the endograft relative to the aneurysm neck ensures adequate apposition between graft and aneurysm wall and is critically important in achieving a proximal seal. Oversizing serves two purposes: (a) Ensuring good graft-aortic wall contact, thus preventing a Type I endoleak, and (b) Adding to the radial compression force of the graft which helps prevent graft migration. Various graft manufacturers differ in their methods of determining how the aneurysm neck is measured and what degree of graft oversizing should be applied. What all have in common, however, is that little attention has been paid to the morphology of the aneurysm neck, and its planning implications. Excessive oversizing may produce a "guttering" effect at the graft-aortic sealing zone, increasing the risk of Type I endoleak, distal migration, and aortic neck dilatation.[8]

Herein we propose a classification system for the shape of the proximal aneurysm neck and examine its relevance to endoluminal graft planning.

PATIENTS & METHODS

The CT scans and manufacturers' endoluminal graft plans were reviewed in a consecutive series of 81 patients who underwent endovascular repair of abdominal aortic aneurysm at Sir Charles Gairdner Hospital from April 2001 to May 2004. Insufficient aneurysm neck length in 11 patients required the use of a fenestrated stent-graft and these patients were therefore excluded. The remaining 70 patients form the basis of this study.

Wall-to-wall aneurysm neck measurements including thrombus, atheroma and/or calcium were taken at 3mm intervals, commencing at the level of the renal arteries and continuing inferiorly until a neck length of 21mm had been assessed. In an angulated neck the minimum diameter seen in an axial image was taken as the real diameter. A difference in diameter of 3mm or greater between consecutive measurements was taken as representing a significant contour change.[9] Aneurysm necks fell into one of six categories based on neck morphology: flared, parallel, conical, barrel, hourglass and irregular (Figure 1).

Aneurysms were repaired using the Zenith stent-graft (W.A. Cook, Brisbane, Australia) in 67 cases and the Talent LPS device (Medtronic AVE, Santa Rosa, U.S.A.) in three cases. Mean aneurysm diameter was 57mm (Range 48-85).

Graft oversizing during planning was performed in accordance with the manufacturers' recommendations. With the Zenith device, graft oversizing of 15% to 25% based on the largest aortic neck diameter was performed. With the Talent device, an average neck diameter was calculated using all the available neck measurements, as described elsewhere[10] and the graft was subsequently oversized by 10-20% (Figure 2).

All patients undergoing EVAR at Sir Charles Gairdner Hospital have been entered onto a prospectively maintained database with follow-up clinical and CT data entered at six weeks, six months and twelve months postoperatively and annually thereafter. Mean postoperative follow-up was 20.2 months (range 4-35). Primary end-points were the presence of Type I endoleak, graft migration and death and secondary end-points were the existence of any other type of endoleak and need for secondary intervention.

RESULTS

Flared necks were the commonest (n=32, 46%), then parallel (n=24, 34%), six (9%) were classified as irregular, four (6%) were conical, two (3%) were barrel and two (3%) were hourglass (Figure 3). Mean maximum neck diameter was 27.1mm (Range 20-34mm), while mean endograft diameter implanted was 29.5mm (Range 22-36mm).

There were nine endoleaks in total (13%), one Type I, seven Type II and one Type III. The Type I endoleak occurred in an aneurysm with a flared neck treated with a Zenith® graft and required the deployment of a proximal extension piece which was successful in excluding the leak. The secondary intervention rate was 11.4% (eight patients). None of the other seven interventions were related to the proximal sealing zone or aneurysm neck. Thirty day mortality was zero and there were six late deaths, none of which were aneurysm related.

Only one incidence of graft migration was recorded. This occurred in an aneurysm with a flared neck treated with a Talent LPS device. While the entire supra-renal portion of the graft now lies below the renal arteries, the patient has not yet developed an endoleak. No instances of graft migration has been identified in the patients treated with the Zenith device.

DISCUSSION

While others have made reference to the shape or contour of the aneurysm neck when planning an endovascular repair,[4-7,11] to our knowledge no formal classification system has ever been proposed. We suggest a classification system based on our experience which is an essential aspect of endograft planning in our institution. Rose and colleagues, in their series of 46 patients, describe 37% of necks as "conical", 28% as "straight", 13% as "reverse conical" and 9% as "barrel".[11] These figures differ somewhat from our series and this may be a reflection of differing definitions of shape, strengthening the case for a common classification system, such as we propose.

Reviewing the planning instructions of two of the principal endograft manufacturers in Australia, we failed to find specific guidelines pertaining to oversizing and neck morphology. As shown, significant diameter differences can exist between different stent grafts for a specific aortic neck configuration (Figure 2). Our planning strategy with the Zenith graft is based on the manufacturers' recommendations and mid term follow-up of this

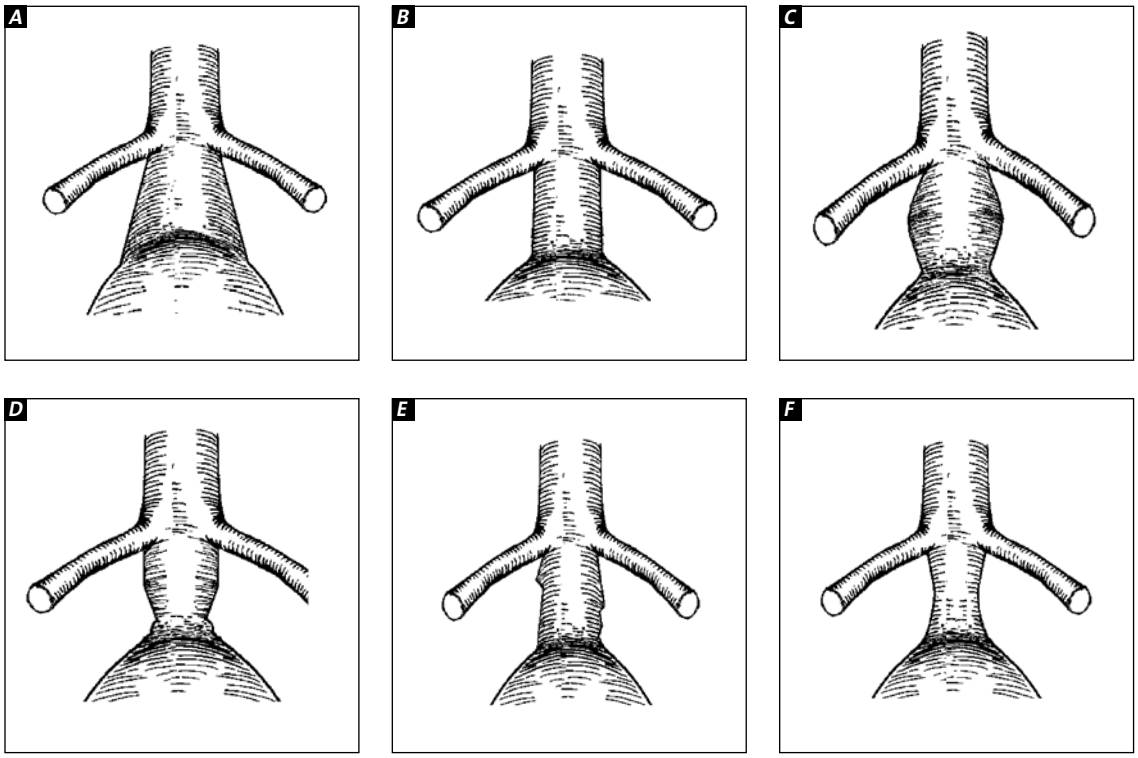
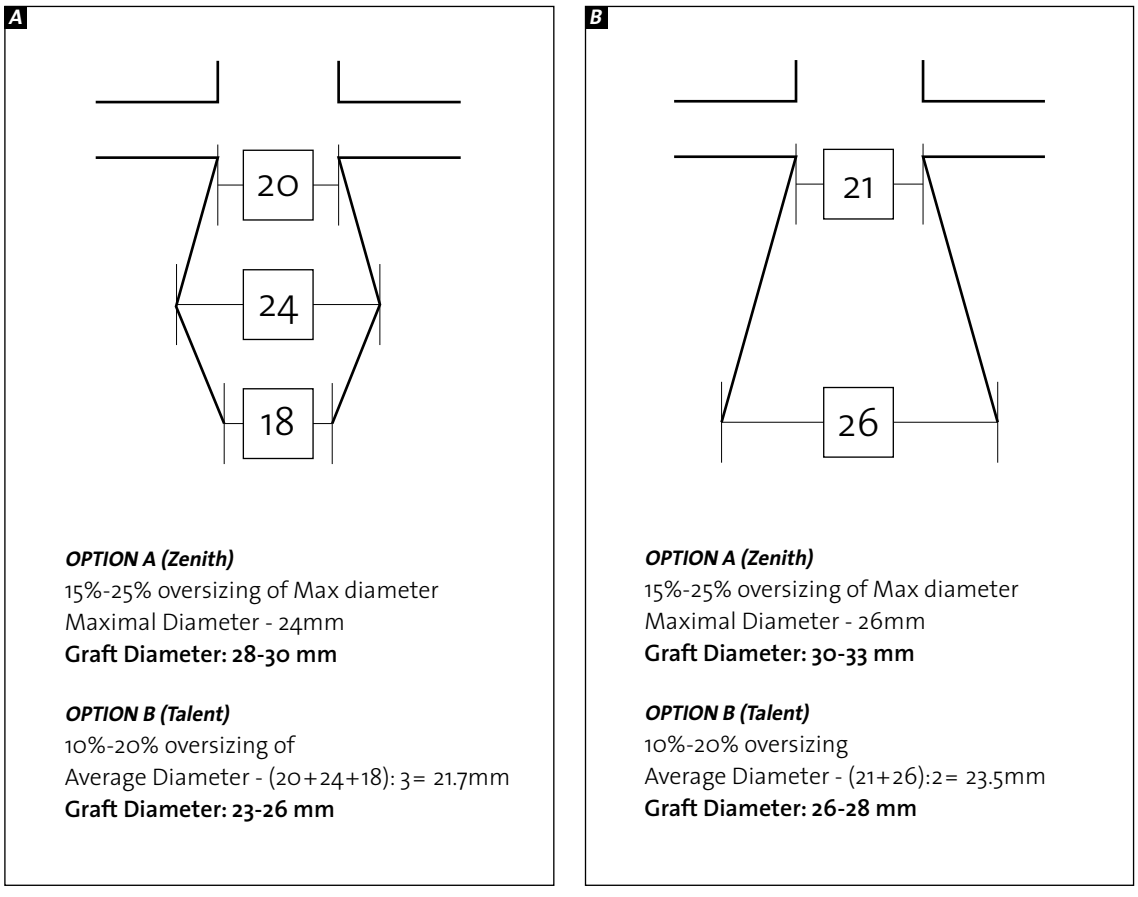


FIGURE 1 — ANEURYSM NECK SHAPES

A. FLARED NECK
B. PARALLEL
C. BARREL
D. CONE
E. IRREGULAR
F. HOURGLASS



OPTION A (Zenith)
15%-25% oversizing of Max diameter
Maximal Diameter - 24mm
Graft Diameter: 28-30 mm

OPTION B (Talent)
10%-20% oversizing of
Average Diameter - (20+24+18): 3= 21.7mm
Graft Diameter: 23-26 mm

OPTION A (Zenith)
15%-25% oversizing of Max diameter
Maximal Diameter - 26mm
Graft Diameter: 30-33 mm

OPTION B (Talent)
10%-20% oversizing
Average Diameter - (21+26):2= 23.5mm
Graft Diameter: 26-28 mm

FIGURE 2 — INFLUENCE OF ANEURYSM NECK MORPHOLOGY ON DIFFERENT OVERSIZING TECHNIQUES IN GRAFT PLANNING

A. BARREL
B. FLARED NECK

Table 1
ANEURYSM NECK TYPES IN PATIENTS WITH ENDOLEAKS

ENDOLEAK TYPE	NO.	ANEURYSM NECK TYPE
I	1	Flare
II	4 2 1	Parallel Flare Hourglass
III	1	Parallel

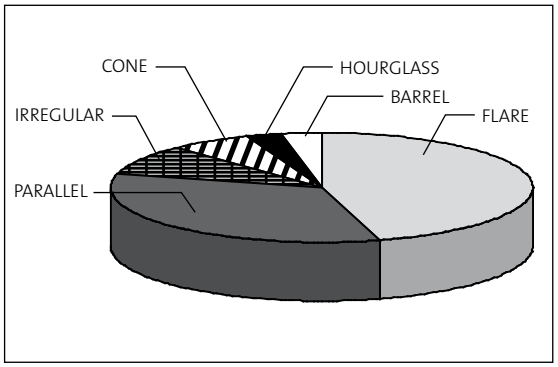


FIGURE 3 — DISTRIBUTION OF NECK SHAPES

series using the neck morphology classification system, and the oversizing strategies during planning revealed no late graft migration or late Type I endoleaks. Our experience with the Talent device is too limited to reach any firm conclusions with regards to the incidence of distal migration. Criado and colleagues make the association between "higher than expected" incidence of Type I endoleaks, and "unfavourable proximal neck anatomy" in their series of Talent grafts but make no specific reference to neck shape.[7]

Sternbergh and colleagues found that endograft oversizing of >30% was associated with a greater incidence of increased aortic neck diameters at six months, device migration at one year and AAA expansion at two years. On the basis of this study they recommended avoidance of excessive oversizing but, as with others, make no reference to the influence of neck shape on either graft planning or outcome.[8]

The total endoleak rate of 13%, while in keeping with other reports, is almost twice that reported in the U.S. pivotal trial of the Zenith® stent-graft.[12] The vast majority of endoleaks in this series were Type II, detected immediately post-operatively and subsequently resolved spontaneously. In our experience almost all aneurysms will demonstrate a Type II endoleak in the immediate postoperative period provided enough intravenous contrast is administered and the x-ray exposure time is long enough. Not surprisingly, there was no association between aneurysm neck classification and endoleak type with respect to the Type II or Type III endoleaks which were observed, reinforcing the view that these phenomena are unrelated to the proximal seal (Table 1). The secondary intervention rate of 11.4% is well within accepted international limits.[13-14]

The low Type I endoleak rate observed in this series despite the variety of neck shapes is encouraging but makes meaningful interpretation of the data difficult. One possibility is that alterations in stent-graft design since the first reported case in 1991 have resulted in continually improving results.[15] The latest modification in the Zenith stent-graft design, the Zenith Flex™ graft, has 5mm gaps between the 1st and 2nd and 2nd and 3rd stents, allowing for greater conformity of the graft to neck angulation and theoretically an improved proximal seal. This may mean that the shape of the aneurysm neck is less relevant today than it would have been in the past, rendering the present study largely irrelevant.

An alternative interpretation of our results is that the numbers included are simply inadequate to provide sufficient data to reach any firm conclusions. A larger series of patients followed-up for a longer period of time will be helpful in resolving this issue and we continue to recruit patients to this study with this in mind. Until then, we feel that assessment of aneurysm neck morphology should form part of the routine pre-operative workup for AAA patients undergoing endovascular aneurysm repair and hope that others will find the proposed classification system in this paper useful.

We believe that taking the aneurysm neck shape into account when planning the graft and oversizing to the largest neck diameter is an important aspect of graft planning as evidenced by the low Type I endoleak observed in this series. The suggested classification system provides straightforward nomenclature of the aortic neck morphology. Its use, along with clear guidelines on oversizing will permit comparison and standardization of the differing views on this contentious issue.

REFERENCES

1. RM Greenhalgh, LC Brown, GP Kwong et al Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. *Lancet* 2004; 364(9437): 843-8.
2. M Prinssen, E Buskens, JD Blankensteijn; Dream Trial Participants. Quality of life endovascular and open AAA repair. Results of a randomised trial. *Eur J Vasc Endovasc Surg*. 2004; 27(2):121-7
3. M Halak, CO McDonnell. Rupture Of An Abdominal Aortic Aneurysm Previously Repaired With An Endo-Vascular Stent-Graft: Successful Management Using An Endovascular Approach. *IMAJ* (In Press)
4. SM Sampaio, JM Panneton, GI Mozes et al Proximal Type I endoleak after endovascular abdominal aortic aneurysm repair: predictive factors. *Ann Vasc Surg*. 2004;18(6):621-8
5. S Elkouri, E Martelli, P Gloviczki et al Most patients with abdominal aortic aneurysm are not suitable for endovascular repair using currently approved bifurcated stent-grafts. *Vasc Endovascular Surg*. 2004; 38(5):401-12.
5. EL Chaikof, JD Blankensteijn, PL Harris et al Reporting standards for endovascular aortic aneurysm repair. *J Vasc Surg* 2002; 35: 1048-1060
7. FJ Criado, RM Fairman, GJ Becker. Talent LPS AAA stent graft: Results of a pivotal clinical trial. *J Vasc Surg* 2003; 37: 709-715
8. WC Sternbergh 3rd, SR Money, RK Greenberg, TA Chuter Zenith Investigators Influence of endograft oversizing on device migration, endoleak, aneurysm shrinkage, and aortic neck dilation: results from the Zenith Multicenter Trial. *J Vasc Surg*. 2004 Jan;39(1):20-6
9. BM Stanley, JB Semmens, Q Mai et al Evaluation of patient selection guidelines for endoluminal AAA repair with the Zenith Stent-Graft: the Australasian experience. *J. Endovasc. Ther.* 2001; 8 (5): 457-464
10. R Singh-Ranger, M Adiseshiah. Differing morphological changes following endovascular AAA repair using balloon-expandable or self-expanding endografts. *J Endovasc Ther.* 2000; 7: 479-485
11. DF Rose, IR Davidson, RJ Hinchliffe et al Anatomical suitability of ruptured abdominal aortic aneurysms for endovascular repair. *J Endovasc Ther* 2003;10(3): 453-457
12. CZ Abraham, TA Chuter, LM Reilly et al Abdominal aortic aneurysm repair with the Zenith stent graft: short to midterm results. *J Vasc Surg*. 2002;36(2):217-24
13. EL Verhoeven, IF Tielliu, TR Prins et al Frequency and outcome of re-interventions after endovascular repair for abdominal aortic aneurysm: a prospective cohort study. *Eur. J. Vasc. Endovasc. Surg.* 2004; 28 (4): 357-364
14. RK Greenberg, TA Chuter, WC Sternbergh 3rd, NE Fearnot. Zenith Investigators Zenith AAA endovascular graft: intermediate-term results of the US multicenter trial. *J Vasc Surg.* 2004 Jun;39(6):1209-18.
15. JC Parodi, JC Palmaz, HD Barone. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg.* 1991; 5:491-9.

Correspondence to: Mr Ciaran McDonnell, Dept of Vascular Surgery, St. James's Hospital, James's Street, Dublin 8. Tel. +353-1-416 2790; Fax. +353-1-410 3599
E-mail: comcdonnell@eircom.net

ORIGINAL PAPER

The impact of the establishment of a surgical high dependency unit on management of Abdominal Aortic Aneurysm

M Cleary, RA Cahill, F Younis, SJ Sheehan, D Mehigan, MC Barry

Dept of Vascular Surgery, St Vincent's University Hospital, Elm Park, Dublin 4

ABSTRACT

Background Our ability to maintain satisfactory levels of outcome after elective abdominal aortic aneurysm (AAA) surgery is increasingly strained by rising levels of co-morbidity in the presenting population. In this study we present a comparative outcome analysis of patients undergoing elective AAA surgery 18 months before and after the establishment of a surgical high dependency unit (HDU).

Methods The preoperative status (ASA & POSSUM scores), operative factors and postoperative outcomes as well as duration of stay were calculated for 104 patients undergoing elective AAA repair (57 prior to the HDU opening and 47 patients afterwards).

Results Patients undergoing surgery in the latter period had significantly higher ASA (2.5±0.06 versus 2.7±0.7; p=0.007), overall POSSUM (33.2±0.5 versus 35.5±0.8; p=0.02) and physiological POSSUM (16.3±0.3 versus 15.5±0.2; p=0.048) scores than those operated on prior to establishment of the HDU (data are mean±SEM; 2-tailed p-score). The two groups had similar total lengths of hospital stay (518 versus 534 days). However, following establishment of the HDU patients occupied fewer ICU bed days (110 versus 181). This resulted in a saving of €50,750.

Conclusion The efficiency and quality of care following elective AAA surgery can be improved by provision of HDU step-down facilities without significantly increased expenditure.

INTRODUCTION

There is a progressively increasing demand on intensive care beds. As the surgical workload increases, more centres perform complex procedures requiring high levels of post-operative care. As a result of the increasing demand, ICU beds may not be available for post-operative monitoring for patients undergoing elective aortic aneurysm surgery. A further problem in this group of patients is the high number of co-morbid conditions present. It is now accepted that patients presenting for elective AAA surgery are increasingly physiologically compromised[1]. This results in frequent case cancellations and postponement of surgery, which is distressing for both patient and family. Significant waste of hospital expenditure on repeated fruitless elective admissions results.

We recently upgraded a regular six-bedded ward to a four-bedded surgical high dependency unit (HDU). Three years after its establishment we have performed a comparative outcome analysis on elective aortic aneurysm operations carried out eighteen months before and after establishment of the unit.

AIMS

The aims of this study were to determine whether provision of a high dependency step-down unit improves management of elective abdominal aortic aneurysm patients and whether the cost associated with elective AAA repair could be reduced.

METHODS

Two time periods were analysed. From January 1998 to June 1999, 57 patients underwent elective AAA repair. Forty-seven patients had surgery in the second time period, January 2002 to July 2003. Only patients having surgery for aortic aneurysmal disease were included in this analysis. Demographic data, intra-operative and post-operative data were recorded. ASA grade (American Society of Anaesthesia) and POSSUM Scores (Physiological and Operative Severity Score for the enumeration of Mortality and

Morbidity) were calculated on the basis of data collected from anaesthetic notes, admission notes and operative notes.

The conventional POSSUM score has two components, a physiological score which comprises 12 preoperative physiological variables and an operative score which contains six operative variables.[2] Each variable is scored and then combined to produce a physiological score and an operative score that increase with increasing physiological dysfunction or severity of operation. Total POSSUM Scores were calculated as the sum of operative and physiological scores.

STATISTICAL ANALYSIS

Differences in distribution of demographics, diagnostic categories and outcomes were examined using Chi-squared proportional analysis. A p-value of less than 0.05 was considered significant.

RESULTS

Patients undergoing surgery in the period 2002-2003 had significantly higher physiological POSSUM scores (pPOSSUM) (19.2±0.7 v 17.5±0.5 p=0.048) (Figure 1) and total POSSUM scores (tPOSSUM) (35.5±0.8 v 33.2±0.5 p=0.02) (Figure 3) compared to those operated on prior to establishment of the HDU. No difference was seen in operative POSSUM scores (oPOSSUM) between the two groups. A higher proportion of the patients presenting in the period 2003-2003 had ASA Grades of >3 compared to the earlier period (p<0.007) (Figure 4).

Mean age, operative POSSUM score, anaesthetic time, operative time, intraoperative blood loss, aortic cross-clamp time and maximum aneurysmal diameter were not significantly different between the two groups (Table 1).

Four patients died post-operatively in the HDU compared to two deaths in the ICU during the preceding 18 months. However, the number of major cardiac, respiratory and renal complications was similar between the groups (Table 2). Although the two groups had similar total lengths of hospital stay (518 versus 534 days), the latter group occupied fewer ICU bed days (110 versus 181) requiring a total stay of 224 days in HDU instead.

When costs of stay were compared, the earlier group's ICU expenditure averaged €287,100 compared to €236,350 for those who were discharged to HDU, a saving of €50,750. This however needs to be offset against a cost of HDU provision of €100,800 in total.

In order to explain the differences in pPOSSUM scores between the groups, we examined the proportion of elective and ruptured aortic aneurysms operated upon over both time periods. Elective repairs formed a higher proportion of the total group in the later period but this was not statistically significant.

DISCUSSION

High dependency units (HDUs) are becoming increasingly important in bridging the gap between the level of care provided in an intensive care unit and the level of care provided on a general surgical ward.[3] They have a vital role in reducing elective case cancellations and, although difficult to quantify, are likely to improve ICU bed turnover. HDUs have been shown to reduce ICU readmission rates and allow earlier discharge of patients.[4,5] While there has been support for high dependency units in recent years, only a minority of hospitals in Ireland and the UK have dedicated surgical high dependency units.[3,6,7] One possible reason for this is a lack of evidence supporting their benefit.[3]

Although several studies have suggested that the introduction of HDU facilities alone does not lead to a reduction in hospital mortality, postoperative management on an HDU has been associated with fewer cardiorespiratory complications, compared to post operative patients treated on a general surgical ward.[4] Postoperative stays in HDU allow patients to be stabilised before returning to the general surgical ward. The facility to provide invasive monitoring should reduce the incidence of unexpected postoperative cardiorespiratory complications.[9] Studies by Gamil *et al* and Leeson-Payne *et al* suggested that many patients on the general wards would benefit from closer observation and monitoring.[10,11]

The impact of high dependency units on the workload and occupancy of the intensive care unit is particularly relevant to vascular surgeons. Frequent case cancellation due to ICU unavailability is an ever-increasing problem. This strain on ICU facilities, coupled with the rising levels of co-morbidity in our elective aortic aneurysm population, challenges our ability to provide satisfactory delivery of service and postoperative care to our patients.

ORIGINAL PAPER

Table 1
DEMOGRAPHIC AND INTRA-OPERATIVE DATA

	1998-1999	2002-2003
Age	71.5 ± 0.95	71.2 ± 1.4
Male : Female	49M : 8F	36M : 11F
AAA Size	5.8 ± 0.16	6.2 ± 0.17
Anaesthetic Time (Mins)	220 ± 9	219 ± 7
Duration of Surgery (Mins)	204 ± 9	200 ± 8
Cross Clamp Time (Mins)	71.88 ± 2	78 ± 3
Blood Loss (mls)	2355 ± 158	2062 ± 175

Table 2
POST-OPERATIVE COMPLICATIONS

		1998-1999	2002-2003
Respiratory	Respiratory Failure	2	4
	Lower Respiratory Tract Infection	7	11
Cardiac	Arrhythmia	4	9
	Myocardial Infarct	2	5
	Pulmonary Oedema	2	3
	Urinary Tract Infection	0	1
	Bleeding	1	1
	Inflammatory Syndrome	1	1
	Wound Infection	1	1
	Colonic Ischaemia	3	2
	Deep Vein Thrombosis/ Pulmonary Embolus	0	1
	Acute Renal Failure	5	4
	Lower Limb Ischaemia	1	2
	Mortality	2	4

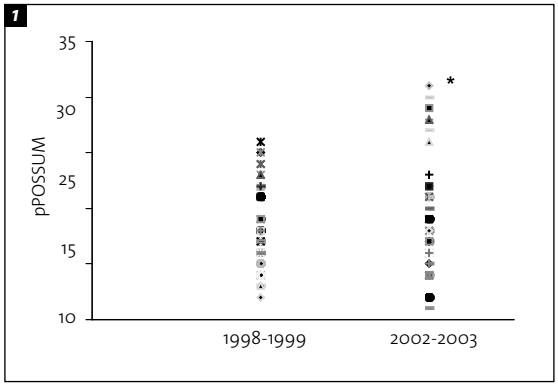


*Figure 1 — Physiological POSSUM (pPOSSUM) scores shown for the two time periods – 1998-1999 and 2002-2003. * p=0.048*

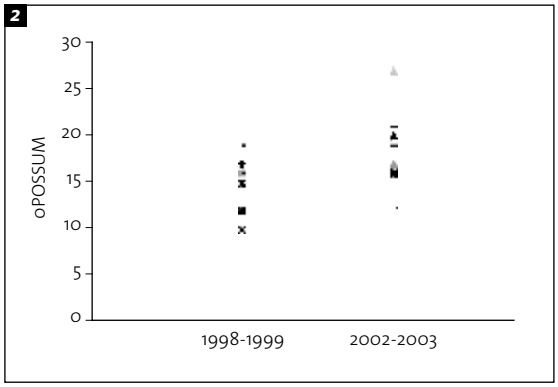


Figure 2 — Operative POSSUM (oPOSSUM) scores shown for the two time periods – 1998-1999 and 2002-2003.

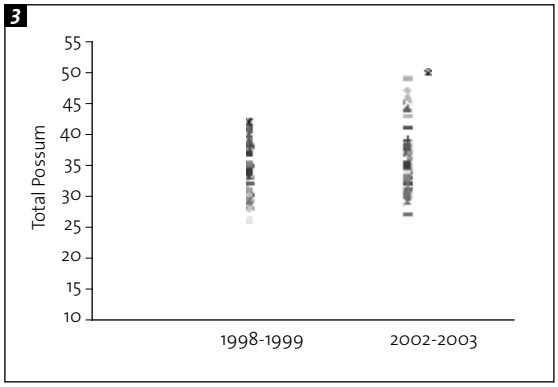


*Figure 3 — Total POSSUM (POSSUM) scores shown for the two time periods – 1998-1999 and 2002-2003. *p=0.02*

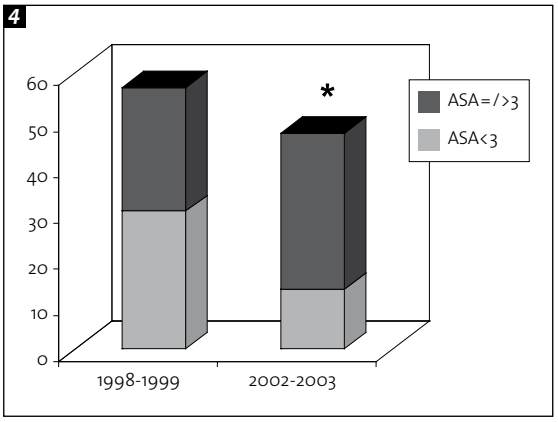


*Figure 4 — Proportion of patients presenting over the time periods studies with ASA scores =/>3 and ASA score <3. *p<0.007*

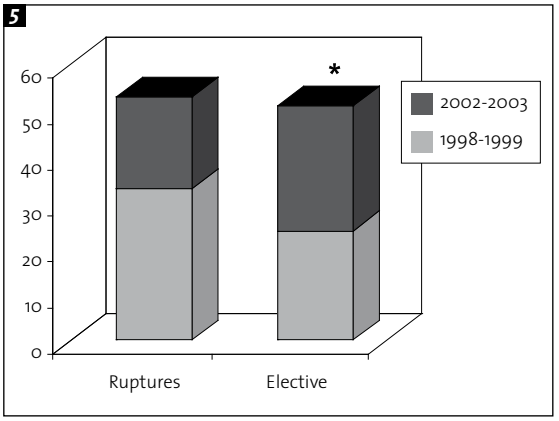


*Figure 5 — Proportion of emergency and elective presentation of abdominal aortic aneurysm during the time periods studied – 1999-2000 and 2002-2003. *p=non-significant.*

Although care provided in a HDU is cheaper than in ICU, there has been no observed reduction in demand for ICU care with the introduction of high dependency units.[9] There are several controversies surrounding the organisation of a HDU, one of which is nurse to patient ratio. Boots *et al* suggest that a defined high dependency service becomes cost-effective when patient care requires more than one nurse for three patients.[7] HDUs vary in terms of their proximity to the ICU, with the majority being geographically distinct from the ICU. They have a variable number of designated consultants, who may be surgeons, anaesthetists or physicians. These units are highly variable in size, ranging from 3 – 13 beds.[8]

In the current study, reduced bed occupancy was compensated for by more prolonged HDU stays. This eliminated any cost saving on ICU expenditure. HDU costs are higher than those of a general surgical ward because of the level of sophisticated care provided. Significantly higher nurse/patient ratios are required. Added to that are the higher costs of consumables, pharmacy costs and capital assets. However, the cost is at most only 50% of that of ICU.[12] The cost can be difficult to quantify as illustrated by other observational studies. Any cost implications are likely to be offset by improvements in the quality of care as inferred by our findings and those of others.[3,9] Once a HDU is established, only observational studies are really possible because of clinical pressure to admit patients if capacity permits. Other well recognised confounding factors, such as fluctuating rates of referral when HDU and ICU are full, and admission criteria vary as the critical care services become busier, making measurement of supply and demand difficult.[9]

Dhond *et al* reported that mid-week was the busiest period for HDU activity as the unit accommodated elective surgical procedures. This would suggest that, although the occupancy in ICU remains the same, the HDU allows a greater elective workload to be undertaken.[9]

CONCLUSION

As outcome after AAA rupture remains poor, it is essential that high-risk patients continue to be treated electively. In our own experience there appears to be a trend towards a greater proportion of elective aortic aneurysm repairs, which may be a result of earlier intervention in high-risk groups. Despite the fact that our patient population is becoming increasingly physiologically compromised, we have maintained acceptable levels of postoperative morbidity. In addition their post-operative stay in ICU was reduced with little increased cost. Although difficult to quantify, as demand for ICU beds is a constant strain, it is likely that vacating ICU beds earlier has a beneficial effect on ICU bed turnover. The quality, and therefore value, of inpatient care can be improved by provision of high dependency step-down facilities.

REFERENCES

1. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991;78:356-360
2. Bayley PJM, Matthews JNS, Dobson PM, Price ML, Thomas DG. In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland. Vascular Anaesthesia Society Audit. *Br J Surg* 2001;88:687-692.
3. Jones HJ, Coggins R, Lafuente J, Cossart L. Value of a surgical high-dependency unit. *Br J Surg*. 1999; 86 (12): 1578-82.
4. Davies J, Tamhane R, Scholefield C, Curley P. Does the introduction of HDU reduce surgical mortality? *Ann R Coll Surg Engl*. 1999; 81 (5): 343-7.
5. Durbin CG, Kopel RF. A case-control study of patients readmitted to the intensive care unit. *Crit Care Med* 1993; 21: 1547-53.
6. Byrick RJ, Mazer CD, Caskennette GM. Closure of an intermediate care unit: impact on critical care utilisation. *Chest* 1993; 104: 876-81.
7. Boots, Lipman J. High dependency units: issues to consider in their planning. *Anaesth Intensive Care* 2002; 30; (3): 348-54.
8. Thompson FJ, Singer M. High dependency units in the UK: variable size, variable character, few in number. *Postgrad Med J*. 1995; 71 (834): 217-21.
9. Dhond G, Ridley S, Palmer M. The impact of a high-dependency unit on the workload of an intensive care unit. *Anaesthesia* 1998; 53 (9): 841-7.
10. Gamil M, Fanning A. The first 24 hours after surgery. A study of complications after 2153 consecutive operations. *Anaesthesia* 1991; 46: 712-5.
11. Leeson-Payne CG, Aitkenhead AR. A prospective study to assess the demand for a high dependency unit. *Anaesthesia*. 1995; 50: 383-7.
12. Singer M, Myers S, Hall G, Cohen SL, Armstrong RF. The cost of intensive care: a comparasion of one unit between 1988 and 1991. *Intensive Care Medicine* 1994; 20: 542-9.

Correspondence to: Ms MC Barry, Dept of Vascular Surgery, St. Vincent's University Hospital, Elm Park, Dublin 4 Tel: 01.2773709; Fax: 01 2773678
E-mail: mary.barry@st-vincents.ie

ORIGINAL PAPER

Haemodynamic determinants of elevated pulse wave velocity during acute isometric handgrip exercise

KF Reid,[1]
MA Conway

Dept of Cardiology, St. Luke's Hospital, Kilkenny

[1]KF Reid is currently at the Jean Mayer USDA Research Center on Aging at Tufts University, Boston, USA

ABSTRACT

Background Measurement of pulse wave velocity (PWV) provides a reliable index of vascular stiffness. Despite its widespread application, the physiological inter-relationships between PWV, blood pressure (BP) and in particular, heart rate (HR), have yet to be fully elucidated. Furthermore, little is known about altered arterial compliance during acute exercise.

Aim To examine the effects of 3-min supine non-dominant isometric handgrip exercise (ISOMEX), performed at 30% of maximum voluntary contraction, on carotid-radial PWV, BP and HR in the dominant arm of 51 healthy subjects.

Results During exercise, PWV correlated strongly with diastolic BP ($r = 0.55$, $p < 0.01$) and mean arterial pressure ($r = 0.51$, $p < 0.01$). PWV and HR failed to correlate at rest or during exercise.

Conclusion ISOMEX invoked an elevated PWV, which is predominantly related to BP or factors determining it, and not HR. The carotid-radial PWV stress test is a simple measurement that may have prognostic potential for use in large-scale population studies.

INTRODUCTION

Pulse wave velocity (PWV), the speed of pulsatile wave transit along an arterial segment, is a sensitive and reliable surrogate of vascular stiffness.[1,2] Resting PWV increases with advancing age, reflecting elevated arterial stiffness, or its inverse, reduced compliance. The progression of arterial stiffness is also accelerated by a number of cardiovascular disorders.[3-6] Studies designed to examine the physiological relationships between PWV and standard resting haemodynamics report conflicting results. Whilst strong, but variable, correlations between PWV and blood pressure (BP) are frequently documented,[3-10] its association with other measured and derived parameters (e.g. heart rate (HR), rate pressure (double) product and pulse pressure) is less clear.[7,11-16] Furthermore, the potential influence of HR on the PWV continues to evoke much controversy despite the use of cardiac pacing to induce tachycardia.[12,14,15,17]

The effects of elevated HR and BP on the PWV of normal subjects during acute exercise are also unclear. Movement artefact tends to restrict reliable measurement of PWV during dynamic exercise. Hence, recent isotonic studies only report acute alterations of compliance during the post-exercise recovery phase.[16,18] Stable recording of PWV can be acquired using isometric exercise and although some studies are reported,[19-21] the detailed inter-relationships between the various haemodynamic parameters and PWV during isometric exercise remain unclear. Most reports on PWV relate to the elastic, carotid-femoral circulation. Less attention has been addressed to the more muscular carotid-radial arterial segment even though it is easily accessed, allows precise measurement using synchronous, dual transducer techniques and is a part of the vasculature that is relatively spared from the effects of both ageing and occlusive atheromatous disease.[2,5]

The current study describes, in control subjects, aspects of the direct physiological inter-relationships between dominant arm carotid-radial PWV and standard non-invasively measured haemodynamics, during acute non-dominant arm isometric handgrip exercise (ISOMEX). This particular mode of exercise was chosen for study not only because of the stability of the recordings, but also due to the acute nature of its sympathetically mediated vasoconstrictive effect.[22-24] Isometric exercise invokes a notable elevation of diastolic BP, in addition to modest increases of systolic

BP and HR. By measuring PWV during ISOMEX, the effect of a concurrent rise of HR, on a background of amplified vascular tone, can be examined. The hypothesis underlying the current study is that BP, or factors causing the BP response, rather than HR, determine the speed of pulse wave transit during ISOMEX. We also propose that measurement of PWV in the upper limb during the standard isometric exercise protocol is practicable for use as a vascular stress test in human population studies.

METHODS

SUBJECTS

The study took place at the exercise laboratory of the Cardiovascular and Coronary Care Unit, St. Luke's Hospital, Kilkenny, Ireland. Institutional ethics approval was obtained and all volunteers provided informed consent. Full data sets were recorded from 51 controls (22 males and 29 females, Table 1), recruited from a local population with a mean total cholesterol of 5.5 ± 1 mmol/l. Participants with a history of diabetes mellitus, a resting BP greater than 140/90 mmHg, Marfan's syndrome or those taking any form of pharmaceutical or alternative medication were excluded from the study. All subjects were free of symptoms or signs of disease with active lifestyles and no previous history of valvular, atheromatous or hypertensive cardiovascular disease. Six subjects were excluded from the final analysis because of failure to obtain a complete compliment of resting and exercise PWV measurements.

PROCEDURES

Following a demonstration of the experimental protocol, each subject rested supine for approximately 10 minutes. After this period, three individual recordings of brachial BP (systolic and diastolic BP) and HR were taken from the dominant arm with an automated digital oscillometric sphygmomanometer (Omron, model 705 – CP, Omron Matsuaka Corp., Japan). Upper limb PWV was determined directly afterwards using an automatic device, Complior II® (Colson, Paris). This allows online pulse wave recording and automatic calculation of PWV, as previously described and validated.[1] Synchronous measurements were obtained by simultaneously positioning two pressure sensitive transducers, one at the base of the neck for the common carotid artery and the other directly over the radial artery of the dominant arm. The PWV was derived using the time delay between the foot of the proximal (carotid) and distal (radial) waves and the superficially calculated distance separating the respective transducers, according to the following equation: PWV (m/sec) = distance (cm) / transit time (secs).[1] The procedures used for calculation of the baseline PWV were identical for exercise and recovery. Since comparison of the PWV was performed at the same sitting for each individual, the length between the transducers was not adjusted to allow for the short distance that the pulse wave travels from the origin of the common carotid into the neck. The pre-exercise values for each subject were based on three individual sets of resting steady state data.

The rate pressure product and the mean arterial pressure were estimated according to standard formulae (rate pressure product = HR x systolic BP and mean arterial pressure = 1/3 (systolic BP – diastolic BP) + diastolic BP).

PROTOCOL

ISOMEX was performed uninterrupted for three minutes at 30% of maximal voluntary contraction using a Baseline ® hydraulic hand dynamometer

Table 1
PERSONAL CHARACTERISTICS

n	MALES (n=22)	FEMALES (n=29)
Age, years	37. 6 ± 13	37.7 ± 16
Height, cm	175 ± 1	162 ± 1
Weight, kg	84.4 ± 3	65.7 ± 2
BMI, kg/m²	27.5 ± 1*	24.9 ± 1
MVC dominant, kg	45 ± 2*	27 ±1
MVC non-dominant, kg	43.8 ± 2*	26.4 ± 1
30% MVC, kg	13.5 ± 0.6*	7.9 ± 0.4

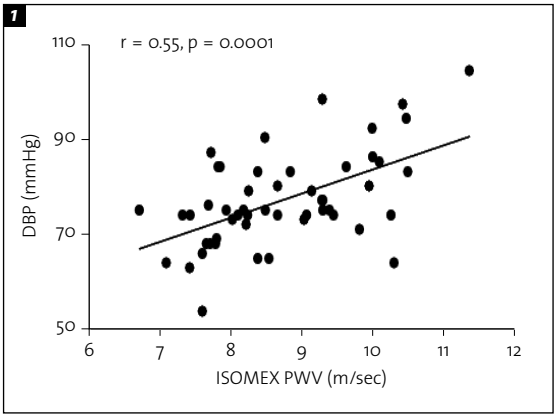
Values are mean ± SE, except age (SD) . BMI, body mass index; MVC, maximum voluntary contraction.
**** = Significant difference compared to females, p ≤ 0.01***

ORIGINAL PAPER

Table 2
HAEMODYNAMIC RESPONSES TO ISOMEX

	REST	EXERCISE	RECOVERY
SBP, mmHg (males n = 22)	120 ± 3	133 ± 4†‡	120 ± 3
(females n = 29)	115 ± 3	123 ± 3	114 ± 4
DBP, mmHg	69 ± 1	80 ± 2†‡	69 ± 2
	66 ± 1	74 ± 2†	68 ± 1
MAP, mmHg	86 ± 2	98 ± 3†‡	86 ± 2
	82 ± 2	91 ± 2†	83 ± 2
PP, mmHg	51 ± 2	52 ± 2	52 ± 2
	50 ± 2	49 ± 2	47 ± 3
HR, beats/min	66 ± 2‡	72 ± 2*‡	65 ± 2
	62 ± 2	66 ± 2*	61 ± 2
RPP	7933 ± 288‡	9646 ± 479†§	7881 ± 312‡
	7087 ± 246	8143 ± 266†	6934 ± 286
PWV, m/sec	8.16 ± 0.18‡	9.18 ± 0.25†§	8.25 ± 0.23
	7.69 ± 0.15	8.38 ± 0.16†	7.78 ± 0.15

Values are mean ± S.E. DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; RPP, rate pressure product; SBP, systolic blood pressure.
(* = Significant difference compared to baseline, P ≤ 0.05; † = p ≤ 0.009)
(‡ = Significant difference compared to females, P ≤ 0.05; § = p ≤ 0.005)



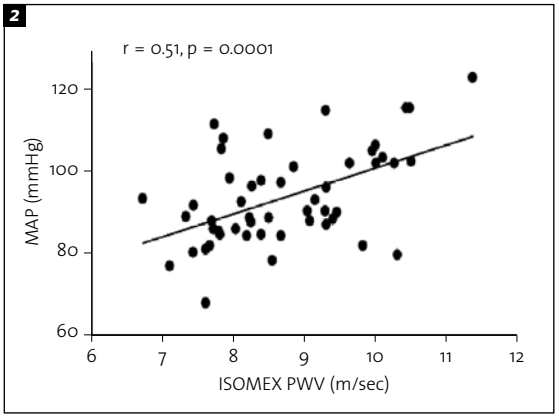
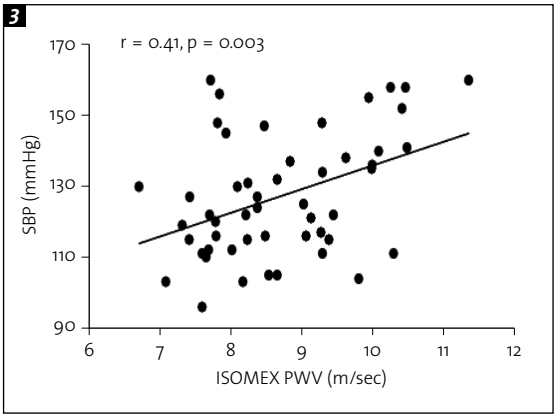


Figure 1 — CORRELATION BETWEEN PWV AND DBP DURING ISOMEX

Figure 2 — CORRELATION BETWEEN PWV AND MAP DURING ISOMEX



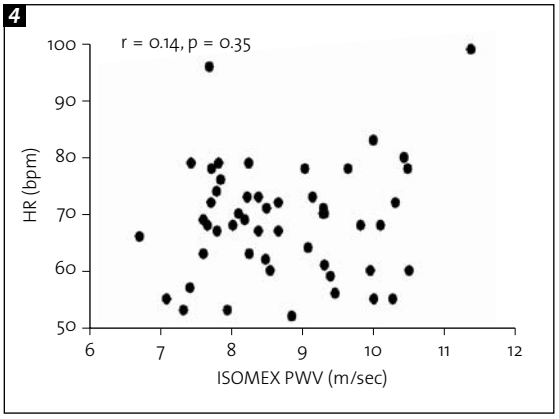


Figure 3 — CORRELATION BETWEEN PWV AND SBP DURING ISOMEX

Figure 4 — CORRELATION BETWEEN PWV AND HR DURING ISOMEX

(FEI, Irvington, New York 10533, U.S.A.). Subjects were encouraged to maintain constant tension on the dynamometer and to breathe normally throughout (avoiding the Valsalva manoeuvre). Recording of all haemodynamic parameters took place during the third minute of ISOMEX in order to determine the BP, HR and PWV during steady state contraction. On completion of exercise, subjects relaxed for one minute before recording of the recovery BP, HR and PWV commenced.

STATISTICAL ANALYSIS

Statistical analyses were applied comparing baseline data to values obtained during exercise and recovery using paired Student t-tests for dependant variables, where appropriate. The Pearson product moment correlation was computed to assess the degree of association amongst variables and all results were analysed with GB-STAT (version 8.0, Dynamic Microsystems, U.S.A.). Statistical significance was accepted at a p value ≤ 0.05. Data are presented as mean ± SE.

RESULTS

Haemodynamic changes were recorded successfully from the 51 subjects at the first sitting. Each participant tolerated the protocol comfortably and elicited the expected, although individually variable haemodynamic changes. Resting PWV correlated significantly with age ($r = 0.31$, $p = 0.02$), resting diastolic BP ($r = 0.33$, $p = 0.02$) and resting mean arterial pressure ($r = 0.29$, $p = 0.04$).

ISOMEX significantly elevated the standard haemodynamics such as systolic BP, diastolic BP and HR compared to rest. The systolic BP increased by an average of 10.1 ± 1 mmHg (9 ± 1%) ($p = 0.002$). The percentage increase of diastolic BP was greater (15 ± 1%, $p < 0.0001$), although the absolute change was similar: 10.0 ± 1 mmHg. The HR increased by an average of 9.5 ± 1% ($P = 0.003$), from a resting rate of 63 ± 1 beats/min to 69 ± 1 beats/min. ISOMEX also significantly elevated the derived parameters, rate pressure product (18 ± 2%; $p < 0.0001$) and mean arterial pressure (12 ± 1%; $p < 0.0001$). Hand-grip exercise also significantly increased the PWV by 10.9 ± 1 %, from 7.89 ± 0.1 m/sec to 8.73 ± 0.2 m/sec ($p < 0.0001$). The pulse pressure was the only standard haemodynamic variable that did not change ($p = 0.94$).

Strong correlations were found between exercise PWV and exercise haemodynamics such as diastolic BP ($r = 0.55$, $p = 0.002$, Figure 1) and mean arterial pressure ($r = 0.51$, $p = 0.002$, Figure 2). The systolic BP ($r = 0.41$, $p = 0.003$, Figure 3) and rate pressure product ($r = 0.35$, $p < 0.01$) also correlated with the ISOMEX PWV. Despite the significant rise in HR and the similar % change of the PWV, these parameters did not correlate (Figure 4).

Table 2 displays the resting, exercise and recovery haemodynamic parameters for males ($n = 22$) and females ($n = 29$). The former presented with higher resting values for all haemodynamics. However rate pressure product, HR, and PWV were the only indices that were significantly greater ($p \leq 0.05$). During exercise, males elicited significantly greater PWV (9.19 ± 0.3 m/sec vs. 8.38 ± 0.2 m/sec, $p = 0.007$) and the systolic BP, diastolic BP, mean arterial pressure, HR and rate pressure product were also significantly elevated ($p \leq 0.05$), compared to females. However, the magnitude of the % changes invoked by ISOMEX were similar for each gender. The PWV, and all of the aforementioned haemodynamic parameters, returned to resting pre-exercise levels during the recovery phase. Gender also had no effect on the recovery values.

REPRODUCIBILITY

Reproducibility of the methods was confirmed in eight, randomly chosen members of the study group, in whom the protocol was repeated less than 5 days after the original measurements. The % increase of PWV during ISOMEX in this subset at the second recording was similar to that initially observed (15.5 ± 6 vs. 15.2 ± 4%, p = ns). Similarly, the induced changes in mean arterial pressure (15.7 ± 4 vs. 16.1 ± 3%, p = ns) and HR (14.1 ± 4 vs. 14.3 ± 4%, p = ns) were comparable between the two days.

DISCUSSION

This study documents the physiological relationships between synchronous dual point carotid-radial PWV and other non-invasive haemodynamics at rest, during acute isometric exercise and recovery. It also provides novel insight into non-dominant forearm exercise, focusing attention on the readily accessible carotid-radial circulation where applicability is widely practicable.[5] The findings support the hypothesis that elevated PWV during isometric exercise is strongly associated with the hypertensive response to this form of physiological exercise stress rather than the rise in HR.

RESPONSES TO ISOMETRIC EXERCISE

A number of previous studies describe the physiological effects of isometric exercise in humans.[22,23,25,26] The present report focuses not only on standard BP and HR changes but also explores the effects of ISOMEX on mean arterial pressure, rate pressure product and pulse pressure. The findings relating to the latter are consistent with those derived from published BP and HR data, even though exercise was performed using the non-dominant arm.[23,27,28] Such an exercise protocol avoids forearm movement, but, as with dominant arm isometric exercise, invokes arterial stiffening or vasoconstriction due to enhanced sympathetic activity to the heart and blood vessels.[22-24] The elevation of BP (particularly diastolic), is directly related to both the intensity and duration of muscle contraction, and to the size of the muscle mass recruited.[25-27] Since the BP changes during ISOMEX are coupled with modest changes in HR, the haemodynamic response that amplifies arterial stiffness operates predominantly through BP related mechanisms.

BLOOD PRESSURE AND PWV

The current findings show that at rest, diastolic BP and mean arterial pressure are significantly related to carotid-radial PWV. This corroborates the findings of Kanda et al[5] in healthy males, and Cameron et al.[29] who report that the resting carotid-radial PWV of controls, but not diabetic subjects, is associated with diastolic BP and mean arterial pressure. Yasmin and Brown[9] concluded that the diastolic BP was the strongest correlate of resting carotid-radial PWV in the healthy offspring of hypertensive patients. Diastolic BP is also reported as the major determinant of aortic PWV in young males.[10] However, in both healthy and diseased subjects, other investigations have found that mean arterial pressure or systolic BP is preferentially related to the PWV in the resting state.[3,4,6-8]

The elevated PWV during ISOMEX in the current study correlates strongest with the exercise diastolic BP. ISOMEX induced elevation of diastolic BP is thought to result from increased peripheral arterial resistance,[22] likely as a consequence of amplified sympathetic nervous system activity. The weaker relationship between exercise systolic BP and exercise PWV may relate to the greater magnitude of the diastolic BP response. The latter was raised by ~15 % compared to the ~9% rise in systolic BP. The pulse pressure did not change significantly during ISOMEX as a consequence of the greater percentage increase of diastolic BP, relative to systolic BP. This is consistent with the original observations of Lind et al.[25] The mean arterial pressure and to a lesser extent, the rate pressure product, which may provide a non-invasive estimate of the ventricular-vascular shear stress component, were also linked to the PWV response during ISOMEX.

HEART RATE AND PWV

Controversy exists with regard to HR and PWV and some authors suggest that PWV should be standardised for the HR level.[15] One postulated mechanism whereby HR may influence PWV is that at faster heart rates, the time available for vessel wall recoil is reduced, thereby decreasing distensibility. A cross-sectional study by Nurnburger et al.[10] describes a significant association between resting HR and aortic PWV amongst healthy young men. Also, ambulatory HR appears to influence aortic PWV amongst older subjects.[11] The present results demonstrate no effect of HR on the upper-limb PWV either at rest, during ISOMEX or recovery. Despite the elevated HR occurring on the background of more taut or stiffened vessels during ISOMEX, it still had no relationship with the PWV. Also, the derived parameter, rate pressure product, elicited a weaker association with PWV than the systolic BP alone, implying that HR in combination with systolic BP has little effect on the PWV, at least in this population of healthy controls.

Similarly, pacing studies designed to simulate exercise tachycardia report conflicting results. Wilkinson et al[17] detected no PWV alteration during incremental atrial pacing, whilst other investigations found that PWV increased significantly by elevating the HR from 40 beats/min to 130 beats/min.[12,15] Albaladejo et al.[13] suggest that a relationship exists between aortic PWV and HR for males but not for females. We found no relationship between PWV and HR in our gender comparisons.

NEUROGENIC REFLEXES AND ISOMEX PWV

The mechanism underlying the raised BP and PWV during ISOMEX in the current study may relate to amplified efferent sympathetic activity. The rise in diastolic BP is consistent with increased peripheral vascular resistance and stiffening of the vasculature, which alters the inherent arterial cushioning function that underlies normal rates of resting PWV. On cessation of exercise, the BP and HR decrease is mirrored by a corresponding fall in PWV, a response consistent with a neurogenic trigger for

the haemodynamic alterations being switched off. This rapid reversal contrasts with the PWV response to acute dynamic exercise. Compliance is elevated by about 66% 30 minutes following moderate intensity cycling exercise and only returns fully to baseline when measured one hour after exercise.[18] Similarly, both upper limb and lower limb PWV are ~10% lower 60 minutes following maximum treadmill exercise.[16] Such delayed responses to isotonic exercise may better reflect metabolic phenomena resulting from this particular mode of physiological stress.

THE CAROTID-RADIAL ARTERIAL SEGMENT

The majority of reports regarding synchronous dual arterial site PWV measurement focus on the carotid-femoral circulation. Few synchronous carotid-radial PWV studies are documented, even though studies employing this component of the circulation have notable advantages.[5] Factors such as ageing and disease, that have a pronounced effect on the aorta, do not overtly affect this part of the arterial tree. Indeed, the first measurements of PWV were recorded in the upper limb vasculature because of its accessibility. Furthermore, the carotid-radial circulation comprises a muscular type vasculature which may also be more dependent on endothelial nitric oxide bioavailability. In addition, because of this large smooth muscle component, for any given increase in sympathetic outflow, greater modification of the intrinsic viscoelastic properties of the arterial wall along this particular segment should occur, compared to elastic type arteries.

CONCLUSION

The current study describes the abrupt, but temporary, elevation of PWV resulting from a single bout of ISOMEX in healthy subjects. This increase is significantly related to BP, particularly diastolic BP and mean arterial pressure, but not HR. The pattern of the haemodynamic response to ISOMEX is consistent with a likely neurogenic mechanism. Studies characterising controls and patients with cardiovascular disease and related disorders using the standard isometric exercise protocol described here, in conjunction with longitudinal lifestyle changes including diet, exercise, pharmaceutical and other interventions, are indicated in order to verify the diagnostic and prognostic potential of assessing PWV during ISOMEX.

ACKNOWLEDGMENTS

Servier, Paris; South Eastern Health Board; Merck Sharp & Dohme

Preliminary results of this study were presented at the 19th Annual Meeting of the American Society of Hypertension in May 2004, New York, USA.

REFERENCES

1. Asmar R, Benetos A, Topouchian J, *et al*. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995; 26: 485-490.
2. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles (4th edition). Arnold, London 1998.
3. Blacher J, Demuth K, Guerin AP, Safar ME, Moatti N, London GM. Influence of biochemical alterations on arterial stiffness in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol* 1998; 18: 535-541.
4. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; 33: 1111-1117.
5. Kanda T, Nakamura E, Moritani T, Yamori Y. Arterial pulse wave velocity and risk factors for peripheral vascular disease. *Eur J Appl Physiol* 2000; 82: 1-7.
6. Amar J, Ruidavets JB, Chamontin B, Drouet L, Ferrieres J. Arterial stiffness and cardiovascular risk factors in a population-based study. *J Hypertens* 2001; 19: 381-387.
7. Sa Cunha R, Pannier B, Benetos A, *et al*. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *J Hypertens* 1997; 15: 1423-1430.
8. Rajzer MW, Klocek M, Kawecka-Jaszcz K, *et al*. Aortic pulse wave velocity in young normotensives with a family history of hypertension. *J Hypertens* 1999; 17: 821-1824.
9. Yasmin, Brown MJ. Similarities and differences between augmentation index and pulse wave velocity in the assessment of arterial stiffness. *QJM* 1999; 92: 595-600.
10. Nurnberger J, Dammer S, Opazo Saez A, Philipp T, Schafers RF. Diastolic blood pressure is an important determinant of augmentation index and pulse wave velocity in young, healthy males. *J Hum Hypertens* 2003; 17: 153-158.
11. Albaladejo P, Asmar R, Safar M, Benetos A. Association between 24-hour ambulatory heart rate and arterial stiffness. *J Hum Hypertens* 2000; 14: 137-141.
12. Albaladejo P, Copie X, Boutouyrie P, *et al*. Heart rate, arterial stiffness and wave reflections in paced patients. *Hypertension* 2001; 38: 949-952.
13. Albaladejo P, Laurent P, Pannier B, Achimastos A, Safar M, Benetos A. Influence of sex on the relation between heart rate and aortic stiffness. *J Hypertens* 2003; 21: 555-562.
14. Lantelme P, Khettab F, Custaud MA, *et al*. Spontaneous baroreflex sensitivity: toward an ideal index of cardiovascular risk in hypertension? *J Hypertens* 2002; 20: 935-944.

15. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. *Hypertension* 2002; 39: 1083-1087.
16. Naka KK, Tweddel AC, Parthimos D, Henderson A, Goodfellow J, Frenneaux MP. Arterial distensibility: acute changes following dynamic exercise in normal subjects. *Am J Physiol Heart Circ Physiol* 2003; 284: H970-H978.
17. Wilkinson IB, Mohammad NH, Tyrrell S, *et al*. Heart rate dependency of pulse pressure amplification and arterial stiffness. *Am J Hypertension* 2002; 15: 24-30.
18. Kingwell BA, Berry KL, Cameron JD, Jennings GL, Dart AM. Arterial compliance increases after moderate-intensity cycling. *Am J Physiol Heart Circ Physiol* 1997; 273: H2186–H2191.
19. Breithaupt-Grogler K, Leschinger M, Belz GG, *et al*. Influence of antihypertensive therapy with cilazapril and hydrochlorothiazide on the stiffness of the aorta. *Cardiovasc Drugs Ther* 1996; 10: 49-57.
20. Breithaupt-Grogler K, Ling M, Boudoulas H, Belz GG. Protective effect of chronic garlic intake on elastic properties of aorta in the elderly. *Circulation* 1997; 96: 2649-2655.
21. Geleris P, Stavrati A, Boudoulas H. Effect of cold, isometric exercise, and combination of both on aortic pulse in healthy subjects. *Am J Cardil* 2004; 15: 265-267.
22. Donald KW, Lind AR, McNichol GW, Humphries PW, Taylor SH, Staunton HP. Cardiovascular responses to sustained (static) contractions. *Circ Res* 1967; 20(Suppl I): I15-I30.
23. Perez-Gonzalez JF. Factors determining the blood pressure responses to isometric exercise. *Circ Res* 1981; 48(Suppl 2): I76-I86.
24. Hietanen E. Cardiovascular responses to static exercise. *Scand J Work Environ Health* 1984; 10: 397-402.
25. Lind AR, Taylor SH, Humphreys PW, Kennelly BM, Donald KW. The circulatory effects of sustained voluntary muscle contraction. *Clin Sci (Lond)* 1964; 27: 229-244.
26. Mitchell JH, Schibye B, Payne FC 3rd, Saltin B. Response of arterial blood pressure to static exercise in relation to muscle mass, force development, and electromyographic activity. *Circ Res* 1981; 48 (Suppl 2): I70-I75.
27. Fontana GA, Pantaleo T, Bongianni F, Cresci F, Manconi R, Panuccio P. Respiratory and cardiovascular responses to static handgrip exercise in humans. *J Appl Physiol* 1993; 75: 2789-2796.
28. Kamiya A, Michikami D, Fu Q, *et al*. Static handgrip exercise modifies arterial baroreflex control of vascular sympathetic outflow in humans. *Am J Physiol Regul Integr Comp Physiol* 2001; 281: R1134-R1139.
29. Cameron JD, Bulpitt CJ, Pinto ES, Rajkumar C. The aging of elastic and muscular arteries: a comparison of diabetic and nondiabetic subjects. *Diabetes Care* 2003; 26: 2133-2138.

Correspondence to: Kieran Reid
Email: kieran.reid@tufts.edu
Dr.Michael.Conway@maila.hse.ie
Tel: + 353 56 7785253 Fax: + 353 56 7785170

Acute haemodynamic effects of cigarette smoking in healthy young subjects

Z Amir, A Mahmud, J Feely

Dept of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St. James's Hospital, Dublin 8

ABSTRACT

Background Invasive studies in middle-aged patients suggest an acute adverse haemodynamic effect of smoking.

Aims To study acute changes in blood pressure (BP), cardiac output, peripheral resistance and aortic compliance following cigarette smoking in healthy young subjects.

Methods Using a non-invasive photoplethysmographic technique we compared the effects of smoking one cigarette with sham smoking in 12 healthy volunteers (22-25 years). Data was analysed using JMP version 5.0.

Results In contrast to sham smoking there was a prompt increase in blood pressure with a maximum effect at 15 min (123±7/75±5 to 143±6/86±6 mmHg, mean±SEM, $p<0.01$) which is attributed to a rise in cardiac output ($p<0.05$) rather than changes in peripheral vascular resistance. There was also a significant ($p<0.05$) increase in heart rate and a reduction in aortic compliance.

Conclusion These results suggest that health or young age do not protect from the adverse effects of smoking.

INTRODUCTION

Although the cardiovascular consequences, ischaemic and peripheral vascular disease, of cigarette smoking are well recognised the relative contribution of the underlying pathophysiological mechanisms e.g. atherosclerosis, increased intimal medial thickness, inflammation, endothelial dysfunction, hypercoagulatibility, platelet activation are less well described.[1] Recently we noted that acute cigarette smoking increased blood pressure and arterial stiffness.[2] An increase in blood pressure (BP) per se can increase vascular stiffness. As BP is largely determined by cardiac output and peripheral vascular resistance we wished to determine if changes in one or both was responsible for the change in BP and whether BP changes antedated changes in arterial stiffness/compliance. We also hypothesised that by using a continuous, non-invasive beat-to-beat recording of the haemodynamic changes induced by smoking one could compare data obtained in a young healthy population to that from a patient population using more invasive techniques.

METHODS

A group of 12 healthy subjects (six female), aged 22-25 years of age, of which six were regular smokers and six non-smokers, volunteered for this study. Subjects were studied supine in a quiet room resting for 10-15 minutes until a stable baseline was achieved. None were on any medication and all had refrained from smoking for at least two hours. Subjects smoked a single cigarette (nicotine content 1.2 mg) over five minutes and completion was taken as time 0. Data recorded in the five minutes prior to smoking were taken as baseline. The six control subjects followed the same protocol with the exception that their cigarette was not lit (sham smoking). Haemodynamic measurements were recorded non-invasively from finger infra-red photopletismographic recordings of arterial BP – Finometer (TNO Biomedical Instruments, Amsterdam, Netherlands) which derives blood pressure (following calibration to brachial blood pressure) cardiac output and peripheral vascular resistance and arterial (aortic) compliance from the computed aortic flow waveform. It has been shown to accurately reflect pressures recorded invasively [3] and has been validated[4] to the standards of the Association for the Advancement of Medical instrumentation (AAMI).

Results, expressed as mean ±SEM, were analysed through JMP (Version 3.2.1. SAS Institute Inc). The difference between the response to smoking and controls was analysed using MANOVA. The study has Institutional Ethics approval.

RESULTS

There were no significant differences in baseline values between the two groups. As there were no

changes in any haemodynamic measurement with sham (control) smoking, only the active smoking data are displayed (Figure).

SYSTOLIC BP

There was a rise from baseline (123 ±7 mmHg) in systolic pressure by one minute after smoking and the main changes were observed during the 5 to 15 minute period when the peak (143 ±6 mmHg) effect after smoking was achieved (Figure). However systolic pressure did not return to baseline even some 20 minutes following smoking. The difference between the two groups was significant ($p<0.01$).

DIASTOLIC BP

The diastolic blood pressure showed similar changes to that of systolic pressure from a baseline 75 ±5 reaching a peak 86 ±6 mmHg at 15 minutes but had not returned to baseline 20 minutes after smoking (Figure). Again the difference between the two groups (smoking/control) was significant ($p<0.01$).

HEART RATE

The baseline heart rate (68 ±4/min) with smoking increased significantly ($p<0.01$) following smoking, reaching a maximum (78 ±5/min) at 10 minutes and declined thereafter. In controls (sham smoking) there was no variation in heart rate.

CARDIAC OUTPUT

Cardiac output rose from a baseline of 5.6 ±1.62 l/min to 6.4 ±0.8 l/min after 3 minutes following smoking, achieving a peak 6.8 ±1.0 l/min at 10 minutes. It then remained quite static without much fluctuation until the end of the study. The difference observed due to smoking was significant ($p<0.001$) as sham smoking did not cause any variation in cardiac output.

TOTAL PERIPHERAL RESISTANCE (TPR)

In the Finometer this is computed from mean pressure/cardiac output and expressed as dyn.s/cm^5 and converted as a unit called MU (medical unit system). There was no change from baseline values in smokers (1.03+0.1) following smoking (Figure).

ARTERIAL COMPLIANCE

Some five minutes after smoking compliance had declined significantly ($p<0.01$) from 2.55 ±0.1 at baseline to 2.34 ±0.1 reaching 2.3 ±0.1 by 15 minutes. In controls it showed no change and again the difference between the two groups was significant $p<0.01$.

CONCLUSION

This study reveals additional information on the acute haemodynamic response to smoking. It also suggests the adverse effects seen in older patients with disease states are applicable to healthy young subjects. This indicates that young age and a healthy vascular system does not offer protection from the adverse haemodynamic effects of smoking. The number of subjects studied was relatively small, in part due to implementation during the course of the study of a ban in Ireland precluding any smoking indoors.

The study illustrates how a sensitive non-invasive photophlethysmographic technique may accurately reflect the effects of smoking. The Finometer device is now established in the detection of acute changes in cardiac function[4] providing data that has hitherto only been available using invasive intra-aortic recording devices, which by their nature are not applicable in healthy subjects. Indeed with appropriate calibration it can quantitatively reflect change in blood pressure, cardiac output and total peripheral resistance in cardiac surgery patients.[5]

Using Doppler echocardiography Kool et al[6] reported an increase in cardiac index, largely due to an increased heart rate, and increased BP but no change in systemic vascular resistance following smoking in middle-aged subjects. Using radionucleotide ventriculography in 12 habitual smokers with suspected ischaemic heart disease Hoilund-Carlsen et al[7] have shown that two cigarettes acutely increased heart rate by 27%, the rate pressure product by 23% and cardiac output by 14%. The total peripheral resistance remained constant. This was accompanied by a 100% increase in plasma adrenaline (but not plasma noradrenaline). In 40 male smokers (mean age 47 years) undergoing diagnostic cardiac catheterisation studied while smoking a cigarette or sham smoking there was a prompt increase in both systolic and diastolic BP reaching a peak after five minutes which had not returned to baseline by 20 minutes. In that study the heart rate increasing from 68±2 to 78±2/min by five minutes and cardiac index (cardiac output divided by body surface area in m^2) by approximately 10% but there was no change in systemic vascular resistance index.[8] There was a significant change in the aortic pressure-diameter relation denoting a deterioration of the elastic properties which was maintained throughout the study with the maximum effect on aortic distensibility at five minutes.

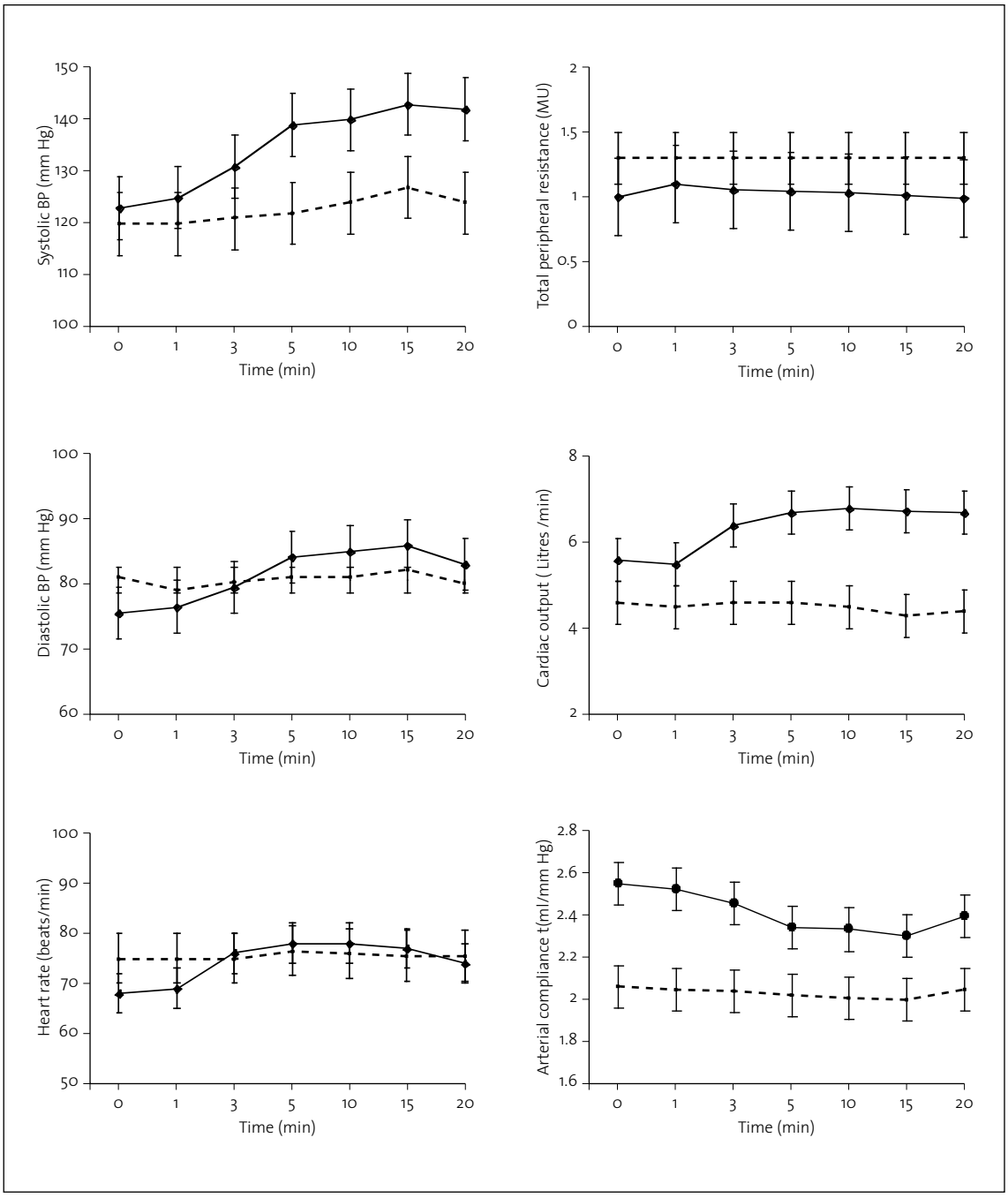


Figure — TIME COURSE OF CHANGE IN SYSTOLIC (TOP LEFT), DIASTOLIC BP (MIDDLE LEFT) AND HEART RATE (LOWER LEFT) AND TOTAL PERIPHERAL RESISTANCE (TOP RIGHT), CARDIAC OUTPUT (MIDDLE RIGHT) AND ARTERIAL COMPLIANCE (BOTTOM RIGHT) FOLLOWING SMOKING ONE CIGARETTE (•—•). IN CONTRAST, SHAM SMOKING(•----•)DID NOT PRODUCE ANY SIGNIFICANT CHANGE (MEAN±SEM).

Our primary findings were a prompt increase in blood pressure, heart rate and cardiac output immediately following smoking but peripheral resistance remained unchanged. The decline in aortic compliance, or increase in stiffness appeared to lag temporarily behind the changes in blood pressure.

Our study using a new non-invasive technique provides results similar to those seen with echocardiography, radio-nucleotide and intravascular catheterisation with micromanometer recordings in a patient population. Although the number of young subjects studied is small it appears that changes in blood pressure pre-date those of aortic compliance suggesting that some of this effect is blood pressure dependent. Nonetheless invasive flow loop studies also show a direct effect on the vascular wall.[6] Our results confirm that the acute rise in blood pressure following smoking is predominantly due to an increase in cardiac output rather than an increase in peripheral resistance.

ACKNOWLEDGEMENTS

Royal City of Dublin Hospital Research Foundation for providing funds to purchase Finometer.

REFERENCES

1. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. An Update. *JACC*. 2004;43:1732-1737.
2. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertens*. 2003;41:183-187.
3. Guelen I, Westerhof BE, Van Der Sar GL, *et al*. Finometer, finger pressure measurements with the possibility to reconstruct brachial pressure. *Blood Press Monit* 2003;8:27-30.
4. Schutte AE, Huisman HW, van Rooyen JM, *et al*. Validation of the Finometer device for measurement of blood pressure in black women. *J Hum Hypertens*. 2004;18:79-84.
5. Jansen JRC, Schreuder JJ, Mulier JP, *et al*. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001;87:212-222.
6. Kool MJ, Hoeks AP, Struijker Boudier HA, *et al*. Short and long-term effects of smoking on arterial wall properties in habitual smokers. *JACC*. 1993;22:1881-1886.
7. Hoilund-Carlsen PF, Marving J, Gadsboll N et al. Acute effects of smoking on left ventricular function and neuro-humoral responses in patients with known or suspected ischaemic heart disease. *Clin Physiol Funct Imaging*. 2004;24:216-223.
8. Stefanadis C, Tsiamis E, Vlachopoulos C, *et al*. Unfavourable effect of smoking on elastic properties of the human aorta. *Circ* 1997;95:31-38.

Correspondence to: Professor John Feely,
Tel:353-1-6081563; Fax:353-1-4539033
Email:jfeely@tcd.ie

Assessment and management of transient ischaemic attack - the role of the TIA clinic

ABSTRACT

Background As the risk of early stroke following transient ischaemic attack (TIA) is increasingly recognised, the management of patients presenting with symptoms suggestive of TIA presents a clinical challenge.

Methods Analysis of prospectively collected data on patients referred to a TIA clinic in St. Vincent's University Hospital, between January 2003 and July 2004.

Results One-hundred-and-seventeen (117) patients (mean age 75.5 years) were assessed. The majority (79%) were referred from Accident and Emergency and 61% were seen within one week of referral. Seventy-two patients (62%) had a final diagnosis of cerebrovascular disease (56 TIA, 16 completed strokes), of whom five (7%) and four (5.5%) had severe (>70%) and moderate (>50%) symptomatic carotid artery stenosis, respectively, whilst seven patients (10%) had newly diagnosed atrial fibrillation, five of whom were anticoagulated. Non-cerebrovascular diagnoses were made in twenty-seven patients (24%).

Conclusion A TIA clinic, in co-ordination with Accident & Emergency Services, provides a safe and efficient alternative to hospital admission for patients with TIA symptoms and a low early stroke risk.

C Fallon, I Noone, J Ryan, D O'Shea, R O'Laoide, M Crowe

Dept of Geriatric Medicine, St. Vincent's University Hospital, Elm Park, Dublin 4

INTRODUCTION

Recent studies have shown that the risk of stroke following transient ischaemic attack (TIA) is 8-12% at seven days and 11-15% at one month.[1] These risks are higher than previously quoted and emphasise the need for rapid assessment with institution of preventive treatment, particularly for carotid stenosis and atrial fibrillation. The Royal College of Physicians National Guidelines on Stroke, recommend that patients with TIA or minor stroke be assessed and investigated in a specialised neurovascular clinic within seven days.[2] An additional role of a neurovascular clinic is the identification of patients with non-cerebrovascular causes for their symptoms, such as syncope, arrhythmias, epilepsy or primary eye disorders, which may require specific treatment. Despite the emphasis on out-patient assessment for stroke and TIA, there is a paucity of information on the efficacy of such a facility.[3,4] In January 2003 a dedicated once weekly TIA clinic was established in the Medicine for the Elderly Day Hospital at St. Vincent's University Hospital, with the co-operation of the Department of Radiology, Vascular Surgery, Neurology and Ophthalmology. Here we report on the activity of the first 18 months.

OPERATIONAL POLICY

Patients over 65 years of age, presenting to the Accident and Emergency (A & E) Department, with symptoms suggestive of a TIA, were referred to the clinic using a specific referral form. It was emphasised that the indications for referral were acute onset of focal neurological symptoms, lasting less than 24 hours. Non-focal symptoms such as dizziness or syncope, on their own, were not TIAs. Furthermore the patient should be 65 years or over and deemed not to need acute hospital admission. Referrals were co-ordinated by the Stroke Nurse Specialist (SNS) and appointments scheduled for the next available clinic. Investigations (radiological and blood) were performed prior to clinical assessment, to ensure that results would be available at time of consultation, in order to facilitate a single visit where possible. The investigations carried out were CT brain scan, carotid doppler ultrasound, ECG, full blood count (FBC), urea, creatinine and electrolytes (U & E), fasting lipids, glucose and erythrocyte sedimentation rate (ESR). CT brain scans were requested unless carried out in A & E. Patients were contacted by telephone on the day preceding clinic attendance by the SNS and appointments for phlebotomy and radiological procedures outlined in detail. The patients attended the day hospital at 8.30am on the appointed morning

and were directed to the appropriate venue for investigation. They subsequently returned to the day hospital where clinical assessment was carried out and lunch was provided. The results of all investigations were made available for the consensus multidisciplinary conference at 2pm on the day of assessment, where the diagnosis was reviewed and management plans instituted.

METHODS

The following information was gathered prospectively on all patients on an agreed proforma; demographic details, referring source, summary of symptoms, past medical history with pre-existing risk factors, smoking, alcohol, current medications, social situation, neurological assessment, results of investigations, classification of the event, drug therapy and other risk factor advice given, and referrals to other services. Patients diagnosed with TIA or completed stroke were classified as cerebrovascular disease. Analysis of this prospectively gathered information forms the basis of this study.

RESULTS

There were 117 new patients seen at the clinic. (Table 1) The mean age was 75.5 years, 71 (61%) were female and 71 (61%) were seen within one week of referral to the clinic. The majority (79%) of patients were referred from the Accident & Emergency Department. Of the 117 referrals to the clinic, 72 (62%) had a final diagnosis of cerebrovascular disease (TIA, completed stroke). The remaining 44 patients had a variety of other primary diagnoses (Table 2).

CT brain scan was performed on 115 patients (98%), with one patient having an MRI brain scan. Non-vascular abnormalities (subdural haematoma 1, cerebral metastases 1) were found in two patients. Carotid Doppler ultrasound studies were carried out on 116 patients (99%).

Sixty-two patients (53%) were seen and completely assessed on one visit to the neurovascular clinic. Five patients were admitted to the acute general hospital for investigations. Fifty-two patients (44%) were recalled for review of requested investigations, whilst 42 patients (35%) were referred to other services, notably ophthalmology, vascular surgery, cardiology, neurology and endocrinology (Table 1).

CVA/TIA GROUP

Of the 117 patients referred to the clinic, 72 (62%) had a final diagnosis of cerebrovascular disease (56 TIA, 16 completed stroke) (Table 2). Pre-existing modifiable risk factors included hypertension (38 patients), diabetes mellitus (11), hypercholesterolaemia (21), cigarette smoking (20) and atrial fibrillation (9), of whom only three had been anticoagulated. There were 60 patients on anti-platelet therapy, which in most cases had been commenced in A & E. Following assessment (Table 3) new diagnoses included hypertension (7), diabetes mellitus (2), hypercholesterolaemia (28). Of seven patients with newly diagnosed atrial fibrillation, five were anticoagulated, one patient refused warfarin, whilst in one case anticoagulation was deferred pending carotid artery surgery. New treatment, consisting of hypotensive therapy (13), aspirin (7), dipyridamole (26), clopidogrel (3), statin therapy (32) and oral hypoglycaemics (2) was commenced. Duplex carotid studies were carried out in 116 patients (Table 4). Of the 72 patients with TIA/stroke, nine (12.5%) had symptomatic carotid artery stenosis (>50%). In five patients (7%) the degree of stenosis was greater than 70%, whilst two patients had a completely occluded carotid artery, corresponding to their symptomatic hemisphere. Of the patients in the non-TIA/CVA group, two had severe carotid stenosis (asymptomatic carotid artery stenosis).

DISCUSSION

Our experience suggests that a TIA service is an effective method of assessing patients with a suspected TIA or minor stroke. Over 55% of our patients were comprehensively investigated and assessed at one visit, whilst over 60% of patients were seen within one week of referral.

In our series, 62% had a final diagnosis of cerebrovascular disease, of whom 7% had symptomatic severe carotid stenosis and 10% were diagnosed with new onset atrial fibrillation, the majority of whom were anticoagulated. In two previous studies[3,4] of patients referred to a neurovascular clinic 61.5% and 50% were found to have cerebrovascular disease, respectively. Of these 16% and 12% respectively had severe carotid stenosis. The lower incidence of severe symptomatic carotid artery disease in our study may reflect hospital admission of patients with more severe transient ischaemic attack or minor stroke via Accident & Emergency, who have a higher seven-day risk of stroke[10] and may have more severe carotid artery stenosis. A further four and two patients had moderate symptomatic and severe asymptomatic carotid stenosis, respectively, in whom carotid

Table 1
CHARACTERISTICS OF PATIENTS, SOURCE OF REFERRAL TO CLINIC AND TO OTHER SPECIALITIES

MEAN AGE (YRS)	75.5	(RANGE 61 – 93)
Age profiles	(n = 117)	%
≤ 65	14	12
66 – 70	29	25
71 – 80	37	32.4
81 – 90	32	27.3
≥ 90	5	4.4
Male: Female	46.71	39.61
Source of referral		
A/E	92	79
GP	17	14
Consultant	8	7
Delay to clinic visit		
< 7 Days	71	61
> 7 Days	46	39
Referral to specialities		
Ophthalmology	12	10.2
Vascular surgery	13	11
Cardiology	9	7.6
Neurology	3	2.5
Endocrinology	5	4.2

Table 2
FINAL DIAGNOSIS

	N=117	%
TIA	56	48
Completed stroke	16	14
Arrhythmia/ Syncope	12	10
Headache / Migraine	2	1.7
Seizure	3	2.5
Transient global amnesia	3	2.5
Temporal arteritis	1	0.8
Parkinsonism	1	0.8
Cerebral metastases	1	0.8
Mononeuropathy	1	0.8
Vertigo	1	0.8
Hypoglycaemia	1	0.8
Benzodiazepines	1	0.8
Uncertain	18	15.3

Table 3
CEREBROVASCULAR RISK FACTORS AND SECONDARY PREVENTION MEDICATION IN TIA / CVA GROUP (N =72)

	PRIOR	NEW
Hypertension	38	7
Atrial Fibrillation	9	7
Diabetes Mellitus	11	2
Hypercholesterolaemia	21	28
Ischaemic heart disease	19	3
Cigarette smoking	20	-
Family history	31	-
Prior CVA / TIA	20	-
Antihypertensives	38	13
Antiplatelet agents	60	*7/26/3
Anticoagulant	3	5
Statin	21	32
Oral hypoglycaemic agents	4	2

**Aspirin / dipyridamole / clopidogrel*

Table 4
CAROTID DOPPLER EXAMINATION (N = 116)

% STENOSIS	CVA / TIA (N = 72)	NON CVA / TIA (N= 45)
> 70%	5	2
50 – 70%	4	7
Occluded	2	1
Not done		1

Where patients in the CVA / TIA group had bilateral internal carotid stenosis only the stenosis in the carotid artery ipsilateral to the affected hemisphere was classified.

artery surgery may reduce the risk of further stroke, particularly in men older than 75 years.[5] There is no information about the incidence of new onset atrial fibrillation in either of the above studies, but patients with atrial fibrillation, associated with symptomatic cerebrovascular disease, are a high risk group in whom appropriate anticoagulant therapy reduces the risk of further stroke by 66%.[6]

The clinic was also valuable in identifying new, potentially treatable, risk factors, including hypertension, hypercholesterolaemia, diabetes mellitus and ensuring all patients were on optimal antiplatelet therapy. An additional feature of our service was the presence of a stroke nurse

specialist, to discuss the diagnosis, relative benefits of therapeutic interventions and lifestyle changes, including diet, exercise, smoking cessation and driving, with patients and their relatives.

A neurovascular clinic has an important diagnostic role as significant numbers of patients with a label of "TIA" may have alternative conditions, requiring specific treatment. In our experience the most common alternative diagnoses were syncope/ arrhythmias, migraine, seizures, transient global amnesia, with single cases of biopsy proven temporal arteritis, Parkinson's disease, subdural haemorrhage and cerebral metastases being recorded. Many of these patients required referral to other specialities and the development of the TIA service, with the co-operation of ophthalmology, neurology, vascular surgery and cardiology, facilitated prompt access to the relevant specialty.

Recent evidence[10] suggests that patients with TIA symptoms, such as prolonged motor weakness, suggesting a high early stroke risk, require immediate in-patient assessment. For TIA patients with a low early risk of stroke, a rapid access TIA clinic provides a safe and efficient alternative to hospital admission.

REFERENCES

1. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services *BMJ* 2004;328:326 – 328.
2. National Clinical Guidelines for Stroke, 2nd Edition, 2004. London: Royal College of Physicians. www.rcplondon.ac.uk
3. Blight, A., Pereira, AC. And Brown MM A single consultation cerebrovascular disease clinic is cost effective in the management of transient ischaemic attack and minor stroke. *J R Coll Physicians* Lond 2000;34:452-5
4. Karunaratne PM, Norris CA, Syme PD. Analysis of six months' referrals to a "one-stop" neurovascular clinic in a district general hospital: implications for purchasers of a stroke service. *Health Bull* (Edinb) 1999;57:17-28
5. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM, For the Carotid Endartrectomy Trialists' Collaboration. Effect of endartrectomy for symptomatic carotid stenosis in relation to clinical subgroups and to the timing of surgery. *Lancet* 2004;363:915-924
6. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255-62
7. PROGRESS: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke of transient ischaemic attack. *Lancet* 2001;358:1033-41
8. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo controlled trial. *Lancet* 2002;260:7-22
9. Diener H-C, Bogousslavsky J, Brass LM et al. . Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high risk patients (MATCH): randomised, double blind, and placebo-controlled trial. *Lancet* 2004;364:331-337.
10. Rothwell PM., Giles MF, Flossman NE. et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005; 366: 29-36.

Correspondence to: Dr. Morgan Crowe, St. Vincent's University Hospital, Elm Park, Dublin 4

The pattern of plasma sodium abnormalities in an acute elderly care ward: A cross-sectional study

KA O'Connor, PE Cotter, M Kingston, C Twomey, D O'Mahony

South Munster Geriatric Training Scheme, Dept of Geriatric Medicine, Cork University Hospital, Wilton, Cork

ABSTRACT

Introduction The combination of ageing, illness, and medications can lead to hyponatraemia or hypernatraemia.

Aims To describe the distribution of plasma sodium levels in older patients admitted to hospital.

Methods We carried out a hospital based cross-sectional study examining 1,511 serum sodium concentrations ([Na^+]) among 336 elderly patients and attempted to elucidate the cause(s) of the abnormal serum [Na^+].

Results The study population had a mean age of 81.4. Ninety-two (27.4%) patients had hyponatraemia and seven patients (2.1%) had hypernatraemia during their hospitalisation. The distribution of [Na^+] results was towards the lower end of the normal range. The mortality rate of patients with hyponatraemia was 14.1% and that of patients with normal serum [Na^+] was 8.9%. Six patients with hypernatraemia died in hospital. Lower respiratory tract infection and medication accounted for the majority of cases.

Conclusions Deranged [Na^+] is common among elderly patients admitted to hospital.

INTRODUCTION

Disorders of fluid and electrolyte balance are common in elderly patients, often manifesting as abnormalities in plasma sodium concentrations ([Na^+]). Hyponatraemia is the most important electrolyte disorder in elderly people and can be a complication of a wide variety of diseases.[1] Abnormal sodium balance is associated with significantly higher mortality, patients with hyponatraemia having twice the risk of death compared to those with normal serum [Na^+].[2]

Hyponatraemia is common in elderly in-patients with an incidence of over 11% in one series.[3] This incidence rate is significantly higher than that of the general hospital population of 1.5%.[4] The incidence of hyponatraemia is reported to be even higher among long-term care residents.[5] Age-related impairment of renal sodium conservation and common illnesses in old age leading to the syndrome of inappropriate antidiuretic hormone (SIADH) are the principal causative factors of hyponatraemia in old age.[6]

The aim of this paper is to calculate the prevalence of plasma [Na^+] abnormalities in an unselected series of elderly people presenting with acute illness to an acute elderly care unit. We also sought to identify the associated illnesses and potentially causative medication in those elderly patients admitted with deranged plasma [Na^+].

METHODS

STUDY DESIGN

This was a descriptive cross-sectional study to calculate the period prevalence of sodium abnormalities in an elderly hospitalised population. The study was carried out in a busy urban teaching hospital, focusing on patients ≥65 years admitted with acute illness to the acute elderly care ward during the four months from January to April inclusive.

STUDY PARTICIPANTS

All patients were aged 65 years and over. We studied all patients admitted in a four-month period to an acute geriatric unit with a variety of medical conditions. Patients were admitted acutely from the emergency department or by direct referral to the ward by the general practitioner.

DATA COLLECTION

Patients included in the study were identified from the hospital's computerised record of admissions.

Patients' plasma [Na^+] results were obtained from the hospital's biochemistry results database. All the plasma [Na^+] results for each subject were obtained by searching the database under both the patient's name and hospital reference number. For the purposes of this study, we used the hospital's biochemistry laboratory's reference range of normal values. This defined hyponatraemia as a plasma [Na^+] less than 132mmol/l and hypernatraemia as a plasma [Na^+] greater than 145mmol/l.

The conditions associated with abnormal sodium results were investigated retrospectively by examining the in-patient notes of all patients with an abnormal plasma [Na^+]. The casenotes were obtained in all cases. A standardised review of the casenotes was undertaken. This included the diagnoses made on admission, all medication used prior to admission, the need for fluid resuscitation and a review of the discharge summaries. Where there was more than one possible cause for the plasma [Na^+] derangement, the investigators came to a consensus on the most significant contributing factor. The in-hospital mortality rate for the entire group and for the hyponatraemic and hypernatraemic subgroups were obtained from routine hospital data records.

RESULTS

The study population was typical of an elderly care ward, with a mean age of 81.4 ± 7.1 years. During the four-month period, there were 336 patients admitted to the ward with acute illness. Each patient had at least one measurement of plasma [Na^+] during their admission. Among the 336 patients, there were a total of 1,511 plasma [Na^+] measurements. The median number of plasma [Na^+] measurements per patient was three, but this ranged from one to twenty-six tests.

Of the 336 patients admitted, 77 (22.9%) had a sodium less than 132mmol/l on admission. There was a wide range of sodium values from 115 – 170 mmol/l. A further 15 patients (4.5%) developed hyponatraemia in hospital. This gave a total of 92 patients (27.4%) who manifested hyponatraemia at some stage during their hospital admission. Nineteen patients (5.7%) had a plasma [Na^+] less than 125mmol/l ie moderate or severe hyponatraemia. Seven patients (2.1%) had a plasma [Na^+] of greater than 145mmol/l ie hypernatraemia, during admission. Of this group, only one developed the abnormality in hospital.

The distribution of plasma [Na^+] on admission has its central tendency towards the lower end of the normal range of [Na^+] for the population (Figure 1). The mean value of plasma [Na^+] for the whole patient population was 134.4mmol/l with the median being 134mmol/l. The distribution has a positive skewness, with an extended right-hand tail in the plasma [Na^+] distribution curve. Both extremes of the plasma [Na^+] distribution were associated with increased mortality. All but one of the patients with hypernatraemia died in hospital. The mortality rate for the hyponatraemic group was 14.1% (13 deaths from 92 patients). This compared with a mortality rate of 8.9% among those patients with no abnormality in plasma [Na^+]. The differences between these groups did not reach statistical significance.

Lower respiratory tract infections (40.2%) and adverse medication (21.7%) accounted for the majority of cases of hyponatraemia in this group of patients (Table 1). Thiazide diuretics, selective serotonin reuptake inhibitor antidepressants (SSRIs) and carbamazepine were the medications most commonly implicated in causing hyponatraemia. Only three patients (3.3%) did not have a recognised cause for hyponatraemia after reviewing the cases. All, but one of the seven patients presenting with hypernatraemia had a known diagnosis of dementia. Two of these patients had diarrhoeal illnesses. Four patients were nursing home residents with significant functional impairment. The other patient had a large middle cerebral artery territory infarct with major dysphagia.

DISCUSSION

One third of these consecutive acutely ill patients admitted to hospital had a derangement of plasma [Na^+] at some stage during their hospitalisation. Hyponatraemia occurred in 27.4% of cases and hypernatraemia in 2.1%. These rates were higher than those reported in previous work, probably reflecting the older mean age of our patient cohort. Most of the abnormalities were present on admission.[2,3] Overall, the distribution of plasma [Na^+] for this population is to the left of the distribution in the general population, with a mean value at the hyponatraemic end of the normal range. Both high and low plasma [Na^+] during the hospital stay was associated with tendency to increased hospital mortality, compared to the mortality rate in those patients with normal plasma [Na^+].

The normal regulation of water and sodium balance involves the interplay of many homeostatic

mechanisms, including thirst perception, the actions of antidiuretic hormone, atrial natriuretic hormone and aldosterone. The normal ageing process is associated with significant changes in some of these homeostatic mechanisms.[6,7] Previous studies have shown that thirst perception is impaired in healthy older compared to healthy younger individuals.[8,9] In particular, elderly patients with dementia fail to drink adequately when exposed to water deprivation.[10] This is in keeping with the high proportion of dementia sufferers in our hypernatraemic group. Evidence suggests that the ageing kidney is more prone to sodium loss.[11] The impaired diluting capacity of the ageing kidney coupled with an enhanced antidiuretic response in old age, make older individuals more prone to hyponatraemia.[12,13] This may, in part, explain why our distribution curve for plasma [Na^+] was centred at the lower end of the normal reference range.

Both hyponatraemia and hypernatraemia are markers of underlying disease and are associated with a poorer prognosis.[2,14,15] Previous studies also confirm our results which suggest an increased mortality with hypernatraemia and hyponatraemia.[2,14] However, our study was not designed to demonstrate increased mortality in these groups, and consequently was not sufficiently powered to do so.

Our cross-sectional study design provides reliable and important information on the distribution of plasma [Na^+] in this elderly group. Because all patients had their plasma [Na^+] measured on admission, we provide an accurate reflection of the prevalence of plasma [Na^+] abnormalities on admission to hospital of elderly sick patients. There is little possibility for information bias in these results, as they come from objective data already in existence. However, there may be under-reporting of new cases occurring in hospital since not all patients will have repeated plasma [Na^+] measurement. As with any cross-sectional study there are limitations with investigating the aetiology of plasma [Na^+] abnormalities. The main associations we report with hyponatraemia are related to respiratory tract infections and medication. Pulmonary disease, particularly pneumonia, can lead to a syndrome of inappropriate antidiuretic hormone release, by a mechanism which remains unclear.[16] Elderly patients, in particular, are predisposed to this abnormal antidiuretic hormone response to infection.[13] Numerous drugs prescribed for elderly patients affect water balance. As one would expect, some of our hyponatraemic subjects (13%) were taking thiazide diuretics. Also, SSRIs were implicated as the cause in 6.5% of hyponatraemic cases. The association between SSRIs and hyponatraemia is well known, especially in older patients.[17,18]

In conclusion, we report a high prevalence of sodium abnormalities in hospitalised elderly patients with acute illness. Overall, there is a trend towards low plasma [Na^+] in elderly hospitalised patients, reflecting derangement of regulatory systems involved in sodium and water balance due to acute illness and adverse medications. A smaller but significant proportion of elderly patients present to hospital with hypernatraemia. Awareness of the increased mortality burden of both hyponatraemia and hypernatraemia should alert clinicians to the more serious impact of illness associated

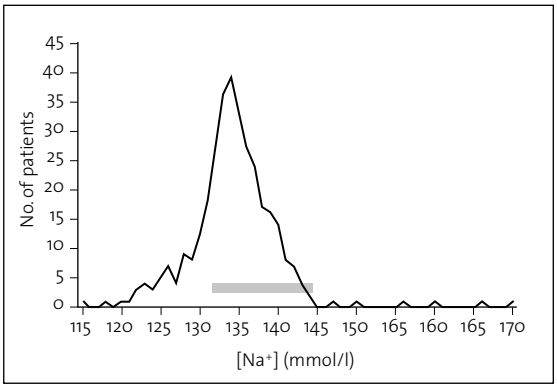


Figure 1 — THE DISTRIBUTION OF ADMISSION PLASMA SODIUM LEVELS IN AN ACUTE ELDERLY CARE UNIT. = NORMAL RANGE OF PLASMA [NA^+]

Table 1
PRIMARY CAUSES FOR HYPONATRAEMIA

DIAGNOSIS	NUMBER (%)
Acute Respiratory Tract infection	37 (40.2%)
Thiazide Diuretic	12 (13.0%)
Acute Stroke	8 (8.7%)
Heart Failure	7 (7.6%)
SSRI Antidepressant	6 (6.5%)
Bronchial Tumour	6 (6.5%)
Hypothyroidism	5 (5.4%)
Inappropriate fluid resuscitation	4 (4.4%)
Carbemazepine	2 (2.2%)
Advanced Renal Failure	1 (1.1%)
Pseudohyponatraemia-Hyperparaprotinaemia	1 (1.1%)
No Obvious Cause found	3 (3.3%)

with plasma [Na^+] abnormalities in acutely ill elderly patients and to respond to these metabolic derangements with a greater sense of urgency.

REFERENCES

1. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 6th Edition, Churchill Livingstone, pp1113-1114.
2. Terzian, C, Frye, EB, Piotrowski, ZH. Admission hyponatremia in the elderly: Factors influencing prognosis. *J Gen Intern Med* 1994; 9:89.
3. Sunderam SG, Manikar GD: Hyponatraemia in the elderly. *Age Ageing* 1983; 12:77-80.
4. Natkunam A, Shek CC, Swaminathan R Hyponatremia in a hospital population. *J Med*. 1991;22(2):83-96.
5. Miller, M, Morley, JE, Rubenstein, LZ. Hyponatremia in a nursing home population. *J Am Geriatr Soc* 1995; 43:1410-3.
6. Hochman I, Cabili S, Peer G. Hyponatraemia in internal medicine ward patients: causes, treatment and prognosis. *Isr J Med Sci* 1989; 25:73-76.
7. Miller M, Gold GC, Friedlander DA. Physiological changes of aging affecting salt and water balance. *Rev Clin Geront* 1991; 1: 215-230.
8. Phillips, PA, Rolls, BJ, Ledingham, JGG, et al. Reduced thirst after water deprivation in healthy elderly men. *N Engl J Med* 1984; 311:753.
9. Dyke, MM, Davis KM, Clark BA, et al. Effects of hypertonicity on water intake in the elderly: An age-related failure. *Geriatr Nephrol Urol* 1997; 7:11.
10. Albert SG, Nakra BRS, Grossberg GT, Cmainal ER. Drinking behaviour and vasopressin responses to hyperosmolality in Alzheimer's disease. *Int Psychogeriatr* 1994; 6: 78-86.
11. Owen JA, Campbell DG. A comparison of plasma electrolyte and urea levels in healthy persons and in hospital patients. *Clin Chem Acta* 1968; 22: 611-618.
12. Crowe MJ, Forsling ML, Rolls BJ, Philips PA, Ledingham JG, Smith RF. Altered water excretion in healthy elderly men. *Age Aging* 1987; 16: 285-293.
13. Asplind, R, Aberg, H. Diurnal variations in the levels of antidiuretic hormone in the elderly. *J Intern Med* 1991; 229:131-4.
14. Snyder, NA, Feigal, DW, Arieff, AI. Hypernatremia in elderly patients. *Ann Intern Med* 1987; 107:309.
15. Kleinfeld M, Casimar M, Borra S: Hyponatraemia as observed in a chronic disease facility. *J Am Geriatr Soc* 1979; 27(4):155-160.
16. Anderson RJ. Hospital-associated hyponatraemia. *Kidney Int* 1986; 29: 1237-47.
17. Liu BA, Mittmann N, Knowles SR, Shear NH. Hyponatraemia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. *Can Med Assoc J* 1996; 155: 519-527.
18. Sharma H, Pompei P. Antidepressant-induced hyponatraemia in the aged. Avoidance and management strategies. *Drugs Aging* 1996; 8:430-435.

Correspondence to: Dr. Paul E Cotter
Unit 4, Merlin Park Regional Hospital, Galway.
Tel 091 775562. Email pecotter@eircom.net;
Denis O' Mahony, Dept of Geriatric Medicine, Cork University Hospital, Wilton, Cork, Tel: 00 353 21 4922396.
Fax: 00 353 21 4922829. Email: omahonyd@shb.ie

Regional variation in prescribing for chronic conditions among an elderly population using a pharmacy claims database

C Naughton, K Bennett, J Feely

Dept Pharmacology & Therapeutics, Trinity College Dublin, Trinity Centre for Health Science, St James's Hospital, Dublin

ABSTRACT

Background Age, gender and geographical regions are recognised factors in inequalities in prescribing for chronic diseases in the elderly.

Aim To compare the health board regional distribution of chronic disease among the elderly and to examine variation in quality prescribing across age, gender and regions.

Methods Population based study of prescribing for chronic disease using a national pharmacy claims database. All individuals aged 70 years and over (n=271,518) were eligible.

Results Over 60% of the elderly in all regions received cardiovascular related medication. The South Eastern, North Western and Western Health Boards had below average prescribing for many chronic conditions. Logistic regression identified age, gender and regional variations in prescribing of preventative therapies for CVD and diabetes.

Conclusion There is a high prevalence of prescribing for chronic conditions in the elderly in Ireland, and there is evidence of gender, age and residing health board inequalities in prescribing.

INTRODUCTION

Ireland, similar to other Western countries, has an increasing ageing population. Those aged 70 years and older account for 8% of the national population.[1] This trend is set to continue with an increase in life expectancy observed in both men and women. There is an associated increase in the number of years spent with a disability, and it is estimated that women live four and men two extra years with a disability.[2] About 80% of those aged 65 years and over suffer from a chronic condition,[3] and both the prevalence of chronic conditions and co-morbidities increases with age. In one study over 87% of community dwelling 75-year-olds received prescription drugs,[4] and in a Swedish study the biggest rise in drug use over a 15-year period was among those aged 80 years and over, followed by those aged 60-79 years.[5]

Previous studies have identified inequalities in the management of chronic conditions such as diabetes and cardiovascular disease with associated risk factors including increasing age, female gender and deprivation.[6-10]

There are very few national or international studies that have attempted to quantify and examine the distribution of chronic disease or explore regional variation in prescribing for chronic conditions among a national elderly population. The most recent estimate of prevalence of chronic conditions in an elderly population was provided by the first Health and Social Service for Older People survey (HeSSOP I) in 2000[11]. This was a random sample of community dwelling people aged 65 years or older living in either the Eastern or Western health boards. People surveyed were asked to identify from a written list which chronic conditions they experienced. This was the largest survey of elderly people in Ireland but only a single question focused on types of chronic illness. Similar to other surveys there are limitations, with those who experience ill health less likely to participate in surveys, also relying on self reported illness is likely to underestimate chronic conditions[12]. In addition only two health boards were sampled and people in nursing homes were excluded.

The potential for national claims prescribing databases to explore such topics is increasingly being recognised.[5;13;14] Data are continuously collected, are often population based and usually contain individual patient level data. The primary limitation is lack of direct diagnosis data, therefore combinations of drug therapies are used as surrogate markers of disease e.g. insulin and diabetes.[15]

The aim of this study is to compare the regional distribution of chronic disease among those aged 70 years and older and to examine variation in quality prescribing across age, gender and regions.

SETTING

The Irish HSE-Primary care reimbursement services (HSE–PCRS) pharmacy database was used. The HSE-PCRS provides free health services, including provision of medicines, without charge to 1.2 million people in Ireland. Since July 2001 it incorporates all those aged 70 years and over. In 2004 there was an estimated 316,928 people aged 70 years and older with HSE-PCRS medical cards; one survey suggests over 95% uptake of the scheme.[16] The HSE-PCRS prescription database records the unique patient identifying number, basic demographic information (age, sex and region residing), and full details of all items dispensed by community pharmacists for people within the scheme. The information is centrally held and coded using the WHO Anatomical Therapeutic Chemical (ATC) classification system.[17] The primary limitation of the prescribing database is the lack of information on diagnosis, thus combinations of drug therapies must be used as surrogate markers of disease. The majority of drugs available in Ireland are eligible for reimbursement under this scheme, with the exception of drugs provided under the 'High Tech medicines scheme' such as some anti-neoplastic, anti-rejection drugs or growth hormones.

Ireland is divided into eight healthcare regions. The largest is the Eastern Regional Health Authority (ERHA) with over 1.4 million people, followed by the Southern (SHB) and South-Eastern (SEHB) with 0.42-0.58 million, the Western (WHB), North-Eastern(NEHB) and Mid Western(MWHB) have over 0.3 million people each and the two smallest Midland (MHB) and North-Western (NWHB) each have over 0.22 million people.[18] The health board the patient is resident in is identified through the unique patient identification number, with each number being specific to the health board in which the number was issued. If a patient avails of healthcare in a different health board they will still be considered according to their health board of residence.

DISEASE IDENTIFICATION

A framework for identifying conditions from the pharmacy database was developed from the chronic disease classification reported by Von Korff et al, and Maio et al and adapted to an Irish healthcare system.[14;15] Nine conditions were identified using the associated drug ATC codes, as indicated in Table 1. Cancer prevalence was estimated using both PCRS and High Tech data, but pharmacy databases underestimate cancer prevalence as over 70% of cancers do not receive drug therapy. More complete information on regional distribution of cancer can be obtained from the national cancer registry.[19] In conditions with overlapping drug therapy only broad disease classification is possible e.g. CVD includes ischaemic conditions such as ischaemic heart disease (IHD), cerebrovascular and peripheral vascular disease (PVD), also heart failure and hypertension. In addition to insulin and oral hypoglycaemic agents, diabetic test kits were included in an attempt to identify those patients managed by diet only, but this is not likely to identify all such patients.

Quality prescribing indicators were used to compare patterns of prescribing across regions. The indicators selected were: (1) a high level of co-prescribing of statins with antiplatelet therapy +/- coronary vasodilators (markers for ischemic cardiovascular conditions), (2) a high level of antiplatelet prescribing in patients receiving coronary vasodilators (marker for IHD) (3) a high level of prescribing of antiplatelet therapy and statins in patients with diabetes,[20] (4) a low level of long acting benzodiazepine prescribing in the elderly (flurazepam, chlordiazaxide and diazepam) and (5) low prescribing of antidepressants with strong anticholinergic and sedation properties (amitripyline, doxepin and imipramine).[21]

The PCRS prescribing database for 2004 covering the eight health boards was used. The individual drug or drug class was identified in the database using their ATC codes. The study population was defined as all individuals aged 70 years and over who were dispensed three or more items associated with a specific chronic condition during the 12-month period. This restriction reduced identification of prescribing associated with misdiagnosis or incidental users.

STATISTICAL ANALYSIS

Simple chronic disease prevalence rates were calculated for the elderly population based on the total number of eligible patients aged 70 years and over with a medical card in each region.[22]

Age and sex standardised prescribing ratios (SPR) were calculated for each region. The SPR is similar to the standardised mortality ratio, where a high

Table 1
COMBINATIONS OF DRUGS USED AS SURROGATE MARKERS OF DISEASE

DISEASE GROUP	SPECIFIC CONDITIONS	ASSOCIATED MEDICATION	WHO ATC CODES
Cardiovascular disease (CVD)	Ischemic Heart disease (IHD), Cerebrovascular disease, Peripheral vascular disease (PVD)	Antianginals e.g. Nitrates Platelet inhibitors	C01DA & C01DA B01AC
	Arrhythmic	Anti- arrhythmic warfarin	C01AA05 & C01B B01AA03
	Hypertension/Heart failure	Antihypertensives Diuretic ACE/AIIA inhibitors Beta blockers Calcium channel blockers	C02 C03 C09 C07 C08
	Hypercholesteraemia	Anti-lipids including statins	C10
Central nervous system (CNS)	Parkinson's disease	L-dopa	N04
	Epilepsy	Anticonvulsants	N03
	Depression psychosis	Psycholeptics	N05A & N06A
	Anxiety	Anxiolytics	N05B
	Sleep disturbance/Sedation	Hypnotics/sedatives	N05C
	Dementia	Antidementia	N06D
Musculo-skeletal	Rheumatoid Arthritis	Anti-inflammatory Anti-rheumatoid	M01A M01C
	Osteoporosis/Pagets disease	Mineral substitutes & Vit D analogues	M05 A11CC
	Gout		M04
Upper Gastro-intestinal (GI)		Antiacids/ anti-ulcer	A02A & A02B
Respiratory	COPD/Asthma	iIpratropium Beta-adrenergic Glucocorticoids	R03BB R03A & R03C R03BA
Diabetes		Insulin Oral hypoglycaemics Diabetic test kits	A10A A10B V04CA
Thyroid			H03
Glaucoma		Ophthalmic miotics	S01E
Cancer		Anti-neoplastics Immunostimulants	L01 & L02 L03

SPR (>100) indicates that prescribing for a particular condition in that region is above the national average. The SPR ratio is the ratio of maximum to minimum prescribing in each category.[23] Logistic regression was used to explore the association between each of the five quality prescribing indicators and the study population age, gender and regional prescribing patterns. Odds ratios and 95% confidence intervals are presented. The availability of specialist consultant services per 100,000 population were calculated based on the number of specialists employed in each HB in 2004,[18] and the associated HB total population size. All analysis was performed using SAS (v 9.1 SAS institute, Cary,NC).

RESULTS

In this population 86% (271,518) of those over 70 years received a minimum of three drug items for a chronic condition in 2004, and a further 8% received less than three items. Males accounted

Table 2
PREVALENCE OF CHRONIC CONDITIONS AMONG ELDERLY POPULATION ACROSS HEALTH BOARD REGIONS

REGION	POP ≥ 70 YEARS	CVD	CNS	MUSCULO-SKELATAL	UPPER GI	RESPIRA-TORY	DIABETES	THYROID	GLAUCOMA	CANCER
	n	%	%	%	%	%	%	%	%	%
ERHA	99,350	73	38	28	27	15	7	8	5	4
MHB	18,810	78	40	32	24	17	9	8	5	5
MWHB	28,271	72	37	30	25	14	8	7	5	4
NEHB	26,687	72	39	28	25	14	9	7	4	4
NWHB	21,636	68	33	24	19	13	7	8	4	4
SEHB	36,301	64	34	25	22	12	8	8	5	3
SHB	49,456	76	38	30	23	14	7	7	6	4
WHB	36,417	70	37	30	20	14	7	7	4	5

Table 3
VARIATION IN PREVALENCE OF CHRONIC CONDITIONS ACROSS REGIONS STANDARDISED FOR AGE AND SEX (SPRs)

REGION	CVD	CNS	MUSCULO-SKELETAL	UPPER GI	RESPIRATORY	DIABETES	THYROID	GLAUCOMA	CANCER
ERHA	101.7	100.6	98.1	111.8	104.8	97.7	103.0	107.3	111.4
MHB	108.2	108.2	113.5	99.6	118.5	120.5	106.7	104.9	101.8
MWHB	100.4	101.2	105.8	103.8	102.1	106.2	95.3	96.9	83.9
NEHB	99.8	105.0	99.0	104.1	102.0	111.1	96.8	90.2	99.4
NWHB	94.4	90.8	86.4	77.7	90.6	91.8	106.9	73.6	87.9
SEHB	89.4	91.9	89.1	93.5	87.9	101.9	104.4	111.4	87.8
SHB	105.6	102.9	106.1	98.5	96.7	93.9	94.6	114.0	93.6
WHB	97.2	99.1	105.3	83.5	96.7	93.7	92.9	73.2	108.3
Ratio*	1.21	1.19	1.31	1.44	1.35	1.31	1.15	1.56	1.33

**Ratio=ratio of maximum to minimum prescribing SPR*

for 41% (136,473) of the total population which dropped to 38% in those aged 75 years or older. There was a significant difference in the gender distribution between the two age groups ($p<0.001$). Not surprisingly the highest concentration of elderly patients was in the most densely populated areas, 32% in the ERHA, 16% in the SHB, 10-11% in the SEHB and WHB, with 6-8% distributed in the MHB, MWHB, NEHB and NWHB.

In Table 2 the most prevalent condition in all regions was cardiovascular disease with over 60% of the elderly population receiving regular cardiovascular medication, followed by CNS with over 30% on regular medication, musculo-skeletal and upper GI prescribing was between 20-30% in most regions. Diabetes, respiratory and thyroid conditions had a prevalence of between 7-17%, while glaucoma and cancer had the lowest prevalence at 2-6%, but cancer is likely to be underestimated in this population.

Table 4
ODDS RATIOS AND 95% CI FOR QUALITY PRESCRIBING INDICATORS IN CVD, DIABETES & CNS

	CARDIOVASCULAR DISEASE				DIABETES		CENTRAL NERVOUS SYSTEM			
	Statins in ischaemic CVD		Antiplatelet with coronary dilators		Antiplatelet & statin		Long acting benzodiazepines		Anticholanergic antidepressants	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
70-74 yrs	2.17	2.12-2.22	1.23	1.16-1.30	1.62	1.53-1.70	1.35	1.28-1.42	1.30	1.23-1.37
Male	1.10	1.08-1.12	1.04	0.98-1.09	1.02	0.97-1.08	1.01	0.96-1.06	0.99	0.94-1.04
ERHA	1.11	1.09-1.14	1.04	0.98-1.09	1.37	1.30-1.45	1.16	1.10-1.21	0.85	0.80-0.89
MHB	1.47	1.41-1.54	0.98	0.88-1.09	1.98	1.79-2.19	0.93	0.84-1.02	1.14	1.04-1.25
MWHB	0.82	0.79-0.85	0.83	0.76-0.91	0.72	0.66-0.79	1.27	1.18-1.37	0.71	0.64-0.78
NEHB	0.81	0.78-0.84	0.81	0.74-0.89	0.72	0.66-0.79	1.16	1.07-1.25	0.91	0.83-1.0
NWHB	0.86	0.83-0.90	1.08	0.98-1.20	0.73	0.66-0.82	0.69	0.62-0.77	1.15	1.04-1.27
SEHB	1.12	1.07-1.16	1.06	0.97-1.16	0.95	0.88-1.03	1.01	0.93-1.09	1.13	1.05-1.22
SHB	0.86	0.83-0.88	1.18	1.09-1.27	0.78	0.73-0.84	0.85	0.79-0.91	1.21	1.13-1.29
WHB	1.04	1.00-1.08	0.95	0.87-1.03	0.95	0.88-1.03	0.78	0.72-0.85	1.10	1.03-1.19

1. Ischaemic conditions= patient receiving antiplatelet or coronary artery vasodilators; 2. Coronary vasodilators e.g. nitrates are used as a surrogate marker for angina; 3. Reference group = age ≥75 years & female gender; 4. Individual regions are compared to all other regions.

Table 5
CONCENTRATION OF SPECIALISTS CONSULTANTS PER HB RATES PER100,000 TOTAL HEALTH BOARD POPULATION

HB	TOTAL HB POPULATION	GERIATRICIAN		CARDIOLOGIST		ENDOCRINE/ DIABETIC		ADULT PSYCHIATRY		PSYCHIATRY OF OLD AGE	
	n	n	rate	n	rate	n	rate	n	rate	n	rate
ERHA	1,401,314	19	1.4	25	1.8	15	1.1	62	4.4	5	0.4
MHB	225,588	2	0.9	3	1.3	0	0.0	9	4.0	2	0.9
MWHB	339,930	4	1.2	2	0.6	2	0.6	14	4.1	2	0.6
NEHB	344,926	5	1.4	2	0.6	2	0.6	12	3.5	3	0.9
NWHB	221,376	5	2.3	2	0.9	0	0.0	11	5.0	2	0.9
SEHB	423,540	8	1.9	3	0.7	3	0.7	16	3.8	4	0.9
SHB	580,605	8	1.4	7	1.2	4	0.7	25	4.3	1	0.2
WHB	380,057	6	1.6	4	1.1	5	1.3	18	4.7	2	0.5

Prescribing for CVD, CNS, and thyroid conditions showed the least variation between regions (see Table 3). Musculo-skeletal, GI, respiratory, diabetes and cancer showed over a 30% variation between the region with the lowest and highest prescribing. Glaucoma had over a 50% variation but this may be exaggerated due to small patient numbers. There were persistent trends across the health boards with the ERHA, MHB, NEHB, and MWHB having similar or above average prescribing for the majority of conditions examined, while the NWHB, SEHB and WHB had below average prescribing for many of the conditions.

Table 4 shows the performance based on the quality prescribing indicators for CVD, diabetes and CNS across the regions adjusting for the effects of age and gender. In ischaemic CVD and diabetes those aged 70-74 years were more likely to receive a statin compared to those aged 75 years and older. Also statin and antiplatelet prescribing tended to be higher in males but this did not always reach statistical significance. The ERHA, MHB, SEHB and WHB had similar or above average stain prescribing in CVD, and higher co-prescribing of antiplatelet and statin in diabetes. In contrast the NEHB, MWHB,

NWHB and SHB had consistently lower levels of prescribing of these therapies in the elderly population after standardising for different gender and age structures within the regions.

The quality prescribing indicators related to CNS prescribing show that the 70-74 year age group were more likely to receive long acting benzodiazepines or antidepressants with anticholenergic side-effects than those aged 75 years and older, however there were no gender differences. The prescribing of the two drug types appear inversely related. Long acting benzodiazepines were more likely to be prescribed in the ERHA, MWHB, NEHB, while anticholinergic antidepressants were more likely to be prescribed in the MHB, NWHB, SEHB, SHB, and WHB.

Table 5 shows the concentration of specialist consultants per HB. There is little association between number of consultant specialist and the prevalence or pattern of prescribing in chronic conditions, except for CVD. Regions with a higher number of cardiologists per 100,000 population tend to have higher prescribing of cardiovascular medication, these regions also performed better on the CVD and diabetes quality prescribing indicators. Concentration of geriatricians was not proportional to the size of the regional populations. The ERHA had 1.4 geriatricians per 100,000 population which is less than both the NW and SE health boards with smaller elderly populations. There was no obvious trend between psychiatric consultants and prescribing in CNS conditions or in the CNS quality prescribing indicators.

DISCUSSION

This study, based on pharmacy claims data, suggests a high prevalence of chronic conditions among the elderly population. In each of the health boards over 60% of those aged 70 years and older were prescribed regular cardiovascular medication. There was also a significant number receiving treatment for CNS, musculo-skeletal and gastrointestinal conditions. The other conditions had a lower prevalence but added to the burden of chronic disease among this population. The SPRs indicate that there is a 20%-40% variation in the treatment of the most common conditions between the regions. Quality prescribing indicators provide more detailed insight into these regional differences. Those aged 70-74 years are more likely to receive CVD and diabetic preventative therapy than those aged 75 years and over while elderly men with CVD are more likely than elderly women to receive statin therapy, but this gender differences is not statistically different in other conditions.

Direct comparison of disease prevalence with the HeSSOP I study is difficult because of the variation in the disease definitions used; also the population in the current study is older and includes people in nursing homes. However for many conditions there is broad agreement. In HeSSOP I, CVD was identified by 56% of the population compared to 60-70% in our study and the reported prevalence in HeSSOP I of CNS conditions (47%) respiratory (14%) and diabetes (6%) were similar to that identified in our study. The widest discrepancy was seen in musculo-skeletal conditions, in HeSSOP I this was reported by 46% of the population compared to 20-30 % in our study. In addition upper GI conditions in HeSSOP I was confined to peptic ulcers which was reported by 6% of the population.[11]

The current study has identified variation in prescribing practices across the regions which can be explored using robust prescribing indicators. Current European CVD guidelines and clinical trials recommend statin therapy in all patients with established cardiovascular disease and diabetes, regardless of age and gender.[20, 24, 25] This study suggests that statins are under prescribed in those aged 75 years and over, females and in some regions. The MWHB, NEHB, NWHB, SHB had 15-30% less prescribing of preventative therapies for patients with ischaemic CVD or diabetes compared to the rest of the country. Age and sex differences in CVD prescribing have been reported elsewhere,[26, 27] but there are few studies looking at regional variation. This study is similar to others which found that prescribing for chronic conditions is not uniform within countries with the same healthcare systems.[28-30]

We find evidence of wide disparities in prescribing for chronic conditions between the regions after adjusting for the age and gender differences in the regional populations. The reasons are likely to be mutifactorial but possible explanations are genuine differences in the health status of individuals within regions, or a more compelling factor may be the level of primary, secondary and specialist healthcare provision within the regions. Cardiovascular disease has only a 20% variation in prevalence across the eight regions, but CVD quality prescribing indicators show that patients in some regions are 10-20% less likely to receive a statin than others. Disparity is also apparent in prescribing secondary preventative therapies

in diabetes. Elderly patients with diabetes in the midlands region, which participated in the 'Diabetic Shared Care Scheme', are nearly twice as likely to receive antiplatelet and statin therapy compared to other regions especially MWHB, NEHB and SHB.

The NWHB had the lowest prevalence for nearly all the conditions investigated and the lowest performance in the quality prescribing indicators. This region is also recognised as having the lowest concentration of healthcare service provision. In contrast, the Eastern region has the highest concentration of acute hospital and specialist services. In our analysis the ERHA had above average drug treatment for all the conditions investigated including higher prescribing of preventative therapies in CVD and diabetes and low use of antidepressants with anticholinergic side-effects. There is a broad association between number of cardiologists employed in the health boards and both the identification of and quality prescribing indicators in CVD. Regions with the highest concentration of cardiologists (ERHA and MHB) had higher levels of statin prescribing in both patients with CVD and diabetes than regions with less than one cardiologist per 100,000 population (NWHB, NEHB and MWHB). Prescribing in the SEHB and MHB may be influenced by proximity to the ERHA and perhaps easier referral to cardiologists.

Concentration of specialist services is one possible factor in explaining regional variation but others are control of drug budgets, individual health board priorities, patient access to services, patient education and socioeconomic status. More specific research is required to fully explain the observed variations and to determine whether this applies across all age groups.

STUDY LIMITATIONS

Using a pharmacy database to estimate prevalence is a new methodological approach and needs to be further validated against Irish survey data ideally with clinical evidence of diagnosis. Validation against such data would allow for identification of under or overestimation of prevalence of a condition. In this database a condition which is not managed with standard medication or for which regular medication is not prescribed e.g. musculo-skeletal disease will be underestimated, while prophylactic use of medication e.g. proton pump inhibitors in GI conditions may overestimate disease prevalence. The database does not contain information on patient socioeconomic status, or whether the original prescription was given by a GP or specialist consultant. Therefore it was not possible to control for these factors in our analysis.

CONCLUSION

There is a lack of primary data estimating disease prevalence in the Irish population. The HSE-PCRS pharmacy claims database can be used to identify disease prevalence and regional variation in those aged 70 years and older. Significant regional variation in the prescribing for chronic diseases, adjusting for population age and gender, was observed. In particular the very elderly, women and those living in more isolated regions such as the north-western and north-eastern areas appear less likely to receive optimal treatment for certain conditions. Current levels of specialist health care provision within these regions may be a factor but more in depth research is required to validate and explain these observations and make recommendations on the appropriate provision of health care in this population.

ACKNOWLEDGEMENTS

We would like to thank the Health Research Board, Ireland for financial support. Also the HSE-PCRS payments board for the data on which this study is based and Prof Hannah McGee for her advice and support.

REFERENCES

1. Central statistics office. Population and migration estimates. www cso ie 2005.
2. EHEMU. Health Expectancy in Ireland. www hs le ac uk/reves/ehemutest 2005.
3. Lamy PP. Prescribing for thr elderly. In: Lamy PP, editor. The health status of the elderly. Littleton Mass: PSG Publicating CO, 1980. 113-117.
4. Barat I, Andreasen F, Damsgaard EM. The consumption of drugs by 75-year-old individuals living in their own homes. *Eur J Clin Pharmacol* 2000; 56(6-7):501-509.
5. Silwer L, Lundborg CS. Patterns of drug use during a 15 year period: data from a Swedish county, 1988--2002. *Pharmacoepidemiol Drug Saf* 2005; 14(11):813-820.
6. Bennett KE, Williams D, Feely J. Inequalities in prescribing of secondary preventative therapies for ischaemic heart disease in Ireland. *Ir Med J* 2002; 95(6):169-172.
7. Bennett KE, Williams D, Feely J. Under-prescribing of cardiovascular therapies for diabetes in primary care. *Eur J Clin Pharmacol* 2003; 58(12):835-841.
8. Dornbrook-Lavender KA, Roth MT, Pieper JA. Secondary Prevention of Coronary Heart Disease in the Elderly. *Ann Pharmacother* 2003; 37(12):1867-1876.

9. Doyle F, De La HD, McGee H, Shelley E, Conroy R. Gender differences in the presentation and management of acute coronary syndromes: a national sample of 1365 admissions. *Eur J Cardiovasc Prev Rehabil* 2005; 12(4):376-379.
10. Williams D, Bennett K, Feely J. Evidence for an age and gender bias in the secondary prevention of ischaemic heart disease in primary care. *Br J Clin Pharmacol* 2003; 55(6):604-608.
11. Garavan R, Winder RMH. Health and Social Services for Older People (HeSSOP). national Council on Ageing and Older People, Dublin 2001; www.ncaop.ie.
12. Adamson J, Lawlor DA, Ebrahim S. Chronic diseases, locomotor activity limitation and social participation in older women: cross sectional survey of British Women's Heart and Health Study. *Age Ageing* 2004; 33(3):293-298.
13. Bjerrum L, Sogaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol* 1998; 54(3):197-202.
14. Maio V, Yuen E, Rabinowitz C et al. Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. *J Health Serv Res Policy* 2005; 10(4):232-238.
15. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992; 45(2):197-203.
16. O'Hanlon A, Mc Gee H, Barker M et al. Health and social service for older people II (HeSSOPII). National Council on Ageing and Older People 2005; 91.
17. WHO. Anatomical therapeutics chemical (ATC) classification index with defined daily doses(DDDs). Geneva 2001.
18. Comhairle na nospideal. Consultant Staffing Jan 2005. www hse ie/comhairle na nospideal 2005.
19. National cancer registry Ireland. Cancer in Ireland 1994-2001. www ncri ie 2005.
20. de Backer G., Ambrosioni E, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). *Atherosclerosis* 2004; 173(2):381-391.
21. American Society of Consultant Pharmacists. Drug Regimen Review Guidelines. www ascp com/public 2003.
22. HSE. GMS(P) B Financial & Statistical analysis of claims and payments 2004. Raven House, Finglas, Dublin 11; 2004.
23. Johnson Z, Hayes C, Dack P. The standardized prescribing ratio--a new method for comparing prescribing between GPs, controlling for patient age and sex. *Pharmacoepidemiol Drug Saf* 1997; 6(5):337-345.
24. DeWilde S, Carey IM, Bremner SA, Richards N, Hilton SR, Cook DG. Evolution of statin prescribing 1994-2001: a case of agism but not of sexism? *Heart* 2003; 89(4):417-421.
25. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360(9346):1623-1630.
26. Bennett KE, Williams D, Feely J. Inequalities in prescribing of secondary preventative therapies for ischaemic heart disease in Ireland. *Ir Med J* 2002; 95(6):169-172.
27. Williams D, Bennett K, Feely J. Evidence for an age and gender bias in the secondary prevention of ischaemic heart disease in primary care. *Br J Clin Pharmacol* 2003; 55(6):604-608.
28. Percudani M, Barbui C, Fortino I, Petrovich L. Antidepressant drug prescribing among elderly subjects: a population-based study. *Int J Geriatr Psychiatry* 2005; 20(2):113-118.
29. Roberts E, Norris P. Regional variation in anti-depressant dispensings in New Zealand: 1993-1997. *N Z Med J* 2001; 114(1125):27-30.
30. Usher C, Bennett K, Feely J. Regional variation in the prescribing for diabetes and use of secondary preventative therapies in Ireland. *Pharmacoepidemiol Drug Saf* 2005; 14(8):537-544.

Correspondence to: C Naughton
email: naughtc@tcd.ie; Tel:01 896 3404 fax 01 453 9033

Pack-size legislation reduces severity of paracetamol overdoses in Ireland

E Donohoe, N Walsh, JA Tracey

National Poisons Information Centre, Beaumont Hospital, Dublin 9

ABSTRACT

Background Legislation was introduced in Ireland in October 2001 to control the sale of paracetamol in non-pharmacy outlets. Preparations are now limited to 12 tablets per pack and only one pack can be sold per transaction.

Aim To assess the impact of this legislation on acute deliberate paracetamol overdoses.

Methods We reviewed acute deliberate paracetamol overdoses reported during two 24-months periods before and after October 2001. We grouped cases according to the number of tablets taken and compared the periods using chi-square and Mann-Whitney tests**.**

Results The number of tablets taken in acute deliberate paracetamol overdose fell significantly after October 2001 (χ^2 =11.663, P=0.0029). Fewer cases involved 12-24 tablets (U=74, P<0.001) and fewer cases involved more than 24 tablets (U=131.5, P=0.0006)

Conclusion Legislation controlling sale and packaging of paracetamol preparations appears to be associated with a significant fall in the number of tablets taken in acute deliberate paracetamol overdoses.

INTRODUCTION

Parasuicide remains a cause for concern in Ireland[1] with an annual incidence of more than 10,000 cases reported by the National Parasuicide Registry. Drug overdoses are the most common method of parasuicide in Ireland making up more than 75% of all incidents, and paracetamol remains one of the top three drugs involved in these cases.[2] It has been shown previously that paracetamol overdoses are often spontaneous or impulsive acts[3] and the ready availability of over-the-counter products allows easy access to large quantities of tables. In October 2001, legislation was introduced in Ireland to restrict the pack-size of single-ingredient paracetamol preparations. Under this legislation, non-pharmacy retail outlets may supply single-ingredient paracetamol products provided that; "in the case of dosage units each of which contains... not more than 500mg, the pack-size does not exceed 12 such units."[4]

The legislation also prohibits the sale of multiple packs of paracetamol in the course of a single transaction. Pharmacy outlets may supply more tablets at the discretion of an authorised person in the pharmacy. A major determinant in the outcome of paracetamol poisoning is the number of tablets taken in the overdose. A limit on the number of tablets available for purchase should reduce the number of tablets being taken in overdose. In other countries with similar legislation, smaller pack-sizes have been associated with a fall in the number of fatalities due to paracetamol, and a fall in the number of people attending liver units after paracetamol overdoses.[5] In 1997, recommendations on pack-size were issued by the Irish Medicines Board and restrictions were implemented on a voluntary basis. These voluntary restrictions did not appear to have any impact on incidents of self-poisoning however,[6] possibly due to non-compliance by retailers.[7] This study asks the question; has legislation governing the pack-size of paracetamol products had any effect on the severity of paracetamol overdoses in Ireland?

METHODS

The National Poisons Information Centre (NPIC) in Ireland receives enquiries about overdose cases from all general hospitals in the Republic of Ireland. We carried out a retrospective study of paracetamol enquiries received by the NPIC during two 24-month periods before and after October 2001. NPIC records were reviewed by a single investigator to identify cases of paracetamol overdoses. *Inclusion* criteria for our data-set were all acute deliberate overdoses involving single-ingredient tablet or capsule formulations in patients over 10 years of age.

Table 1
TOTAL PARACETAMOL OVERDOSES EXPRESSED AS A PROPORTION OF TOTAL DELIBERATE SELF-POISONINGS

	BEFORE LEGISLATION	% OF DSP	AFTER LEGISLATION	% OF DSP	RELATIVE RISK (95% CI)
Total paracetamol	1198	14.09%	934	14.10%	0.99 (0.90-1.0)
Total DSP	8502		6618		

Table 2
PARACETAMOL OVERDOSES GROUPED ACCORDING TO NUMBER OF TABLETS TAKEN

# OF TABLETS	BEFORE LEGISLATION (N=1198)	AFTER LEGISLATION (N=934)	P
0-12	379	358	0.242
13-24	412	272	<0.001
>24	407	304	0.0006

χ^2 = 11.663, P=0.0029

Overdoses were classified as acute if they occurred as a once-off incident over a short period of time. Exclusion criteria were children under 10, chronic overdose, and staggered overdoses. Also excluded were any cases where the number of tablets taken in the overdose not known at the time of the enquiry.

STATISTICAL ANALYSIS

We performed a Relative Risk assessment on the number of paracetamol overdoses relative to the total number of deliberate self-poisonings reported during the same period. We then analysed our data by grouping the cases according to the number of tablets taken (0-12, 13-24, >24). We used the non-parametric Chi square test to compare the incidence of cases in each group before and after legislation was introduced. We then assessed each group using directional Mann-Whitney tests to determine where changes had occurred. P values less than 0.05 were considered statistically significant.

RESULTS

A total of 2132 paracetamol overdoses met the inclusion criteria for this study; 1198 cases in the period before October 2001, and 934 cases in the period after October 2001. The ratio of paracetamol overdoses to deliberate self-poisoning cases remained the same before and after October 2001 (Table 1). There was, however, a significant change in the size of acute deliberate paracetamol overdoses after introduction of pack-size restrictions (χ^2 = 11.663, P = 0.0029) (Table 2). There was a small but not significant decrease in the number of cases involving 12 tablets or less (U_A = 253.5, $P_{(1)}$ =0.242). There was a significant decrease in the number of cases involving 13-24 tablets (U_A =74, $P_{(1)}$ <0.001). There was also a significant drop in the number of cases involving potentially hepatotoxic doses of paracetamol (i.e. more than 24 tablets) (U_A = 131.5, $P_{(1)}$ = 0.0006).

DISCUSSION

It has been suggested that smaller pack-sizes of paracetamol preparations can reduce paracetamol related morbidity and mortality.[8] In the majority of cases, the number of tablets ingested in a paracetamol overdose largely determines the outcome; it is rare for doses <150mg/kg to cause toxicity in patients unless additional risk factors are present.[9] Over-the-counter preparations of paracetamol in Ireland contain no more than 500mg of the drug. An average sized adult of 60-70kg can tolerate no more than 18-20 tablets without toxicity. Single packets of paracetamol preparations available in non-pharmacy retail outlets previously contained up to 24 tablets (12g). The main aim of pack-size restrictions is to reduce the severity of toxic paracetamol overdoses. Similar legislation introduced in Britain in 1998 seemed to result in less severe paracetamol poisoning.[10,11] In this study, we looked at the size of paracetamol overdoses in terms of tablets taken. We observed a significant drop in the number of cases involving between 12 and 24 tablets. There was also a significant drop in the number of overdoses involving more than 24 tablets of paracetamol.

The spontaneous nature of paracetamol overdoses implies that patients will often take whatever

medication is readily to hand.[3] A partially used or unused packet of paracetamol found in the home will now contain a maximum of 12 tablets where previously it could contain up to 24. The legislation introduced in Ireland does not limit the number of retail outlets where paracetamol can be obtained. However, purchase of numerous packs of paracetamol in one outlet is not permitted. We observed no change in the frequency of paracetamol overdoses after October 2001 but the possibility of taking a large number of tablets, and therefore a toxic dose of paracetamol, has been reduced. There is no reason to believe that compliance by retailers will diminish in the future, and it is reasonable to believe that access to large numbers of paracetamol tablets will remain difficult. Further follow-up studies over a longer period of time will be useful to determine whether pack-size restrictions have continuing benefits.

STUDY LIMITATIONS

Our study was carried out as a retrospective observational "before and after" study using data reported to the Poisons Information Centre. We acknowledge that other unknown factors may have contributed to a drop in our actual numbers, but by assessing the proportional incidence of paracetamol cases relative to total deliberate self-poisonings, we could allow for any underlying trends.

CONCLUSION

There was a significant fall in the proportion of paracetamol overdoses involving more than 12 tablets after October 2001. No significant change was seen in overdoses involving less than 12 tablets. It is reasonable to assume that these observations may be related to the reduction of paracetamol pack-sizes from 24 tablets to 12. Legislation governing the sale of single-ingredient paracetamol preparations appears to have successfully reduced the availability of large quantities of tablets and thus the severity of paracetamol overdoses.

REFERENCES

1. Corcoran P, Keeley HS, O'Sullivan M, Perry IJ. Parasuicide and suicide in the south-west of Ireland *IJMS* 2003; 172 (3): 107-8
2. National Parsuicide Registry Ireland, Annual Report 2003
3. Hawton K, Ware C, Hamant M, *et al* Paracetamol Self-Poisoning, Characteristics, Prevention and Harm Reduction. *Br J Psych* 1996; 168:43-8
4. Hawton K, Simkin S, Deeks J, *et al* UK legislation on analgesic packs: before and after study of long term effect on poisonings. *BMJ* 2004; 32: 1076
5. Donohoe E, Tracey JA. Restrictions on the sale of paracetamol in Ireland had no impact on the number of tablets ingested in acute deliberate overdose. *J Toxicol Clin Toxicol* 2000 ;38: 251 [abstract]
6. Laffoy M, Byrne G, Scallan E. Paracetamol availability and overdose in Ireland *IMJ* 2001; 94(7):212-4
7. Gunnell D, Hawton K, Murray V, *et al* Use of paracetamol for suicide and non-fatal poisoning in the UK and France; are restrictions on availability justified? *J Epidemiol Community Helath* 1997; 51 (2): 175-9
8. Prescott LF, Illingworth RN, Critchley JA *et al* Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. *BMJ* 1979; ii: 1097-1100
9. Hughes B, Durran A, Langford NJ, Mutimer D. Paracetamol poisoning-impact of pack size restrictions. *J Clin Pharm Therap* 2003; 28:307-10
10. Hawton K, Townsend E, Deeks J, *et al* Effects of legislation restricting pack sizes of paracetamol and salicylate on self-poisoning in the United Kingdom; before and after study. *BMJ* 2001; 322:1-7

Correspondence to:Elaine Donohoe
Tel: 01-809 2566 / 01-837 9964
e-mail: elainedonohoe@beaumont.ie

ORIGINAL PAPER

Socio-economic gradients in self-reported health in Ireland and Northern Ireland

D O'Reilly,[1] KJ Thompson, AW Murphy,[2] G Bury,[3] A Gilliland,[4] A Kelly,[5] T O'Dowd,[5] K Steele[4]

Dept of Epidemiology and Public Health,[1] Queen's University Belfast; Dept of General Practice,[2] National University of Ireland, Galway; Dept of General Practice,[3] University College Dublin; Dept of General Practice,[4] Queen's University Belfast; Dept of Public Health and Primary Care,[5] Trinity College Dublin

ABSTRACT

Background Research and policy related to reducing health inequalities has progressed separately within Ireland and Northern Ireland. This paper describes the first exploration of the socio-economic influences on health on the island of Ireland since 1922.

Methods Postal survey.

Results The response rate was 52%; 11,870 respondents. Men reported more long-standing illness (LLTI) or poor general health (PGH); depression was more common amongst women. Socio-economic gradients in health were evident in both jurisdictions, with the effects of household income being particularly marked. Overall, morbidity levels were significantly better in Ireland than in Northern Ireland: adjusted odds ratio of 0.79 (95% CI 0.71- 0.88) for LLTI; 0.64 (0.57 – 0.72) for PGH; 0.90 (0.82 – 0.99) for depression.

Conclusions There is evidence of strong and similar socio-economic gradients in health throughout the island of Ireland. This would suggest joint policy approaches or at least further comparative evaluation of the initiatives in each jurisdiction.

INTRODUCTION

In 1922 the island of Ireland was partitioned into Northern Ireland (NI) and Ireland. The last census to be undertaken of the island as a whole was in 1911 and the last all-Ireland Registrar General's report was in 1921. Since then each jurisdiction has produced separate demographic statistics, separate recording of vital registration events and health policy has developed along separate lines.

There has been a realisation in recent years that the respective health strategies have much in common and that it made sense for such close neighbours to share information and see what could be learnt from the others' experiences. This is particularly so in the field of health inequalities which is now a priority for both governments. Research into inequalities in health has been slow to develop on the island[1] and it has been suggested that the health status of Ireland's diaspora has probably been better studied than those who remained behind.[2] Research has also progressed on independent, albeit parallel lines within the two jurisdictions and there has been a noticeable paucity of studies that have attempted to compare and contrast the relative health of the two populations or the magnitude and relative distribution of health inequalities. This has been due to a combination of methodological difficulties, differing perspectives and, initially, a lack of political will.

Obtaining comparable data for socio-economic and health indicators has been a major problem for researchers. NI has tended to follow the UK and use deprivation indicators such as the Townsend[3] or Carstairs;[4] Ireland has developed a modification of these that is quite distinct from either.[5] Alternatively, researchers in Ireland sometimes also use the proportion of GMS patients as a proxy for low income, but this has no equivalent in NI where, as in the rest of the UK, all services are free at the point of delivery. It was only recently that a comparison of mortality by cause, sex and socio-economic status in Ireland and NI was attempted though the researchers experienced difficulties with data incompatibilities at all stages, occupation classifications proving particularly troublesome.[6] The respective Cancer Registries, because they are conforming to internationally agreed definitions and protocols, have been able to collate their findings and produce an all-Ireland report on the incidence and mortality from cancer.[7]

Morbidity data are more relevant to public health[8] but present the greatest dearth of comparable studies.[9] A good example of the lack of coordination and missed

opportunities for North/South comparative work is the parallel development of health surveys. The SLÁN survey in Ireland[10] and the Health and Wellbeing Survey in NI[11] (modelled on the Health Surveys in England[12]) used completely different questionnaires and contrasting survey methods.

The development of health information systems with standardisation of datasets is seen as prerequisite for integrating public health within the European arena.[13] However, recent reports on cross-border cooperation in health services[14] and mental health and social wellbeing[15] have highlighted the absence of harmonized datasets, which is one of the obstacles to collaboration. Within the health inequalities arena this means that socio-economic and health status of the population be assessed using exactly the same measurement tools, which in the absence of harmonized existing datasets, requires a dedicated study.

The aim of this paper is to report on an analysis of data from such a dedicated survey that was carried out simultaneously in Ireland and NI using the same questionnaire and survey methodology.

METHODS

The data for this study was collected as part of a larger study comparing aspects of the primary care systems in the two jurisdictions. The first part of that study involved conducting a baseline survey of the health and socio-economic status of patients in selected practices. It is an analysis of these data that forms the basis for the current paper.

Twenty practices were selected in Ireland to provide a representative mix of national practice according to location (rural, small town, city) and practice size (one of three groups based on whole-time-equivalent GPs principals).[16] Practices in NI were then classified according to these criteria and a random selection of twenty practices drawn to match those in Ireland. A random selection of 625 patients were selected from the patient lists of each practice in Ireland and NI including no more than two people from a household. Randomisation was based on computer generated random numbers. The survey was preceded by a personalised letter from the patient's GP and non-responders were sent two reminders, the second containing another copy of the questionnaire. Parents/guardians were asked to complete questionnaires on behalf of patients aged less than 16 years old. Mailing took place during October and November 2003.

The selection of variables for inclusion into the questionnaire was informed by those factors which previous studies had demonstrated to be important determinants of GP attendance. In addition to the usual demographic variables, an array of socio-economic data was collected based on questions asked in the UK 2001 census. This included car ownership (categorised as no car, one or more car, two or more cars); tenure (dichotomised into renting and non-renting) and academic attainment (three levels of educational attainment; primary school only, secondary level, and tertiary level were used to accommodate differences in academic qualifications in Ireland and NI). The survey also captured data relating to gross annual household income, the question being identical to the one initially proposed for the 2001 UK census. Income from all sources was assessed, including earned income, pensions, benefits, allowances, interest or annuities etc., with no deductions for taxes, national insurance contributions, etc. Respondents were asked which of fourteen income bands (in pounds or Euros) best represented their household income.

Health measures included the limiting long-term illness (LLTI) and general health questions and two questions on depression (see Box 1). The LLTI question was identical to that used in the UK 2001 census. The general health question has been used in both of the SLÁN surveys and also the Health Survey in England. Limitations on space and a desire to keep responder burden to a minimum precluded the inclusion of a more recognised measure of mental health status such as the GHQ12[17] and so we used a two-question

Box 1 — HEALTH QUESTIONS USED IN THE SURVEY

LLTI

Do you have any long-term illness, health problem or disability which limits your daily activities or the work that you do? Include problems that are due to old age.
Responses: Yes: No

GENERAL HEALTH

In general, would you say your health is: Excellent; very good; good; fair; poor.

CASE-FINDING FOR DEPRESSION

Q1. During the past month, have you often felt bothered by feeling down, depressed or hopeless? *Responses: Yes: No*

Q2. During the past month, have you been bothered by having little interest or pleasure in doing things? *Responses: Yes: No*

instrument that has been recommended for use in a primary care setting as an aid for detecting patients at high risk of depression.[18] Only adult respondents were asked to complete the two mental health questions.

A series of logistic regression analyses were undertaken to examine the relationship between each of the three measures of self-reported health and demographic and socio-economic factors within each jurisdiction. A final set of regression analyses was undertaken for the Island as a whole with jurisdiction entered as a covariate to compare the health of the respondents in Ireland and NI.

RESULTS

The overall response rate was 52% (Ireland=50%, NI=54%). In Ireland almost 10% (1195) of the sample was returned as 'undeliverable mail' and were excluded from the study. In NI the figure was only 3% (398). The high rate of undeliverable mail was most likely due to the difficulties of maintaining up-to-date patient addresses in Ireland. For this reason, although the response rates were relatively similar, the number of respondents in NI was notably larger (6579) than in Ireland (5291). Respondents in Ireland and NI had a similar demographic profile (Table 1), though there were a slightly greater proportion of people who were never married in Ireland. Over 80% of people in both jurisdictions owned their own house and had access to at least one car, though the proportion renting or without a car in Ireland was almost twice that in NI. This may by partially explained by the greater proportion of city dwellers amongst the Irish sample.

The age-specific rates of LLTI and poor general health were generally higher in NI than in Ireland (Figure 1) with the differences more marked for poor general health. The prevalence of depression does not vary greatly with age in either jurisdiction but, in NI, appears highest between the ages of 35 and 54.

The results of the separate logistic regression analyses with each of the three health indicators as dependent are shown in Table 2. A second series of analyses, stratified by sex within jurisdiction was also undertaken but, as there were few differences, these are reported in the context of the overall results. The expected sharp increase in the likelihood of LLTI and poor general health with age was seen in both jurisdictions, though the gradients were more marked in NI than in Ireland. Men in both Ireland and NI showed greater age-related increases in the likelihood of poor general health than women. The association between age and depression was markedly different to that of the other two health indicators. After controlling for other socio-demographic factors, in Ireland there was a gradual decline in the prevalence of depression with age for women, such that a woman aged 75 or over was only half as likely to suffer from depression as one aged 16-24. A marked increased likelihood of depression in middle age was evident for both sexes in NI and for men in Ireland.

Table 1
BASIC DEMOGRAPHIC, SOCIAL AND SOCIO-ECONOMIC CHARACTERISTICS OF THE RESPONDENTS IN IRELAND AND NI

		NI	IRELAND
RESPONDENTS		5143	4175
AGE MEAN (SD)		47.9 (18.1)	47.7 (18.3)
SEX	Men	2985 (45.5%)	2297 (43.7%)
	Women	3574 (54.5%)	2965 (56.3%)
MARTIAL STATUS	Single	1080 (21.4%)	1072 (26.0%)
	Married	3303 (65.3%)	2534 (61.5%)
	Sep/widowed/Div.	672 (13.3%)	517 (12.5%)
CAR OWNERSHIP	0	496 (9.7%)	711 (17.2%)
	1	2000 (39.1%)	1673 (40.4%)
	2+	2613 (51.1%)	1760 (42.5%)
TENURE	Not renting	4363 (85.5%)	3346 (80.9%)
	Renting	742 (14.5%)	790 (19.1%)
EDUCATION ATTAINMENT	Primary level	1520 (31.1%)	1216 (30.4%)
	Secondary level	2189 (44.5%)	1706 (42.7%)
	Tertiary level	1182 (24.2%)	1072 (26.8%)
LOCATION	Rural	1893 (37.3%)	1424 (34.5%)
	Small town	973 (19.2%)	452 (11.0%)
	Large town	1528 (30.1%)	1048 (25.4%)
	City	682 (13.4%)	1199 (29.1%)
INCOME BAND	Lowest	759 (15.6%)	926 (23.3%)
	2nd	741 (15.2%)	615 (15.5%)
	3rd	659 (13.5%)	545 (13.7%)
	4th	974 (20.2%)	691 (17.4%)
	5th	884 (18.1%)	573 (14.4%)
	6th	642 (13.2%)	459 (11.6%)
	Highest	222 (4.5%)	157 (4.0%)

People with lower educational attainment and of lower socio-economic status were more likely to suffer from poorer health however measured, though the relationship with indicators of material deprivation varied somewhat between jurisdictions and according to the measure of health status. Tenure was more strongly linked with LLTI and poor health in NI than in Ireland, though for depression the converse was true. Educational attainment was more predictive of poor health in Ireland. Household income levels were strongly linked to health status with similar steep gradients evident in both jurisdictions. The slightly more muted relationship between income and likelihood of depression in Ireland was due to the virtual absence of an association between income and depression for Irish women.

Table 3 shows the results of the final regression models for the island of Ireland as a whole. As the data are combined, the odds ratios here are almost an average of those presented earlier. Women were respectively 22% and 23% less likely to have a LLTI or to have poor general health and 30% more likely to suffer from depression. When age, gender and socio-economic factors had been considered, there was no significant association between marital status and the prevalence of LLTI though single people reported better general health and less depression while widowed, separated or divorced respondents had poorer general health and more depression. The main point of interest of this table is the comparison of health status in the two jurisdictions, which shows NI to be in the less favourable position. All other things considered, respondents in Ireland were 21% (95% confidence intervals 12-29%) less likely to have a LLTI, 36% (95%CI 28-43%) less likely to report poor general health and 10% (1-18%) less likely to suffer from depression, than people in NI.

DISCUSSION

To the authors knowledge this is the first time that the same questions have been asked to assess both socio-economic status and health in a large-scale survey in both jurisdictions, thereby obviating problems of comparability and contemporaneousness. The shortcomings of the study should be acknowledged. The response rate raises concerns about response bias and the representativeness of the results to the wider population. Inaccuracies in the GP lists, which were used as the sampling frame, may have contributed to the low response rate, especially in Ireland where there is no universal registration and therefore it

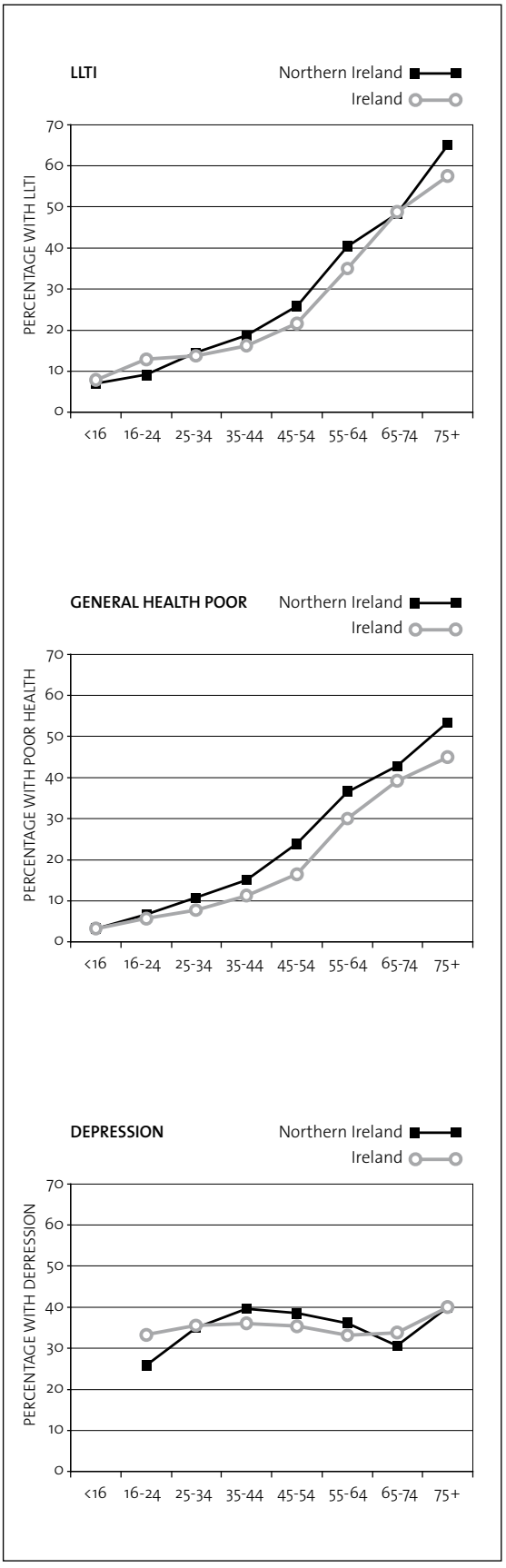


Figure 1 — VARIATIONS IN PREVALENCE OF LLTI, POOR GENERAL HEALTH AND DEPRESSION BY AGE IN IRELAND AND NI

Table 2
THE ASSOCIATION BETWEEN HEALTH AND DEMOGRAPHIC, SOCIAL AND SOCIO-ECONOMIC FACTORS FOR EACH JURISDICTION SEPARATELY. DATA REPRESENTS THE RESULTS OF MULTIPLE LOGISTIC REGRESSION ANALYSES (ODDS RATIOS AND 95% CONFIDENCE INTERVALS) WITH HEALTH MEASURES AS THE DEPENDENT

	LLTI		GENERAL HEALTH 'POOR'		DEPRESSION *	
	N. Ireland	**Ireland**	**N. Ireland**	**Ireland**	**N. Ireland**	**Ireland**
AGE	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P= 0.011
16-24	1.00	1.00	1.00	1.00	1.00	1.00
25-34	1.7 (1.1, 2.6)	1.2 (0.8, 1.8)	1.8 (1.1, 2.9)	1.2 (0.7, 2.1)	1.4 (1.0, 1.8)	0.9 (0.7, 1.2)
35-44	2.4 (1.6, 3.6)	1.4 (0.9, 2.1)	2.8 (1.8, 4.5)	1.7 (1.1, 2.8)	1.8 (1.3, 2.4)	0.9 (0.7, 1.3)
45-54	3.4 (2.3, 5.2)	1.9 (1.3, 2.8)	4.7 (2.9, 7.5)	2.4 (1.5, 3.9)	1.7 (1.2, 2.2)	0.9 (0.7, 1.2)
55-64	5.5 (3.6, 8.3)	3.2 (2.2, 4.7)	6.4 (4.0, 10.3)	4.1 (2.5, 6.7)	1.2 (0.8, 1.6)	0.7 (0.5, 0.9)
65-74	6.1 (3.9, 9.4)	4.8 (3.2, 7.2)	6.5 (4.0, 10.6)	4.7 (2.8, 7.7)	0.8 (0.5, 1.1)	0.6 (0.4, 0.9)
75+	9.5 (6.0, 15.1)	6.1 (3.9, 9.4)	7.2 (4.3, 11.9)	4.6 (2.7, 7.8)	0.8 (0.6, 1.2)	0.6 (0.4, 0.9)
SEX	P= 0.002	P= 0.001	P= 0.073	P= 0.150	P= 0.001	P<0.001
Male	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.78 (0.69, 0.92)	0.77 (0.65, 0.90)	0.87 (0.74, 1.01)	0.87 (0.73, 1.05)	1.24 (1.01, 1.41)	1.37 (1.19, 1.58)
MARITAL STATUS	P = 0.171	P = 0.716	P= 0.236	P= 0.237	P= 0.902	P= 0.003
Single	1.00	1.00	1.00	1.00	1.00	1.00
Married	1.26 (0.98, 1.60)	0.91 (0.72, 1.15)	1.25 (0.96, 1.63)	1.24 (0.95, 1.62)	1.00 (0.82, 1.23)	0.96 (0.79, 1.17)
Sep/Wid/Div	1.26 (0.94, 1.68)	0.97 (0.71, 1.31)	1.22 (0.90, 1.66)	1.28 (0.92, 1.77)	1.05 (0.81, 1.36)	1.45 (1.10, 1.90)
TENURE	P= 0.002	P= 0.782	P< 0.001	P= 0.343	P= 0.237	P< 0.001
Not renting	1.00	1.00	1.00	1.00	1.00	1.00
Renting	1.42 (1.14, 1.76)	0.97 (0.77, 1.21)	1.71 (1.37, 2.14)	1.29 (0.88, 1.45)	1.13 (0.92, 1.38)	1.46 (1.12, 1.77)
EDUCATION	P= 0.305	P= 0.032	P= 0.001	P<0.001	P= 0.144	P= 0.002
Primary level	1.00	1.00	1.00	1.00	1.00	1.00
Secondary level	0.89 (0.74, 1.06)	0.86 (0.71, 1.05)	0.69 (0.57, 0.82)	0.71 (0.58, 0.86)	0.97 (0.82, 1.15)	0.80 (0.67, 0.95)
Tertiary level	0.86 (0.68, 1.07)	0.72 (0.56, 0.92)	0.54 (0.42, 0.69)	0.45 (0.34, 0.61)	0.83 (0.68, 1.02)	0.69 (0.56, 0.86)
CAR AVAILABILITY	P= 0.08	P= 0.006	P= 0.004	P= 0.001	P= 0.002	P= 0.085
0	1.00	1.00	1.00	1.00	1.00	1.00
1	0.88 (0.67, 1.14)	0.80 (0.63, 1.00)	0.93 (0.72, 1.22)	0.72 (0.57, 0.92)	0.83 (0.65, 1.06)	0.84 (0.68, 1.04)
2+	0.74 (0.55, 0.99)	0.64 (0.49, 0.84)	0.69 (0.51, 0.94)	0.57 (0.42, 0.76)	0.66 (0.51, 0.87)	0.76 (0.60, 0.97)
INCOME BAND	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P< 0.001
Lowest	1.00	1.00	1.00	1.00	1.00	1.00
2nd	0.82 (0.65, 1.04)	0.93 (0.73, 1.18)	0.74 (0.59, 0.94)	0.79 (0.61, 1.01)	0.81 (0.64, 1.01)	1.08 (0.86, 1.35)
3rd	0.52 (0.40, 0.67)	0.63 (0.48, 0.83)	0.43 (0.33, 0.57)	0.60 (0.45, 0.80)	0.59 (0.47, 0.76)	0.83 (0.65, 1.06)
4th	0.44 (0.34, 0.57)	0.49 (0.37, 0.65)	0.40 (0.30, 0.52)	0.41 (0.30, 0.56)	0.49 (0.39, 0.62)	0.72 (0.56, 0.91)
5th	0.39 (0.29, 0.52)	0.49 (0.36, 0.68)	0.39 (0.29, 0.53)	0.34 (0.23, 0.50)	0.42 (0.32, 0.54)	0.59 (0.45, 0.78)
6th	0.23 (0.16, 0.33)	0.55 (0.39, 0.78)	0.23 (0.18, 0.34)	0.23 (0.14, 0.37)	0.38 (0.28, 0.51)	0.61 (0.45, 0.83)
Highest	0.19 (0.10, 0.29)	0.24 (0.12, 0.46)	0.23 (0.13, 0.40)	0.13 (0.05, 0.38)	0.29 (0.19, 0.44)	0.52 (0.33, 0.80)

Table 3
THE ASSOCIATION BETWEEN HEALTH AND DEMOGRAPHIC, SOCIAL AND SOCIO-ECONOMIC FACTORS FOR THE WHOLE ISLAND OF IRELAND. DATA REPRESENTS THE RESULTS OF MULTIPLE LOGISTIC REGRESSION ANALYSES (ODDS RATIOS AND 95% CONFIDENCE INTERVALS) WITH HEALTH MEASURES AS THE DEPENDENT

	LLTI	GENERAL HEALTH 'POOR'	DEPRESSION
AGE	P< 0.001	P< 0.001	P< 0.001
16-24	1.00	1.00	1.00
25-34	1.45 (1.09, 1.92)	1.50 (1.05, 2.14)	1.15 (0.94, 1.40)
35-44	1.89 (1.42, 2.50)	2.29 (1.63, 3.22)	1.34 (1.09, 1.65)
45-54	2.64 (1.99, 3.49)	3.55 (2.54, 4.98)	1.23 (0.99, 1.52)
55-64	4.32 (3.25, 5.73)	5.33 (3.80, 7.49)	0.91 (0.73, 1.13)
65-74	5.41 (4.02, 7.28)	5.72 (4.03, 8.12)	0.68 (0.53, 0.86)
75+	7.75 (5.65, 10.64)	6.04 (4.19, 8.70)	0.71 (0.54, 0.92)
SEX	P< 0.001	P= 0.017	P<0.001
Male	1.00	1.00	1.00
Female	0.78 (0.70, 0.87)	0.87 (0.77, 0.97)	1.30 (1.18, 1.42)
MARITAL STATUS	P = 0.555	P = 0.045	P= 0.021
Single	1.00	1.00	1.00
Married	1.08 (0.91, 1.28)	1.26 (1.04, 1.52)	1.00 (0.86, 1.15)
Sep/Wid/Div	1.12 (0.91, 1.37)	1.26 (1.01, 1.57)	1.24 (1.03, 1.49)
TENURE	P= 0.022	P< 0.001	P< 0.001
Not renting	1.00	1.00	1.00
Renting	1.20 (1.03, 1.40)	1.42 (1.20, 1.67)	1.28 (1.12, 1.47)
EDUCATION	P= 0.012	P< 0.001	P= 0.002
Primary level	1.00	1.00	1.00
Secondary level	0.87 (0.76, 0.99)	0.70 (0.61, 0.80)	0.88 (0.78, 0.99)
Tertiary level	0.79 (0.67, 0.93)	0.50 (0.42, 0.61)	0.77 (0.66, 0.89)
CAR AVAILABILITY	P< 0.001	P<0.001	P< 0.001
0	1.00	1.00	1.00
1	0.84 (0.71, 0.99)	0.81 (0.68, 0.97)	0.84 (0.72, 0.98)
2+	0.69 (0.56, 0.84)	0.62 (0.50, 0.76)	0.71 (0.59, 0.85)
INCOME BAND	P< 0.001	P< 0.001	P< 0.001
Lowest	1.00	1.00	1.00
2nd	0.88 (0.75, 1.04)	0.76 (0.64, 0.90)	0.94 (0.80, 1.10)
3rd	0.57 (0.47, 0.69)	0.49 (0.40, 0.60)	0.71 (0.60, 0.85)
4th	0.47 (0.39, 0.57)	0.40 (0.33, 0.49)	0.60 (0.51, 0.72)
5th	0.45 (0.36, 0.55)	0.38 (0.30, 0.48)	0.51 (.042, 0.61)
6th	0.35 (0.27, 0.45)	0.23 (0.17, 0.31)	0.49 (0.39, 0.60)
Highest	0.20 (0.13, 0.31)	0.20 (0.12, 0.33)	0.39 (0.29, 0.53)
JURISDICTION	P< 0.001	P< 0.001	P= 0.033
NI	1.00	1.00	1.00
Ireland	0.79 (0.71, 0.88)	0.64 (0.57, 0.72)	0.90 (0.82, 0.99)

is difficult to keep patient lists current. Even in NI, where central monitoring of patient registration occurs, it is known that there are inaccuracies in the lists with an inflation (compared to census estimates) of approximately 6% and address inaccuracies of perhaps 20% in some practices. The low response rates are similar to other field studies, for example 53% for the 2001 SLAN survey (Friel S, personal communication) and perhaps reflects a growing disenchantment or survey fatigue amongst the general population.

The study has demonstrated marked socio-economic gradients in self-reported health in both Ireland and NI. The likelihood that this represents health selection effects can be discounted, as it is now fairly well established that they have only a relatively minor role to play in explaining socio-economic gradients.[19] It is difficult to know whether the differences in the explanatory power of the various indicators represents variation in the underlying determinants of health inequalities or, some subtle difference in the meaning of the indicators, as other studies have reported difficulties finding indicators that had the same understanding across international boundaries.[20, 21] What the analyses do underscore is the importance of income in determining health status, which is in keeping with health inequalities research throughout Europe.[22-28]

The study also shows that, when assessed using levels of self-reported ill-health, Ireland appears to be appreciably healthier than NI. This is not the picture that is obtained using other, 'objective' indicators of health status. Life expectancy at birth has been remarkably similar over the last 40 years in Ireland and NI[29] and a comparison of all-cause mortality between 1989 and 1999 showed that, while they both compare unfavourably with the rest of Europe, they were 6% higher in Ireland than in NI.[5] A comparison of cancer incidence on the island of Ireland[7] provides a mixed picture, for while incidence rates were very slightly higher in NI; mortality rates were slightly higher in Ireland. These findings may be due to differences in case ascertainment and/or case survival rates. Collectively, these objective measures of health suggest that the two jurisdictions enjoy remarkably similar levels of health, though where differences exist, it would appear to favour NI. There is therefore a dissonance between 'objective' and 'subjective' measures of health which prompts the question; to what extent are these due to perceptual rather than 'real' differences?

One possibility is that self-reported measures of health are 'picking up' conditions, such as musculo-skeletal complaints or minor psychological problems that are poorly reflected in mortality or cancer data. A comparison of national health surveys showed that NI has higher levels of minor psychological disturbance (as measured by the GHQ12) than the rest of the UK and (if differences in survey methodology are disregarded) also higher than those in Ireland.[30] It is possible that the recent economic success in Ireland[31] has produced a feel-good factor that has percolated through to produce a more generally favourable view of health.[2]

Another possibility is that current mortality patterns reflect the morbidity status of previous decades but not current health status which is best assessed using the self-reported measures. If this is true then the better levels of self-reported health in Ireland now may predict a change in the trajectories of the relative mortality experience of the two jurisdictions.

A third possibility is that there are systematic differences between the two jurisdictions in the way that health is perceived and reported and the inclusion of anchoring vignettes has been proposed as a way of identifying and overcoming differences in both health expectations and reporting between populations.[32] These describe fixed levels of health and responses to them can then be used to adjust the self ratings of health, making them more comparable across populations. This is something that could be considered as a next step before definitively concluding that the differences in levels of self-reported ill health between Ireland and NI are substantive.

ACKNOWLEDGEMENTS

Sincere thanks go to all the staff at the following GP practices who agreed to take part in the research: In NI – Dr Morrison, Cherryvalley Family Practice; Glenavy Family Practice, Glenavy; Oriel Surgery, Antrim; Tramways Medical Centre, Newtownabbey; The Bell Practice, Holywood Arches Health Centre; Dr Robert Henry Surgery, Comber; The Health Centre, Comber; Rathfriland Surgery, Rathfriland; Dr JG McAnallen's Practice, The Health Centre, Portadown; The Surgery, Crossgar; Irvinestown Health Centre, Irvinestown; Errigal Medical Centre, Ballygawley; The Health Centre, Richill; Dr Finlay, Dr McQuillan, and Dr Ollerenshaw, Bovally Medical Centre, Limavady; Dr J D Lennox Practice, Skegoneill Health Centre; The Health Centre, Downpatrick; The Montalto Medical

Centre, Ballynahinch; Campbell Surgery, Dungannon; The Archway Surgery, Armagh; The Meadows Family Practice, Portadown.

In Ireland – Coombe Healthcare Centre, Dublin; Whitworth Medical Centre, Dublin; Rialto Medical Centre, Dublin; Blackrock Medical Centre, Blackrock; Dr Emer Loughrey / Dr Conor Geaney, Inchicore; Springfield Medical Centre, Tallaght; Dr Connolly, 1 Duncairn Terrace, Bray; Lifford Health Centre, Donegal; Dr Cryan's Practice, Galway; Dr Desmond Bluett, Dr Mairead Cashman and Dr Terese Dillon, Galway; Health Centre, Roundstone; Turloughmore Health Centre, Lackagh; Dr Flynn's Practice, Shannon; No 47 Medical Practice, Drogheda; Skreen Family Practice, Sligo; Bedford Place, Navan; The Palms, Gorey; Ennistymon Medical Centre, Main Street; Moy view Family Practice, Ballina; Garden Vale Court, Athlone.

FUNDING

Health Research Board, Ireland & Research and Development Office, Northern Ireland

REFERENCES

1. Campbell R. Research into inequalities in health in NI: what research? *Crit Publ Hlth* 1993; 4, 2: 5-8.
2. Kelleher C, Friel S, Nic Gabhainn S, Tay J. Socio-economic predictors of self-rated health in the Republic of Ireland: findings from the National Survey on Lifestyle, Attitudes and Nutrition, SLAN. *Soc Sci Med*. 2003; 57; 477-486.
3. Townsend P, Philimore P, Beattie A. Health and inequalities in the North. London: Croom Helm 1988.
4. Carstairs V, Morris R. Deprivation and health in Scotland. Aberdeen: Aberdeen University Press 1991.
5. Kelly A. A national deprivation index for health and health services research Technical report No 2. Small Area Health Research Unit. Trinity College Dublin 1997.
6. Balanda K, Wilde J. Inequalities in mortality 1989-1998; A report on all-Ireland mortality data. Institute of Public Health 2001.
7. Walsh P, Comber H, Gavin A. All-Ireland cancer statistics 1994-1996: A joint report on incidence and mortality for the island of Ireland. National Cancer Registry (Ireland), Cork and NI Cancer Registry, Belfast 2001
8. Joffe M, Mindell J. A framework for the evidence base to support Health Impact Assessment. *J Epidemiol Comm Hlth* 2002; 56: 132-138.
9. McQuoid J. Feasibility study for a crossborder assessment of social deprivation need and service provision. Centre for policy research University of Ulster, Jordanstown and Economic and Social Research Institute, Dublin 1994.
10. Friel S, NicGabhainn S, Kelleher C. The National health and lifestyle surveys: SLAN and HBSC. Centre for Health Promotion Studies, NUI, Galway 1999.
11. O'Reilly D, Browne S. Health and Health Services Use in NI: Social Variations. Report to the Dept of Health, Social Services and Public Safety. Queen's University Belfast 2001.
12. Breeze E, Maidment A, Bennett N, Flatley J, Carey S. Health Survey for England,1992: A survey carried out by the Social Survey Division of OPCS on behalf of the Dept of Health. London: HMSO 1994.
13. Metcalfe O. Implications of European Public Health. Public Health in Europe the Irish Connection: A report. The Institute of Public Health 2001.
14. Jamison J, Butler M, Clarke P, McKee M, O'Neill C. Cross-border cooperation in Health Services in Ireland. A report for the Centre for Cross Border Studies. The Centre for Cross Border Studies 2001.
15. Barry M, Friel S, Dempsey C, Avalos G, Clarke P. Promoting mental health and social well-being: cross border opportunities and challenges. A report for the Centre for Cross-Border Studies & the Institute of Public Health in Ireland. Centre for Cross-Border Studies 2002.
16. Nic Gabhainn S, Murphy AW, Kelleher CC. A national general practice census: characteristics of rural general practices. *Fam Pract* 2001; 18: 622-626.
17. Goldberg D, Williams PA. Users guide to the General Health Questionnaire, NFER-Nelson 1988
18. Whooley MA, Avins AL, Miranda J, Browner WS. Case-Finding Instruments for Depression: Two Questions Are as Good as Many. *J Gen Int Med* 1997; 12: 439-45.
19. Blane D, Harding S, Rosato M. Does social mobility affect the size of the socioeconomic mortality differential?: evidence from the Office for National Statistics Longitudinal Study. J R Stat Soc Series A. 1999; 162: 59-70.
20. Mackenbach J, Kunst A, Cavelaars A, Groenhof F, Geurts J, EU Working Group on Socio-economic Inequalities in Health Socio-economic inequalities in morbidity and mortality in Western Europe. *Lancet* 1997; 349; 1655-59.
21. Cook S, Poole M, Pringle D, Moore A. Comparative Spatial Deprivation in Ireland North and South: A cross-border analysis. Dublin: Oak Tree Press 2000.
22. Davies, H., Joshi, H., and Clarke, L. Is it cash the deprived are short of? *J R Stat Soc*. 1997; 160, 107-26.
23. Osler M, Prescott E, Grønbæk M, Christensen U, Due P, Engholm G. Income inequality, individual income, and mortality in Danish adults: analysis of pooled data from two cohort studies *BMJ* 2002; 324: 13-16.
24. Shibuya K, Hashimoto H, Yano E. Individual income, income distribution, and self rated health in Japan: cross sectional analysis of nationally representative sample. *BMJ* 2002; 324: 16-20.
25. Sturm R, Gresenz C. Relations of income inequality and family income to chronic medical conditions and mental health disorders: national survey. *BMJ* 2002; 324: 20-24.
26. Deaton A. Commentary: The convoluted story of international studies of inequality and health. *Int J Epidemiol* 2002; 31: 546-549.
27. Lynch J, Davey Smith G. Commentary: Income inequality and health: The end of the story? *Int J Epidemiol* 2002; 31: 549-551.

28. Mackenbach JP. Income inequality and population health. *BMJ* 2002; 324; 1-2.

29. Garvey D, Caven N. Ireland, North and South: A Statistical Profile 2003 Edition. NI Statistics and Research Agency and Central Statistics Office 2003.

30. O'Reilly D, Stevenson M. Mental health in NI: have 'the Troubles' made it worse? *J Epidemiol Comm Hlth*. 2003; 57: 488-492.

31. O'Hearn D. Inside the Celtic Tiger. The Irish economy and the Asian model. London: Pluto Press 1998.

32. Salomon J, Tandon A, Murray C, World Health Survey Pilot Collaborating Group. Comparability of self rated health: cross sectional multi-country survey using anchoring vignettes. *BMJ* 2004; 328; 258-261.

Correspondence to: Dr D O'Reilly, Dept Epidemiology and Public Health, Mulhouse Building, Royal Group of Hospitals, Grosvenor Road, Belfast BT12 6BJ
Tel: 028 90 240503 ext 2738; Fax: 028 90 231907
Email: d.oreilly@qub.ac.uk

Completeness and accuracy of the drug treatment reporting system in Dublin, Ireland

P Kavanagh[1], J Long[2], J Barry[1]

Dept of Public Health and Primary Care[1], Trinity College Centre for Health Sciences, Adelaide and Meath Hospitals, incorporating the National Children's Hospital, Tallaght, Dublin 24; Drug Misuse Research Division[2], Health Research Board, Holbrook House, Holles St, Dublin 2

ABSTRACT

Background The National Drug Treatment Reporting System (NDTRS) is the Irish treated-drug misuse surveillance system.

Aim To measure completeness and accuracy of the NDTRS

Methods Cross-sectional survey of clinical records and matching NDTRS reporting forms of a random sample of 520 clients attending 4 Dublin treatment centres. Using clients' clinical records as the gold standard, system completeness (proportion of sample reported to the NDTRS) and accuracy of selected variables (proportion of reported clients' information on the NDTRS that matched clinical record information) were measured.

Results 452/520 (87%) selected records were retrieved. The NDTRS was only 61.1% (95% CI 56.5-65.5) complete; completeness differed across treatment centres (21.8%-85.6%, p<0.0001) and was greater for new and returning clients than for continuing clients (81.7% versus 53.9% respectively, p<0.0001). Problems were identified with the accuracy of some key variables.

Conclusions Urgent actions have been taken to improve the completeness and accuracy of the reporting system.

INTRODUCTION

Evidence is increasingly used to inform public health policy and practice.[1] An evidence-based approach requires the collection and use of high quality health information,[2] which can identify priorities, steer the implementation of policies and plans and facilitate evaluation of interventions.[3] In relation to drug misuse in Ireland, the current national drug strategy identifies the importance of valid, timely and comparable data on the extent of drug use as the cornerstone which underpins its actions.[4]

Drug treatment data are viewed as an indirect indicator of drug misuse as well as a direct indicator of demand for treatment services.[5] The National Drug Treatment Reporting System (NDTRS) is an epidemiological database on treated problem drug use in Ireland. It was established in 1990 in the Greater Dublin Area and was extended in 1995 to cover other areas of the country. The reporting system was originally developed in line with the Pompidou Group's Definitive Protocol,[6] and subsequently refined in accordance with the Treatment Demand Indicator Protocol.[7] Data are collected on treatment status, demographic profile, current problem drug use, risk behaviour and initial intervention(s). Compliance with the NDTRS requires that one form be completed for each person who receives treatment for problematic drug use at each treatment centre in a calendar year: some clients are new or returning after a period of absence to treatment providers ("new or return clients"); some are continuing in treatment from the preceding year ("continuing clients"); and a subset of those new to treatment providers have never been previously treated ("true incident clients").[8] Service providers at drug treatment centres throughout Ireland collect data on each individual treated for drug misuse, and make reports to the NDTRS. At national level, staff at the Drug Misuse Research Division (DMRD) of the Health Research Board (HRB), who manage the NDTRS, compile anonymous, aggregated data for use at a local and national level. The NDTRS also provides data to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), a key component of the knowledge infrastructure underpinning drug policy for the European Union.[9]

There is concern over the quality of information used for drug policy.[10] In the UK, drug treatment surveillance systems have been found to be incomplete and inaccurate.[11-16] Given that the Irish Government endorses the intelligence role of the NDTRS in its drugs strategy, and that co-operation

with the system is a stated action for treatment providers,[4] we set out to estimate the completeness of reporting and measure the accuracy of the data reported to the NDTRS.

METHODS

We restricted the study to statutory treatment centres in the Greater Dublin Area with more than 100 clients who were treated with methadone. This allowed us to use the Central Treatment List (CTL) as a sampling frame. All individuals dispensed methadone in Ireland are, by statutory requirement, notified to this list. Eleven of the 55 treatment centres in the Dublin area had over 100 clients. These eleven treatment centres comprised 46.3% of notifications to the CTL in 2001 (personal communication, Central Treatment List). The Dublin area has three health board areas and one large treatment centre was randomly selected from each. In addition, a large tertiary specialist drug treatment centre located in the city centre was included in the study. Thus, four large treatment centres were included in the study.

Based on previous studies,[11 13 14] we estimated that the completeness of the NDTRS was 70% (with a precision of ± 5% at the 95% confidence level) and the required sample size for measurement was 520. We randomly selected 130 records on the CTL from each of the study centres for the reporting year 2001.

For each selected client, the clinical notes were examined for 2001 and data on each client, within a six-month period of entry, were extracted using a pre-designed data collection tool. The data collection tool contained key variables from the NDTRS reporting form: client's case number, age, gender, date of treatment contact, incident versus prevalent client status, previous treatment status, name of main problem drug, route of main problem drug, frequency of main problem drug and lifetime injecting status.

One author (PK) located the clinical records and extracted the data from each clinical file. Each client was identified using his/her case number. PK then matched the case number to the NDTRS form stored in the filing system at the DMRD and extracted the individual data already submitted to the NDTRS. Matching by date of birth was attempted for clients not initially identified by case number.

A client was classified as reported to the NDTRS if the client's NDTRS form for 2001 was located in the filing system. The proportion of clients treated that were correctly reported to the NDTRS was calculated using a sensitivity calculation and this estimated the completeness of the NDTRS;[17] 95% confidence intervals (CI) were calculated around this estimate. Associations between treatment centre, client treatment status and completeness of data were tested.

Using the clinical records as the gold standard, the clients' information for a particular variable on the original NDTRS form was compared to the information extracted from the clinical record by PK. The accuracy of the data collected by the NDTRS for each of the selected variables was measured using a positive predictive value calculation:[17] the denominator was the total number of clients classified as reported who had information extracted for the variable, and the numerator was the proportion whose corresponding information on their NDTRS original submission matched the extracted information. Clients who had no information in their clinical records for a particular variable were excluded from the denominator of this measurement. Ninety-five per cent confidence intervals were calculated around the estimates of accuracy for each variable. JMP-In and STATA were used for all data analysis.[18 19]

RESULTS

Of the 520 records randomly selected, 452 (87%) were retrieved and reviewed; 68 records (13%) could not be located at the centre. Of these 452, 276 (61.1% (95% CI 56.5-65.5%)) of the clients receiving methadone treatment in the study centres were correctly reported to the NDTRS in 2001. Table 1 presents the distribution of completeness across client type and study centre. New and returning clients were more likely to be reported than those clients continuing in treatment from the preceding year (98/120 (81.7%) versus 178/330 (53.9%) respectively, $p<0.01$). The level of completeness differed across the four study centres and ranged between 24/110 (21.8%) and 95/111 (85.6%), $p<0.001$. Stratified analysis illustrates that centres also varied in their completeness by client type. Of note, a higher proportion (78.6%) of continuing care cases was reported by treatment centre number 2 than their new and returning cases (62.5%). For the other three centres, the opposite reporting pattern was found.

Table 2 presents the accuracy of the data reported to the NDTRS for each of the selected variables. The accuracy of the data reported to the NDTRS was

Table 1
DISTRIBUTION OF COMPLETENESS ACROSS CLIENT TYPE AND STUDY CENTRE

	CHARACTERISTIC		TOTAL	COMPLETENESS		95% CONFIDENCE INTERVAL	P VALUE*
			n	n	%		
ALL CLIENTS	CLIENT TYPE	New and returning	120	98	81.7	73.8-87.6	
		Continuing	330	178	53.9	48.5-59.2	p < 0.001
		Total	*450*[†]	*276*			
	Study centre 1		111	95	85.6	77.9-90.9	
	Study centre 2		105	80	76.2	67.2-83.3	
	Study centre 3		126	77	61.1	52.4-69.2	
	Study centre 4		110	24	21.8	11.1-30.4	p < 0.0001
	Total		*452*	*276*			
NEW AND RETURNING CLIENTS	Study centre 1		28	26	92.9	77.4-98.0	
	Study centre 2		16	10	62.5	38.6-81.5	
	Study centre 3		44	41	93.2	81.8-97.7	
	Study centre 4		32	21	65.6	48.3-79.6	p < 0.001
	Total		*120*	*98*			
CONTINUING CLIENTS	Study centre 1		83	69	83.1	73.7-89.7	
	Study centre 2		89	70	78.6	65.1-85.9	
	Study centre 3		82	36	43.9	33.7-54.7	
	Study centre 4		76	3	4.0	1.4-11.0	p < 0.0001
	Total		*330*	*178*			

**Chi square tests of difference in completeness across characteristics shown*
[†]2 records had undetermined client type

Table 2
ACCURACY (PREDICTIVE VALUE POSITIVE) OF SELECTED NDTRS VARIABLES

	CHARACTERISTIC	REPORTED (N)	PREDICTIVE POSITIVE VALUE (%)	95% CI
GENDER	Male	162	100.0	97.7-100.0
	Female	111	96.4	91.1-98.6
AGE CATEGORIES	≤ 19	16	100.0	80.1-100.0
	20-24	70	98.6	92.3-99.7
	25-29	89	97.8	92.2-99.4
	30-34	46	97.8	88.7-99.6
	35-39	39	94.9	83.1-98.6
	≥ 40	16	93.8	71.7-98.9
CLIENT TYPE	New or returning	98	95.7	89.6-98.3
	Continuing	178	95.6	91.6-97.8
PREVIOUS TREATMENT	No	37	70.3	54.2-82.5
	Yes	231	97.4	94.5-98.8
MAIN DRUG	Heroin	269	99.6	97.9-99.9
	Other opiate	7	0.0	
ROUTE	Inject	190	97.4	94.0-98.9
	Smoke	76	73.7	62.8-88.8
	Eat/drink	4	0.0	
FREQUENCY	Daily	78	96.2	89.3-98.7
	Less than daily use in last month	11	27.3	9.7-56.6
	No use last month	13	23.1	8.2-50.3
EVER INJECTED STATUS	Yes	225	99.1	96.8-99.8
	No	48	85.4	72.8-92.8

greater than 90% for the variables age, gender, new versus old client status and main problem drug. The data for some important variables had low levels of accuracy. Only 70% of true incidence cases (no previous treatment) were correctly reported. Non-injector status was correctly reported for 85.4% of cases. Less than daily use of the main problem drug was correctly reported for only one-fifth of cases.

DISCUSSION

MAIN FINDINGS

Reporting to the NDTRS in 2001 was incomplete and not representative of the methadone treatment population in the Greater Dublin Area. Benchmarked against the clinical records, most variables reported to the NDTRS were accurate. However some key policy indicators, in particular true incidence and non-injector status, were less accurate.

STRENGTHS AND LIMITATIONS OF THE STUDY

The study sample was extracted from the CTL. Since it is a statutory requirement to notify all clients to be dispensed methadone in Ireland to this list, it is unlikely that the sampling frame was incomplete. In addition, a manual review of clinical records was undertaken to ensure that clients sampled were active in treatment at the study centres in 2001 and therefore required a report to the NDTRS. This approach to measurement of completeness has greater internal validity than the use of incomplete or uncorroborated client lists[12,15]. The extent to which the clinical records represent a gold standard for accuracy is arguable. Since the reporting form may be completed by face-to-face interview, no other reference standard was available. However, the inaccurate variables of concern in this study (true incidence, non-injector and infrequent drug user status) are also important for clinical decision-making in methadone initiation and maintenance. Therefore the clinical records would be expected to approach a gold standard for these variables. These results cannot be generalised outside the Greater Dublin Area (2% of clients dispensed methadone in 2001, personal communication CTL) or to clients not prescribed methadone. Within this population, we confined our study to four clinics, one of which (centre 4) had an extremely low completeness, particularly for continuing clients. While this may have biased the result for overall completeness of the system, further investigation by the NDTRS showed that it reflected reporting practices of centres in that health administrative area (personal communication NDTRS).

COMPARISON WITH OTHER STUDIES

The NDTRS was less complete than UK drug treatment monitoring systems evaluated using similar methods.[11,13,14] However, at the time of these studies, UK systems only required reports of new clients and those returning to treatment after an absence of over six months, whereas the NDTRS required reports on all treated clients. NDTRS completeness for new and returning clients was 81.7% (95% CI 73.8-87.6%) and compared favourably with the UK systems. Subsequent to a review in 1999, the UK drug treatment monitoring system was extended to include reports on clients continuing in treatment from the previous year.[20] Since this extension of reporting requirements, there has not been a published evaluation of the completeness and accuracy of UK drug monitoring systems. A recent paper examining the trends in demand for drug treatment in the South West of England from 1996/7 to 2000/1 reported a rise in the incidence of treatment for drug misuse and unexplained variations in the pattern of reporting over the period.[16] We found incomplete and inaccurate reporting that was not representative of true drug treatment service activity in a system requiring reports on all clients in treatment. This would suggest that changes in reporting practices of treatment providers, subsequent to the extension of reporting requirements, may be contributing to observed variations in the treatment population size and characteristics in the UK. There are no published evaluations of other systems in Europe that have implemented the EMCDDA treatment demand protocol. Such evaluations could improve the quality of this indicator for national and European drugs policy. Estimates of the completeness and accuracy of treatment demand indicators should be provided on a regular basis if valid comparisons between countries and time periods are to be drawn with confidence.

IMPLICATIONS FOR POLICY, PROCEDURES AND PRACTICE

As soon as the results of this analysis became apparent urgent actions were taken by one of us (JL), to improve the completeness and accuracy of the reporting system for data from 2001 onwards. This included a crude comparison of the number of reports to NDTRS in the three area health boards with the number of notifications to the Central Treatment List for 2001, 2002 and 2003. It was noted that returns were incomplete for the majority of clinics in the three area health boards of the Greater Dublin area. The staff of the NDTRS presented summary findings to and negotiated solutions with

the management teams of these health boards. By June 2004 all health boards had submitted complete data. NDTRS staff agreed that they would revise the methods used to collect the number of clients continuing in care from the previous year from 2004 onwards. Each health board would send the total number of clients in treatment on January 1st each year to the staff of the NDTRS and a form would be completed for each client new to or returning to treatment that year. It was also agreed that the Addiction Service's performance indicators would be included in the NDTRS and that data would be collected on clients reporting alcohol as their main problem drug. This complies fully with the EMCDDA requirements for implementation of the treatment demand indicator. This demonstrates that when research institutions present facts and identify barriers to compliance to service managers, solutions can be found and the completeness, accuracy and usefulness of reporting systems can be improved.

ACKNOWLEDGEMENTS

We wish to thank Dr Hamish Sinclair and Ms Fionnola Kelly at the Drug Misuse Research Division of the Health Research Board, Dr Eamon Keenan at the Drug Treatment Centre Board, Ms Fionnuala Rafferty at the Central Treatment List, the Area Operations Managers of each of the area health boards included in the study, the General Manager of the Drug Treatment Centre Board and the staff at the study centres for their support and assistance in undertaking this study.

REFERENCES

1. Rychetnik L, Hawe P, Waters E, Barrat A, Frommer M. A glossary for evidence based public health. *J Epidemiol Community Health* 2004; 58:538-545.
2. Heller RF, Page J. A population perspective to evidence based medicine: "evidence for population health". *J Epidemiol Community Health* 2002; 56:45-47.
3. Brownson RC, Baker EA, Leet TL, Gillespie KN. Evidence-based public health. Oxford, New York: Oxford University Press, 2003.
4. Government of Ireland: Department of Tourism, Sport and Recreation. Building on experience: national drug strategy 2001-2008. Dublin: The Stationary Office, 2001.
5. Kraus L, Augustin R, Frischer M, Kummler P, Uhl A, Weissing L. Estimating the prevalence of problem drug use at a national level in countries of the European Union and Norway. *Addiction* 2003; 98:471-85.
6. Hartnoll R. Drug treatment reporting systems and the first Treatment Demand Indicator. Definitive Protocol. Strasbourg: Council of Europe Press, 1994.
7. European Monitoring Centre for Drugs and Drug Addiction. EMCDDA Scientific Report: Treatment demand indicator standard protocol 2.0. Lisbon: EMCDDA, 2000.
8. Drug Misuse Research Division HRB. Occasional Paper No. 8/2002: trends in treated drug misuse in the Eastern Health Board area 1996-1999. Dublin: Health Research Board, 2002.
9. The Council of the European Union. EU Drugs Strategy, 2005-2012 - Cordrogue 77. Brussles: General Secretariat, 2004.
10. Sutton M, Maynard M. Are drug policies based on fake statistics? *Addiction* 1993; 88:455-458.
11. Crabbe T, Donmall M, Millar T. Validation of the University of Manchester Drug Misuse Database. *J Epidemiol Community Health* 1999; 53:159-164.
12. Frischer M, Norwood J, Heatlie H, *et al* A comparison of trends in problematic drug misuse from two reporting systems. *J Public Health Med* 2000; 22:362-367.
13. Hickman M, Sutcliffe H, Sondhi A, Stimson G. Validation of a regional drug misuse; implications for policy and surveillance of problem drug use in the UK. *Br Med J* 1997; 315:581.
14. Hickman M, Sutcliffe H, Sondhi A, Stimson G. Surveillance of problem drug use in the UK; a review of a regional drug misuse database. *J Public Health Med* 1999; 21(271-277).
15. Mott J, Caddle D, Donmall M. A comparison of doctors' practice in notifying addicts to the Home Office and reporting them to the North Western Dug Misuse Database. *Addiction* 1993; 88:249-256.
16. Wilkinson S, Soteriou T, Gray S, Orme J, Myles J. Artefact or reality? Increases in persons notified to the Regional Drug Misuse Database in the South West of England, 1996-2001. *J Public Health* 2004; 26:3-5.
17. Centre for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems: recommendations from the guidelines working group. *MMWR Recomm Rep* 2001; 50 (no. RR-13):1-29.
18. JMP [program]. Version 4.0.4. version: SAS Institute Incorporated, 1989-2001.
19. STATA [program]. Version 7 version: STATA Corporation, 1984-2001.
20. Department of Health. Statistics from the Regional Drug Misuse Databases on drug users in treatment in England, 2000/01. London: Department of Health, 2001.

Correspondence to: Paul Kavanagh,
Health Protection Surveillance Centre,
25-27 Middle Gardiner Street, Dublin 1.
E-mail: paul.kavanagh@mailx.hse.ie

ORIGINAL PAPER

Coracoid Impingement Syndrome: A treatable cause of anterior shoulder pain

SJ Roche, MT Kennedy, AJ Butt, K Kaar

Dept of Orthopaedic Surgery, Merlin Park Regional Hospital, Galway

ABSTRACT

Background Coracoid Impingement Syndrome is a relatively uncommon but generally treatable cause of anterior shoulder pain that can be easily overlooked. It typically presents with anterior shoulder joint pain in activities involving forward flexion, adduction and internal rotation.

Aims To assess the outcome of a cohort of patients diagnosed with Coracoid Impingement Syndrome.

Methods Patients were investigated clinically and radiologically. They received appropriate therapeutic measures and were followed-up in an orthopaedic outpatient setting.

Results Twelve patients were identified over a four-year period. All patients have made good progress. Thus far, none have needed operative intervention for symptom relief.

Conclusion Coracoid impingement syndrome is an uncommon cause of anterior shoulder pain but diagnosed patients can expect good symptomatic relief following referral to a dedicated shoulder unit. An increase in clinical awareness of the condition may prevent undue diagnostic delay in such cases.

INTRODUCTION

Anterior shoulder pain can be particularly difficult to diagnose. The differential diagnosis includes impingement syndromes, rotator cuff injury and shoulder instability. Overlap between diagnoses can be present in certain cases leading to complex clinical findings. This can lead to diagnostic delay and therefore prolonged symptomatology. Many clinical shoulder tests have been documented but these sometimes prove difficult to interpret if the examiner does not routinely treat advanced shoulder problems.

Coracoid Impingement Syndrome is a relatively uncommon but treatable cause of shoulder pain. It usually presents with anterior shoulder discomfort in activities involving forward flexion, adduction and internal rotation. A literature review identifies three main causes of the condition: idiopathic, traumatic and iatrogenic.[3] The condition is usually very difficult to diagnose due to the paucity of consistently reproducible clinical signs. This syndrome is sparsely documented but has been shown to be treatable with both conservative and operative measures. The coracoid impingement test is presently the best diagnostic indicator of the condition.[1] We found that patients with a positive coracoid impingement test often reported that their pain was also aggravated by a shoulder position of abduction and internal rotation. In this case series we have demonstrated that diagnosed patients can expect good symptom relief from appropriate therapeutic regimens. An increased clinical awareness of this condition may obviate undue diagnostic delay in otherwise unresolved cases of chronic anterior shoulder pain.

MATERIAL AND METHODS

A prospective review of patients presenting with anterior shoulder pain to a regional orthopaedic shoulder service was carried out. Each individual was assessed both clinically and radiologically in an outpatient clinic setting by a single consultant orthopaedic surgeon.

Radiographic views comprised antero-posterior views in internal and external rotation of the shoulder in addition to axillary lateral views. In all cases these revealed no obvious radiological abnormality. Although magnetic resonance imaging and shoulder arthrography may prove helpful in diagnosing certain cases of anterior shoulder pain, we employed the former as a baseline investigation whenever other diagnoses were strongly suspected.

Tenderness was present in the antero-medial shoulder over the coracoid process in all patients Neurological function was normal and muscle power was MRC grade 5 in the affected limbs. Other causes of shoulder pain were excluded. Subacromial

impingement syndromes, rotator cuff pathology, biceps disorders, labral lesions and radiculopathy were out-ruled as the primary cause of each patient's symptoms. Specific impingement tests were undertaken including Yergason's and Speed's tests and all proved to be negative. The entire cohort had a positive coracoid impingement test on the side of the affected shoulder.

All cases were initiated on a treatment ladder that progressed in a stepwise fashion from activity modification and further courses of non-steroidal anti-inflammatory drugs with physiotherapy, to infiltration of the coraco-humeral interval with a lignocaine/hydrocortisone solution. The same consultant surgeon reassessed each patient at subsequent clinic visits. The duration of follow-up was largely determined by the response to treatment. The results were recorded in a computerised database enabling detailed analysis *(Microsoft® Access, Microsoft Corporation)*.

RESULTS

The duration of the study was a four-year period (1999 to 2003). Twelve patients in total were identified as having coracoid impingement syndrome. The study group comprised eight men and four women. The average age was 44.3 years (range 26 to 54 years). The average duration of patient follow-up was 14.4 months (range 3 to 35months).

The mean duration of shoulder symptoms, namely point tenderness of the coracoid and anterior shoulder pain or discomfort, was 8.9 months (range 1 to 25 months; standard deviation 6.33months). Two thirds of the cases involved the dominant side (Table 1).

Six of the cases were of idiopathic origin and six were associated with trauma of varying aetiology. The traumatic cases comprised a fall down stairs, a fall from a stepladder, two road traffic accidents, an old lifting injury and a case of presumed repeated micro-trauma to the shoulder joint secondary to strenuous gym activity. There were no incidences of iatrogenic causation. None involved major trauma (i.e. there were no associated fractures of the shoulder girdle or upper limb). All cases involved anterior shoulder pain of a chronic nature. Every patient experienced activity related symptomatology. The age distribution of the patients was slightly different to other published series[2,6] in that there was preponderance towards individuals over 50 years of age (42%).

Only one patient had definite signs of concurrent shoulder pathology. This 54-year-old male was diagnosed with coracoid impingement syndrome in addition to evidence, of rotator cuff degeneration as confirmed by clinical findings and magnetic resonance imaging. This patient responded well to treatment with a subcoracoid nonsteroidal anti-inflammatory injection in addition to rotator cuff strengthening physiotherapy.

The entire study group was evaluated with plain films. The diagnostic yield was poor as no cases of the ailment could be confirmed based on these findings. In one instance, the plain films showed an aberrant coracoid morphology but no definite coraco-humeral narrowing. Five patients were further assessed with magnetic resonance imaging and this measure served mainly to exclude concurrent shoulder pathology i.e. rotator cuff lesions and other bony abnormalities. None of these cases showed conclusive evidence of abnormal spatial relationships between the position of the coracoid process in relation to either the humeral head or glenoid. One set of MRI films suggested a reduced coraco-humeral interval while another showed evidence of rotator cuff degeneration.

All patients were tender in the region overlying the coracoid process. All cases were positive for the coracoid impingement test. Pain and discomfort was elicited to a varying degree when the shoulder was placed in a position of cross arm adduction, forward elevation and internal rotation.

It was also noted that discomfort was evoked in extremes of shoulder abduction and internal rotation. Five of the patients were able to voluntarily identify this position as a source of discomfort and described situations such as depressing the door lock button in their cars as being painful. The arm is in a position of ninety degrees of abduction and maximal internal rotation during this manoeuvre.

All cases were given trial courses of non-steroidal anti-inflammatory medication. Most cases had already been trialled previously with anti-inflammatories by their primary healthcare providers. One patient responded well to activity modification and physiotherapy alone. The remainder had symptomatic relief following an injection of local anaesthetic and steroid solution into the subcoracoid region. Seven have had complete resolution of normal shoulder function

ORIGINAL PAPER

Table 1
PATIENT DETAILS

GENDER	AGE	CAUSE	TREATMENT	SYMPTOM DURATION (MONTHS)	FOLLOW-UP (MONTHS)	DOMINANT HAND AFFECTED	SYMPTOMS		OBJECTIVE TESTS		MRI CARRIED OUT
							Functional Pain in Abduction/ Internal Rotation	Functional Pain in Forward Flexion/ Internal Rotation	Coracoid Impingement Test +ve	Pain on Abduction/ Internal Rotation	
M	26	Idiopathic	Injection	12	9	No	No	Yes	Yes	Yes	
M	54	Trauma	Injection	9	12	No	No	Yes	Yes	Yes	Yes
M	54	Idiopathic	Injection	1	21	Yes	No	Yes	Yes	Yes	Yes
M	30	Idiopathic	Injection	5	3	Yes	No	Yes	Yes	Yes	Yes
F	48	Microtrauma	Injection	13	12	Yes	Yes	Yes	Yes	Yes	
M	30	Trauma	Injection	3	12	Yes	No	Yes	Yes	Yes	
F	54	Trauma	Injection	8	17	No	No	No	Yes	Yes	Yes
M	53	Idiopathic	Injection	25	7	Yes	Yes	No	Yes	Yes	
M	40	Idiopathic	Injection	6	35	Yes	No	Yes	Yes	Yes	Yes
F	41	Idiopathic	Physio/analgesia	9	7	Yes	Yes	No	Yes	Yes	
M	53	Trauma	Injection	4	27	No	Yes	No	Yes	Yes	
F	48	Trauma	Physio/analgesia	12	11	Yes	Yes	Yes	Yes	Yes	

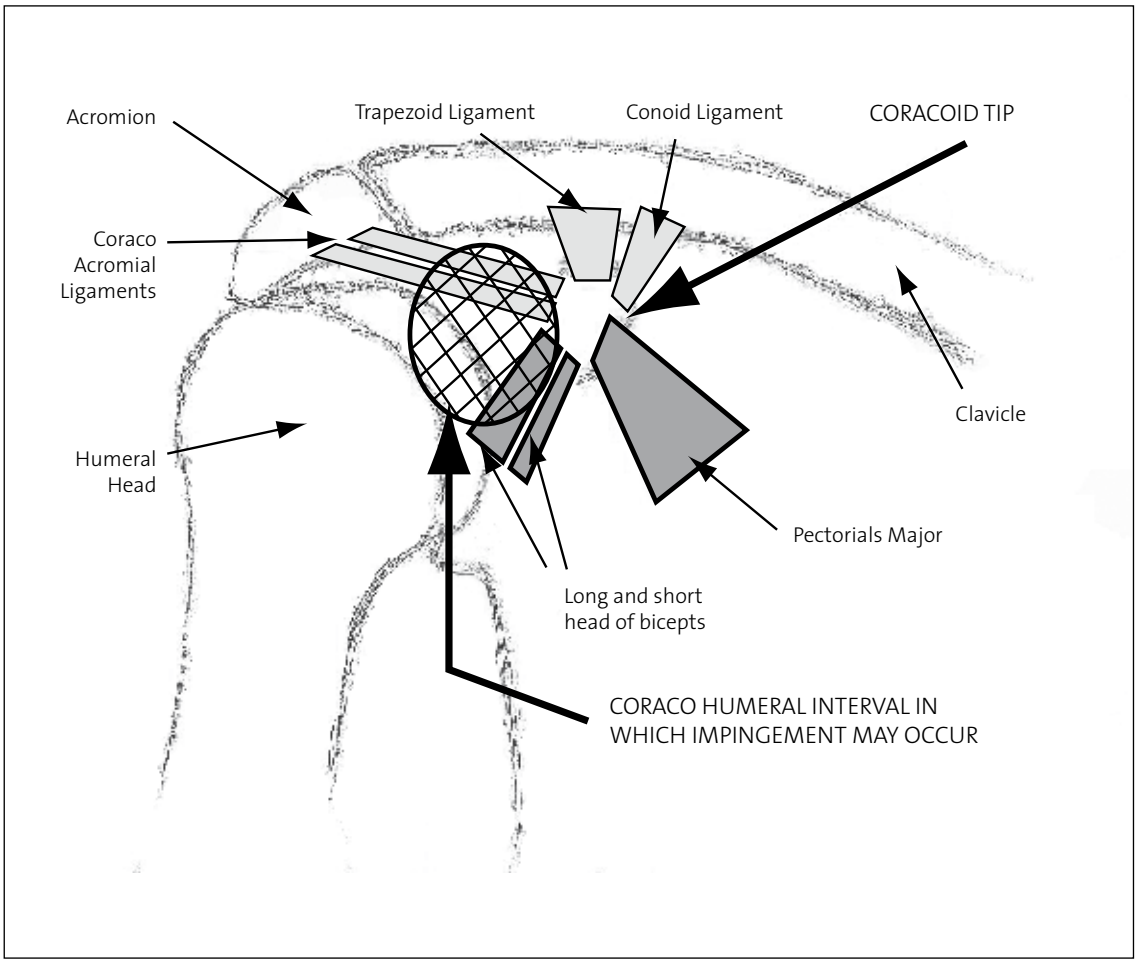


Figure 1— ANTERIOR VIEW OF THE SHOULDER JOINT DEMONSTRATING THE CORACOID PROCESS AND SURROUNDING STRUCTURES

following intra-articular injection. The remainder obtained temporary relief of varying durations and are being actively reviewed on an outpatient basis with further physiotherapy. Nobody in the series has undergone a coracoplasty but this may be necessary if symptoms persist on present treatment regimens.

DISCUSSION

Although coracoid impingement is an acknowledged cause of chronic shoulder pain since 1909,[4] it may still go unrecognised when evaluating affected patients. The classical presentation is chronic anterior shoulder pain with marked tenderness to palpation over the coracoid.[1] The condition is precipitated by idiopathic, traumatic and iatrogenic causes.[3] Any process which diminishes the coracohumeral interval can lead to significant impingement.[1]

Many studies have attempted to definitively outline the pathogenesis of this condition. It is thought that impingement of the rotator cuff between the lesser tuberosity of the humeral head and the lateral aspect of the coracoid leads to shoulder pain.[9] Spatial relationships between the coracoid tip and surrounding bony structures have been analysed with both radiographic and cadaveric studies.[6, 10] Rotator cuff outlet morphology has also been assessed in affected patients.[6]

Gerber et al[3] were first to assess the significance of the coracohumeral interval (Figure 1). Dines et al[1] later showed that coracohumeral decompression by excision of the lateral 1.5cm of the coracoid and re-attachment of the conjoint tendon lead to reproducible relief of symptoms. Friedman et al[2] were the first to note degeneration of the subscapularis tendon in affected patients. This degeneration of the subcoracoid soft tissue was interpreted as the result of mechanical bony irritation and thus the morphologic pathological correlative for the coracoid impingement syndrome.

A recent cadaveric study suggests that anatomic variations of the coracoid are not the main cause of the pathology in this condition.[10] It suggests that the problem is functional with anterior instability leading to a functional narrowing of the coracohumeral distance.

As has been stated in the literature, the diagnosis of coracoid impingement syndrome can be made most reliably on clinical findings.[3] Radiological findings can help but no single radiological test can guarantee the diagnosis. MRI has been shown to be the most useful imaging modality as it can assess both the subcoracoid space and the coracohumeral distance.[2, 8] Shoulder arthrography can also be used to out-rule other diagnoses. The clinical test presently regarded as the gold standard is the coracoid impingement test.[1] It describes painful clicking in a position of forward flexion and medial rotation of the shoulder in varying degrees of horizontal adduction. As has been demonstrated in cadaveric studies and MRI findings, internal rotation reduces the coracohumeral distance, thus leading to soft tissue subcoracoid impingement.[2, 10] The subscapularis is the tendon most likely to be involved. Forward flexion with internal rotation is a functional position of the shoulder and will readily be identified as a provocative position even before the test is carried out in most patients.

Coracoid impingement is generally treatable once identified. The usual treatment regime involves a stepwise process encompassing both conservative measures as a first line preference before proceeding to operative intervention in a minority of cases. It is important to remember that a possible overlap with other shoulder pathology may occur even in cases that respond to conventional therapeutic measures for this unusual condition. Most patients, as was seen in this series, will benefit from avoidance of the painful shoulder position, physiotherapy, anti-inflammatories and injections of local anaesthetic into the affected subcoracoid area. Various surgical procedures are documented and have proven successful in those not benefiting from other treatment modalities.[1, 6] In addition to open surgical decompression of the coracohumeral space with limited coracoplasty, arthroscopic treatment has also been shown to be effective.[5, 7] Assuming that no other significant cause of shoulder pain in present, patients can expect effective relief from symptoms without compromising shoulder function in the long-term. This can be postulated from analysis of follow-up data in this unit and other published series.[1, 6]

CONCLUSION

Coracoid impingement syndrome is a relatively rare but well-defined clinical diagnosis that is worthy of consideration in the differential diagnosis of anterior shoulder pain. Further investigation is required to conclusively delineate its pathogenesis. This case series demonstrates the effectiveness of present treatment options once the diagnosis has been established. Clinical detection of the condition

is not unduly difficult when given appropriate consideration by the clinician. A heightened clinical awareness can help avoid undue diagnostic delay in cases where the condition is the primary cause of unresolved anterior shoulder pain.

REFERENCES

1. Dines DM, Warren RF, Inglis AE, Pavlov H. The coracoid impingement syndrome. *J Bone Joint Surg Br* 1990;72(2):314-6.
2. Friedman RJ, Bonutti PM, Genez B. Cine magnetic resonance imaging of the subcoracoid region. *Orthopedics* 1998;21(5):545-8.
3. Gerber C, Terrier F, Ganz R. The role of the coracoid process in the chronic impingement syndrome. *J Bone Joint Surg Br* 1985;67(5):703-8.
4. Goldthwait JE. An anatomic and mechanical study of the shoulderjoint, explaining many of the cases of painful shoulder, many of the recurrent dislocations and many of the cases of brachial neuralgia or neuritis. *Am.J.Orthop*. 1909;6(4),579-606.
5. Karnaugh RD, Sperling JW, Warren RF. Arthroscopic treatment of coracoid impingement. *Arthroscopy* 2001;17(7):784-7.
6. Kragh JF, Jr., Doukas WC, Basamania CJ. Primary coracoid impingement syndrome. *Am J Orthop* 2004;33(5):229-32.
7. Lo IK, Burkhart SS. Arthroscopic coracoplasty through the rotator interval. *Arthroscopy* 2003;19(6):667-71.
8. Masala S, Fanucci E, Maiotti M, *et al* [Impingement syndrome of the shoulder. Clinical data and radiologic findings]. *Radiol Med (Torino*.1995;89(1-2):18-21.
9. Paulson MM, Watnik NF, Dines DM. Coracoid impingement syndrome, rotator interval reconstruction, and biceps tenodesis in the overhead athlete. *Orthop Clin North Am* 2001;32(3):485-93, ix.
10. Radas CB, Pieper HG. The coracoid impingement of the subscapularis tendon: a cadaver study. *J Shoulder Elbow Surg* 2004;13(2):154-9.

Correspondence to :Simon Roche, 50 Carrigeen, Knocknacarra, Galway. Tel: 00353 87 9180248
E-mail: sroche1975@yahoo.co.uk

Nicorandil related anal ulcer

Z Al-Hilli, R Pritchard, G Roche-Nagle, J Deasy, D A McNamara

Dept of Colorectal Surgery, Beaumont Hospital, Dublin 9

ABSTRACT

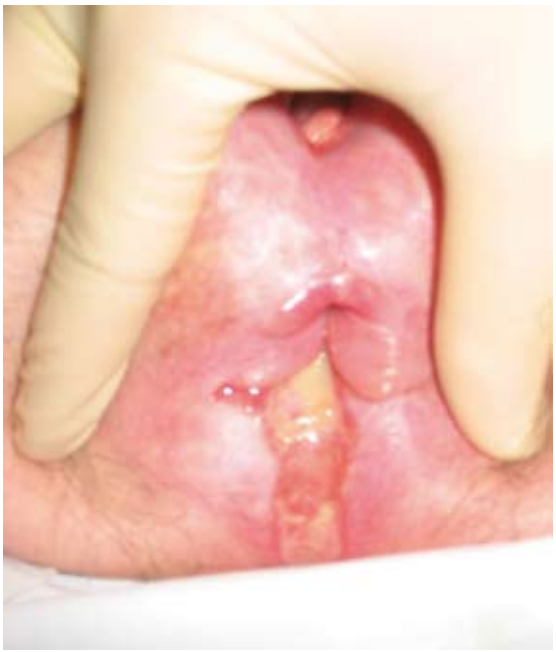
Background Anal ulceration is uncommon. Patients are typically referred because of severe anal pain, bleeding, discharge, and ulceration. It is important to exclude anal carcinoma, and to consider more unusual causes.

Methods A 74-year-old lady presented with severe anal pain and ulceration. This was subsequently noted to be related to nicorandil, a potassium channel activator used in the treatment of angina. Discontinuation of nicorandil and faecal diversion allowed symptom relief and ulcer healing.

Conclusion Knowledge of the association between nicorandil and anal ulceration is essential in order to appropriately diagnose and manage this condition.

CASE REPORT

A 74-year-old lady presented with a four-month history of constant severe perianal pain, constipation, bright red PR bleeding, and anal discharge. She had a history of ischaemic heart disease and hypertension. She was on several cardiac medications including aspirin, clopidogrel, amlodipine, doxazosin, lisinopril, and nicorandil. On perianal examination a well-circumscribed 3x4 cm posterior anal ulcer was noted. This was a deep 'punched out' ulcer with slough, and visible fibres of the internal anal sphincter in its base (photo 1). The surrounding skin was normal, and the ulcer was remote from pressure points. EUA and ulcer biopsy was performed. Histology revealed fibroadipose tissue with fibrosis and chronic inflammation, but no evidence of granulomata or malignancy. Stains for *Mycobacterium tuberculosis* and *Treponema pallidum* were negative. Colonoscopy and small bowel follow through were normal. Despite treatment with oral laxatives and regular dressings, her severe pain persisted with no evidence of ulcer healing. Defunctioning loop colostomy was performed to address her debilitating anal pain.



Around this time the authors became aware of nicorandil induced anal ulceration,[1] the macroscopic and microscopic features of which are similar to those described in our patient. On this basis nicorandil was discontinued. The combination of faecal diversion and discontinuation of nicorandil resulted in progressive ulcer healing.

DISCUSSION

Nicorandil is an oral potassium channel activator with a nitrate component, used as a third line adjunct in the treatment of resistant angina. The potassium activation dilates coronary and systemic arteries, while its nitrate component dilates venous capacitance vessels, thereby reducing both preload and afterload. However, it has been hypothesized that this drug results in a vascular steal phenomenon leading to redistribution of blood at vulnerable sites.[2]

Nicorandil associated anal ulceration was first reported in 2002.[3] Our patient commenced nicorandil 10mg twice daily four years prior to developing anal ulceration, and her dose was increased to the maximal dose of 40mg twice daily ten months before presentation with the ulcer. All reported cases have ulcer morphology similar to that seen in our patient, specifically a deep 'punched out' ulcer with well-circumscribed

edges. Our patient also had severe debilitating pain in common with other reported cases. Histology of this ulcer revealed inflamed epithelium with no evidence of granulation tissue or malignancy and gastrointestinal visualization failed to show other abnormalities. Histological and serological tests for other causes of anal ulceration, namely neoplastic, inflammatory (Crohn's disease and Behcet's disease), and infective causes (tuberculosis, syphilis, and HIV) were negative. Schistosomiasis and amebiasis were both excluded on the basis of a negative travel history. Analgesics, laxatives, and local debridement were unsuccessful in either healing the ulcer or relieving the pain, so a loop colostomy was fashioned prior to noting the association between nicorandil and anal ulcerations. This has resulted in complete pain relief and re-epithelialisation of the ulcer. Future cases might best be managed by discontinuation of the medication with cardiology input, reserving surgery for resistant cases only.

CONCLUSION

Anal ulceration is a debilitating condition that patients may be reluctant to discuss with their cardiologist, and they are frequently referred to another specialist. Increased awareness of the potential link between nicorandil and anal ulceration may lead to more timely, and less aggressive management, by early modification of anti-anginal treatment.

REFERENCES

1. Katory M, Davies V, Kelty C et al. Nicorandil and idiopathic anal ulceration. *Dis Colon Rectum* 2005;48:1442-6
2. http://www.medicines.ie/emc/assets/c/html/DisplayDoc.asp?DocumentId=2863 accessed 23 November 2005
3. Watson A, Al-Ozairi O, Fraser A, Loudon M, O'Kelly T. Nicorandil associated anal ulceration. *Lancet* 2002;360:536-7
4. Watson A, Suttie S, Fraser A, O'Kelly T, Loudon M. Nicorandil associated anal ulceration. *Colorect Dis* 2004;6:330-1
5. Passeron T, Lacour JP, Mantoux F, Fabiani P, Dubois D, Ortonne JP. Chronic anal ulceration due to nicorandil. *Br J Dermatol* 2004;150:394-6
6. Vella M, Molloy RG. Nicorandil-associated anal ulceration. *Lancet* 2002;360:1979
7. Cooke NS, Tolland JP, Dolan OM. Nicorandil-associated perianal ulceration: a case series of 10 patients. *Br J Dermatol* 2004;154:199-200
8. Renwik A, Chong D, McMahon A. Chronic non-healing anal ulceration and nicorandil: further evidence of an emerging problem. *ANZ Journal of Surgery* 2004;74:1128-1129

Correspondence to: Ms. D. McNamara, Consultant General and Colorectal Surgeon, Suite 18, Beaumont Private Clinic, Beaumont Hospital, Dublin 9
Tel:01-8574885; Fax:01-8574885
Email:d_mcnamara@eircom.net

Taxane-resistant lymphoepithelial-like carcinoma: Excellent response to VIP chemotherapy

AG Duffy, G Wyse, AM Horgan, M O'Keefe, S O'Reilly, OS Breathnach

Dept of Medical Oncology, Mercy University Hospital, Cork

ABSTRACT

Background Lymphoepithelial-like carcinoma is a rare tumour type. The optimal treatment for this disease is not known. No effective therapies are described in the literature.

Aims This report describes a case of lymphoepithelial-like carcinoma and documents a therapeutic strategy which has proved effective.

Results The patient was initially treated with a common platinum-based chemotherapy regimen incorporating a taxane (Carbplatin and Docetaxel). Disease stabilization initially occurred but the patient soon progressed. The patient was then treated with VIP chemotherapy and had a complete response.

Conclusion VIP chemotherapy appears to be an effective therapeutic strategy in lymphoepithelial-like carcinoma.

CASE REPORT

A 29-year-old man presented with a month-long history of left-sided groin discomfort. He was unable to straighten his left leg and had to stoop on walking. He had no 'B' symptoms. Physical examination revealed non-bulky right inguinal lymphadenopathy and fullness in the left flank. Testicular examination was normal. Haematological and biochemical parameters were normal. AFP and bHCG were normal.

Computed tomography (CT) showed invasion of the left psoas muscle and extensive intra-abdominal adenopathy involving the inguinal, iliac, para-vertebral, pre-vertebral and mesenteric nodes (Figure 1a). There was also left-sided hydronephrosis and hydroureter identified. Positron emission tomography (PET) showed areas of increased uptake of fluorodeoxyglucose (FDG) in the abnormal areas identified on CT (Figure 2a). There were no additional areas of increased tracer uptake identified. Excisional biopsy of the right inguinal node showed lymphoepithelial – like carcinoma.

The patient was commenced on Docetaxel and Carboplatin chemotherapy. After two cycles of therapy, the patient underwent repeat CT scanning. This showed stable disease when compared to his baseline scan. His symptoms, which had initially improved, recurred and he once more complained of back pain on straight leg raising and his posture became stooped. It was decided to alter his chemotherapy and he was commenced on Etoposide, Cisplatin and Ifosphamide (VIP). The patient's symptoms improved dramatically after cycle 1 chemotherapy. After three cycles of VIP, a restaging CT scan was performed (Figure 1b). This demonstrated resolution of the extensive lymphadenopathy previously identified and disappearance of the hydronephrosis. The only abnormality was some residual asymmetry of the ileopsoas musculature. At this point, the patient reported tinnitus affecting his right ear. Audiometry showed a mild high frequency hearing deficit. For the remaining treatment course, carboplatin was interchanged with cisplatin. The patient received six cycles of VIP chemotherapy in total. At the end of treatment, a repeat CT scan showed persistence of asymmetry in the ileopsoas region with no other abnormality. A PET scan was performed which showed no evidence of active disease (Figure 2b). In view of his excellent response to treatment, the patient was referred for consolidation radiotherapy to the paraaortic, psoas, iliac, inguinal, and upper femoral nodal areas and he received 45 Gy in 25 fractions (left dog-leg distribution).

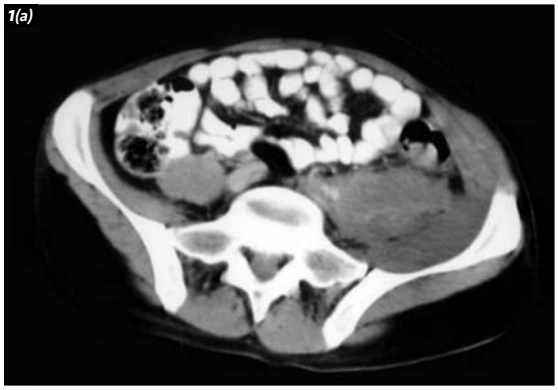
Lymphoepithelial-like carcinoma is a rare tumour type which has been described in multiple sites including uterine cervix, lung, stomach, skin and salivary glands.[2-4] Its aetiology is unknown, however EBV-encoded RNA transript has been detected in the lymphoepithelial-like genome of tumour cells from various primary sites.[1] It is possible therefore that Epstein-Barr virus is involved in tumorigenesis. There is scant information in the literature regarding

prognosis and the natural biology of the disease. In an attempt to provide the most effective therapy, we conducted an extensive literature search of searchable databases. However we were unable to find any case series or even any reference to therapeutic regimens. We commenced the patient on a Taxane/ Platinum combination as this is a well-tolerated regimen and effective against a broad range of cancer types. Though the patient had an initial clinical response, he quickly relapsed and VIP chemotherapy was commenced. The rationale behind this choice was that it is an effective regimen in the treatment of germ cell tumours and sarcomas. The patient responded very well to this regimen with resolution of his symptoms and normalisation of his PET scan. The use of consolidation external beam radiotherapy is not supported by any evidence based medicine and was employed here empirically. On last review, eighteen months after completion of treatment the patient remains in remission.

REFERENCES

1. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelial-like carcinomas. *Am J Clin Pathol* 1995; 103:308-315
2. Tseng TJ, Pao CC, Tseng LH, et al. Lymphoepithelial-like carcinoma of the uterinr cervix: association with Epstein-Barr virus and human papillomavirus. *Cancer* 1997;80:91-97.
3. Chen FF, Yan JJ, Lai WW, Jin YT, Su IJ. Epstein-Barr virus associated non-small lung carcinoma: undifferentiated 'lymphoepithelial-like' carcinoma as a distinct entity with better prognosis. *Cancer* 1998;82:2334-2342.
4. Lind AC, Breer WA, Wick MR. Lymphoepithelial-like carcinoma of the skin with apparent origin in the epidermis – a pattern or an entity? A case report. *Cancer* 1999;85:884-890.

Correspondence to:
Austin Duffy, email:austinduffy@hotmail.com



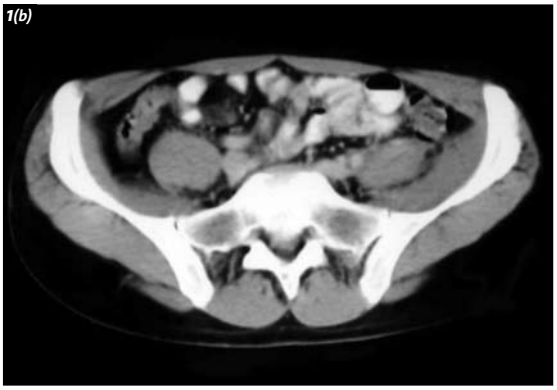
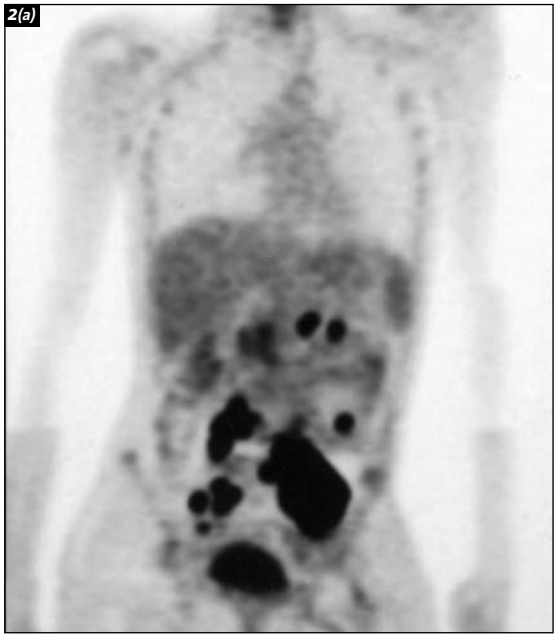


Figure 1a—CT SHOWED INVASION OF THE LEFT PSOAS MUSCLE

Figure 1b—AFTER 3 CYCLES OF VIP, A RESTAGING CT SCAN WAS PERFORMED



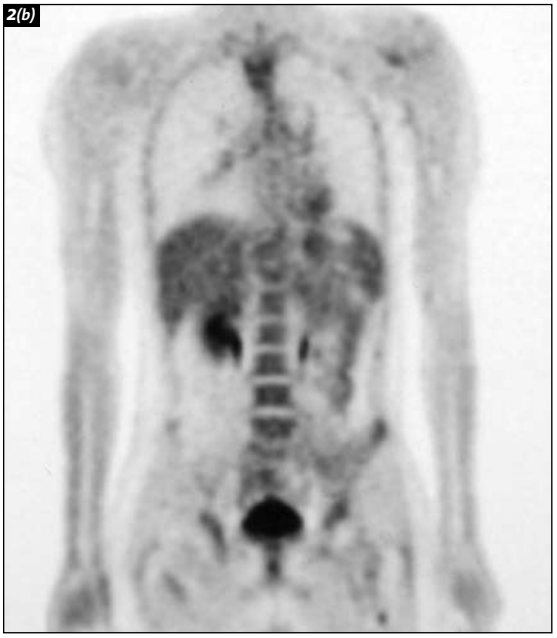


Figure 2a—PET SHOWED AREAS OF INCREASED UPTAKE OF FDG

Figure 2b—A PET SCAN SHOWED NO EVIDENCE OF ACTIVE DISEASE

Collecting Duct Carcinoma of the kidney: A case report with variable immunohistochemistry

ABSTRACT

Background Collecting duct carcinoma of the kidney is a rare tumour with distinctive clinical and histopathological features. Management of this malignancy remains a challenge because of advanced stage at presentation and aggressive clinical course.

Aims We describe a case of Collecting Duct Carcinoma with variable immunohistochemistry and review the pathology and management.

Results Our patient died shortly after commencing systemic chemotherapy.

Conclusion Advances in immunohistochemistry have aided in diagnosis of this tumour. Early detection and nephrectomy offer the best chance of cure. Newer chemotherapeutic regimens may improve survival in more advanced disease.

RM Connolly, P Downey, JA McCaffrey

Depts of Medical Oncology and Histopathology, Mater Misericordiae Hospital, Dublin, Ireland

INTRODUCTION

Bellini Duct carcinoma, or Collecting Duct carcinoma (CDC), is a rare and aggressive tumour believed to arise from the distal collecting ducts of the nephron.[1] It has been classified as a variant of renal cell carcinoma by the WHO.[2] It has distinctive clinical and histopathological features, and there have been approximately 100 case reports in the English literature since it was first reported in 1976.[3]

CASE REPORT

A 61-year old man complained of a short history of back pain and fatigue. He had no relevant past medical history. No signs were evident on clinical examination. An irregular 3.5cm cystic lesion was seen on CT in the lower pole of the left kidney, with stranding of adjacent fat (Figure 1). MRI lumbar spine demonstrated a large L4 metastatic deposit with extension into the spinal canal. (Figure 2) PET scan revealed multiple bony metastases only. A biopsy of L4 revealed metastatic adenocarcinoma. Immunohistochemistry was strongly positive for CK 20. CK 7 and CAM5 were negative. Renal biopsy reported an infiltrating adenocarcinoma in a desmoplastic stroma positive for low molecular weight cytokeratins, with perineural invasion (Figure 3). These tumour cells stained strongly CK7 positive (Figure 5) and there was focal restaining of CK20 (Figure 4). Despite the variation in immunohistochemistry findings, a diagnosis of Collecting Duct Tumour of the kidney with vertebral metastases was made. In January 2005, chemotherapy was commenced. After his second cycle he became profoundly neutropaenic and was treated for MRSA septicaemia. He succumbed to this over a short time.

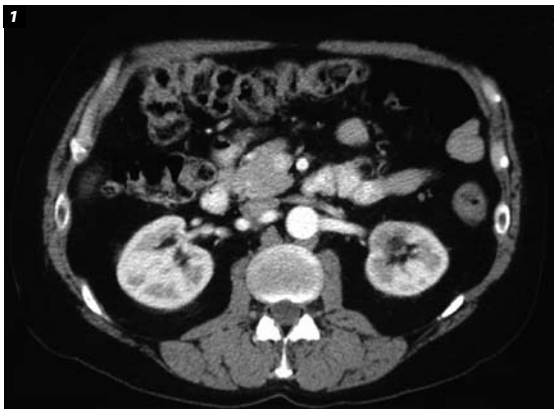
DISCUSSION

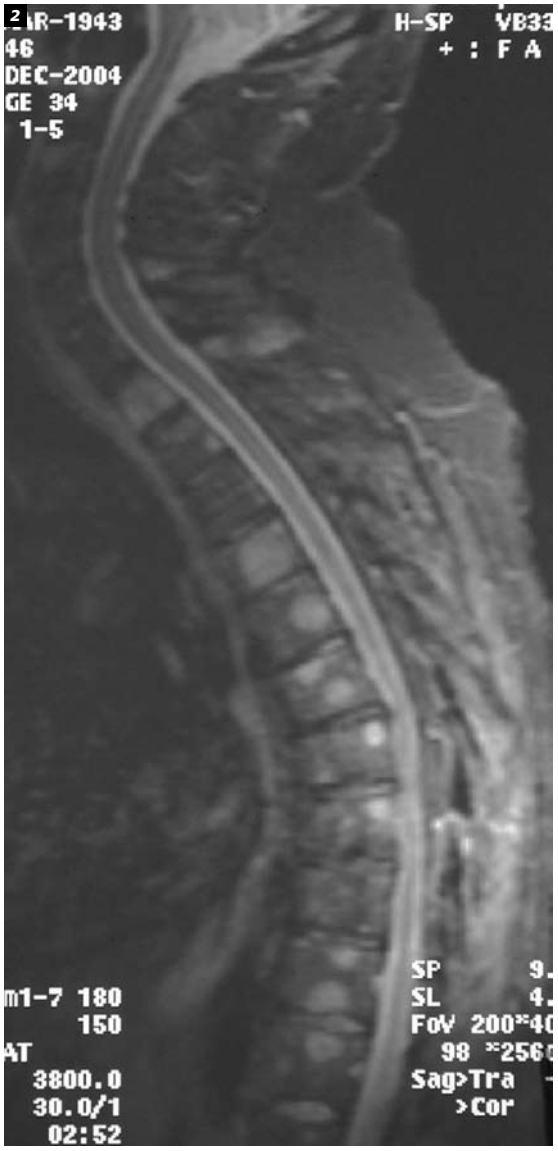
Renal carcinoma accounts for 3% of all adult malignancies, 0.4-2% of which are Collecting Duct Carcinoma.[1] It affects a young population, the mean age at presentation being 55 years.

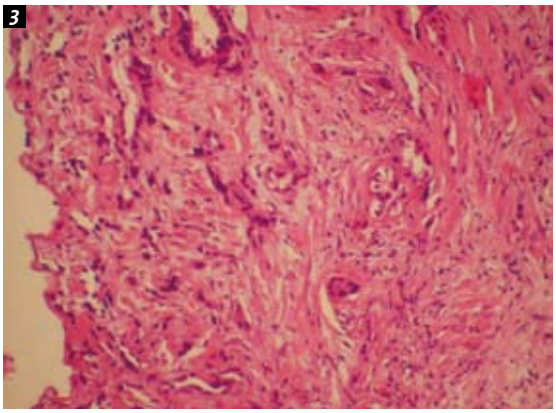
The majority of patients with CDC will present with stage IV disease, one series reporting a figure of 83%.[4] It is associated with a higher incidence of regional node involvement (50%), distant metastases (67%) and capsular invasion (83%) than other forms of renal neoplasm. Median survival after nephrectomy is 22 months.[5]

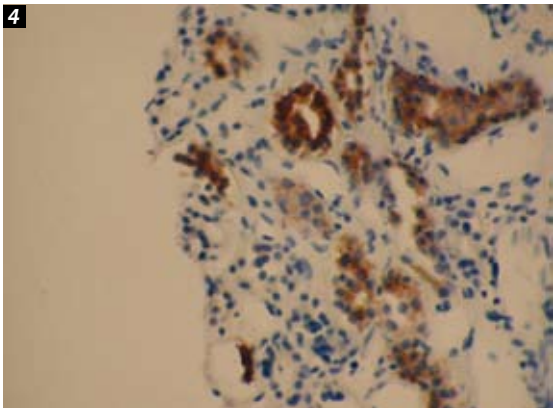
The diagnosis of CDC should be considered in those with a rapidly progressive cancer, or a large invasive renal tumour on CT imaging. A biopsy should be performed to distinguish it from other renal neoplasms as the prognosis is dismal despite radical nephrectomy.

The microscopic appearance is non specific, with a duct like or papillary architecture surrounded by a desmoplastic stroma. The columnar or cuboidal shaped cells can give rise to a hobnail appearance. The papillary appearance of the tumour can make it difficult to distinguish from papillary renal cell carcinoma.[6]









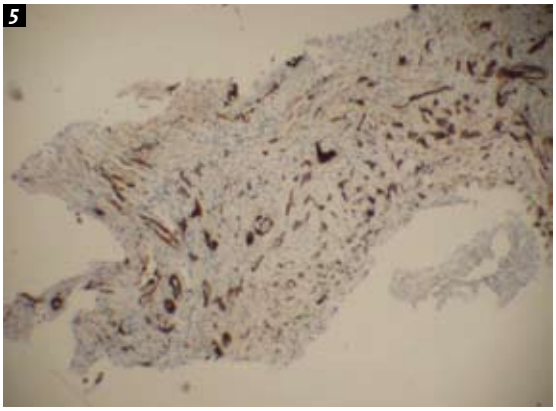


Figure 1— AN IRREGULAR 3.5CM CYSTIC LESION WAS SEEN ON CT IN THE LOWER POLE OF THE LEFT KIDNEY, WITH STRANDING OF ADJACENT FAT

Figure 2— MRI LUMBAR SPINE DEMONSTRATED A LARGE L4 METASTATIC DEPOSIT WITH EXTENSION INTO THE SPINAL CANAL

Figure 3— RENAL BIOPSY REPORTED AN INFILTRATING ADENOCARCINOMA IN A DESMOPLASTIC STROMA POSITIVE FOR LOW MOLECULAR WEIGHT CYTOKERATINS, WITH PERINEURAL INVASION

Figure 4— THERE WAS FOCAL RESTAINING OF CK20

Figure 5— THESE TUMOUR CELLS STAINED STRONGLY CK7 POSITIVE

Immunohistochemistry has been used to make a more definitive diagnosis in recent times. Staining of lectins such as soyabean, peanut, wheatgerm and Ulex europaeus 1 agglutinins and antibodies to high molecular weight keratins indicate a distal collecting duct origin to these tumours.[7] This is in contrast to most renal cell cancers which express vimentin, and antibodies to low molecular weight cytokeratins. Immunohistochemistry results have not always been consistent, however, and diagnostic confusion can still occur.

Because of its low incidence, CDC does not have a cytogenetic characteristic but a variety of heterogeneous chromosomal alterations unrelated

to other variants of renal cell carcinoma have been reported.[8,9] It has been postulated that a better understanding of the genetics of this tumour will help explain the biological aggressiveness of most CDCs, while a small subset follow a relatively benign course.

Management of patients with CDC remains a challenge because of the advanced stage of presentation and often aggressive clinical course. Radical nephrectomy and loco-regional lymphadenectomy appears to be curative for organ confined cancer. Longterm disease-free survival has been reported in this setting after treatment with adjuvant therapy.[6] Several combinations of chemotherapy have been investigated previously for advanced disease and have been found to be ineffective, such as MVAC and vincristine/actinomycin D.[6] In recent times it has been suggested that CDC may behave more like urothelial than clear cell renal cancer. To investigate this theory a French group used the combination of cisplatin and gemcitabine, known to be effective and well tolerated in patients with transitional cell carcinoma. A complete response was achieved in two patients with metastatic disease.[5] They have recently reported further success in treating twenty patients with this regimen, resulting in 7.9 and 9.5 months progression free survival and overall survival respectively.[10] Other studies have used combinations such as paclitaxel/carboplatin[4] and doxorubicin/gemcitabine alternating with ifosfamide/paclitaxel/cisplatin (TIP).[11]

In conclusion, Collecting Duct Carcinoma is a rare tumour, with an aggressive clinical course. Recent advances in immunohistochemistry have aided immensely in diagnosis. Further studies to investigate the genetic characteristics of the disease will allow better understanding of its biology and classification. Early detection and subsequent nephrectomy appears to offer the best chance of survival. Newer combinations of chemotherapy or targeted therapies may have a greater role in the future.

REFERENCES

1. Fleming S, Lewi HJE. Collecting duct carcinoma of the kidney. *Histopathol* 1986;10:1131-41.
2. Mostofi FK, Sesterhenn IA, Sobin LH. Histological typing of kidney tumours: International histological classification of tumours, No.25, Geneva, WHO 1981.
3. Mancilla-Jimenez R, Stanley RJ, Blath RA. Papillary renal cell carcinoma. A clinical, radiological, and pathological study of 34 cases. *Cancer* 1976;38:2469-80.
4. Chao D, Zisman a, Pantuck AJ et al. Collecting Duct Renal Cell Carcinoma: clinical study of a rare tumour. *J Urol* 2002;167:71-74.
5. Peyromaure M, Thiounn N, Scotte F et al. Collecting Duct carcinoma of the kidney: A clinicopatholgical study of 9 cases. *J Urol* 2003;170:1138-1140.
6. Dimopoulos MA, Logothetis CJ, Markowitz A et al. Collecting duct carcinoma of the kidney. *Br J Urol* 1993;71:388.
7. Thoenes W, Storkel S, Rumpelt HJ, Moll R. Cytomorphological typing of renal cell carcinoma-a new approach. *Eur Urol* 1990;18:6-9.
8. Antonelli A, Portesi E, Cozzoli A etal. The collecting duct carcinoma of the kidney:a cytogenetical study. *Eur Urol* 2003;43(6):680-5.
9. Vecchione A, Galetti TP, Gardiman M et al. Collecting duct carcinoma of the kidney:an immunohistochemical study of 11 cases. *BMC Urol* 2004;4(11)1471-2490.
10. Culine S, Oudard B, Duclos E et al. A phase II prospective study of gemcitabine and platin-based combinations as first-line chemotherapy for metastatic Bellini duct carcinoma patients. Results of GETUG study. *Proc Am Soc Clin Onc* 2005, 4543.
11. Milowsky MI, Rosmarin A, Tickoo SK et al. Active chemotherapy for collecting duct carcinoma of the kidney:a case report and review of the literature. *Cancer* 2002;94(1):111-6

Correspondence to: Dr. Roisin M Connolly,
Tel: 00 353 1 6581334; Fax- 00 353 1 4972782
Email- roisinconnolly@gmail.com

Walking on water: The biomechanics of Michael A. MacConaill (1902-1987)

Biomechanics is a subject that draws on knowledge from many disciplines. One of its great practitioners in the last century was the Irish anatomist M.A. MacConaill. In this paper, we review some of MacConaill's fundamental contributions to biomechanics, namely: the hydrodynamic theory of synovial joint lubrication, the kinematics of joint motion and conjunct rotations; and the theory of spurt and shunt muscles. The aim is to revisit these topics in the light of current research, and to draw some conclusions about the import of his research in the context of recent developments in the field. The paper concludes with a discussion of science in Ireland, the development of the field of biomechanics since MacConaill's time, and some other matters.

PJ Prendergast,[1] TC Lee[1,2]

Trinity Centre for Bioengineering,[1] School of Engineering, Trinity College, Dublin; Dept of Anatomy,[2] Royal College of Surgeons in Ireland, Dublin

Figure 1 — Anatomical Society of Great Britain and Ireland, Summer Meeting, Queen's University, Belfast, May, 1931. Front Row, L to R; EJR Evatt, T Walmsley, TH Bryce (President), G Elliott-Smith, AF Dixon, Second Row: L to R; CM West, SR Shea, MA MacConaill, Miss JL McNeill, F Davies, AJE Cave

INTRODUCTION

Michael Aloysius MacConaill was born in Ballymena, Co. Antrim in 1902,[1] the eldest of five children; his father was a merchant and his mother was a mezzo-soprano. His family moved to Belfast and Michael attended St Mary's Christian Brothers School from where, in 1919, he obtained first place in the Queen's University entrance scholarship examination.[1] The first Dáil had met in Dublin's Mansion House on the 21st of January in that year and MacConaill joined its "parliamentary army", becoming a field ambulance officer in Belfast during the War of Independence.[2]

At Queen's, he broke the mould by becoming the first Catholic to be elected to the Students' Representative Council and to become President of the Literary and Scientific Society.[3] In the Medical School, he was encouraged by the Professor of Anatomy, Thomas Walmsley, to take an intercalated BSc degree and he graduated in Human Embryology and Anthropology with honours in July 1922.[4] He was a clinical student in the Mater, graduating in 1925, and was a house-surgeon there. Walmsley wished to appoint him as an Anatomy Demonstrator and, when this was blocked,[3] Walmsley arranged for a postgraduate scholarship.

He was, however, appointed a Demonstrator in the following year and promoted to Senior Demonstrator in 1928. He was awarded his MSc in July 1928 for a thesis titled "The correlations of length, breadth, and height in forty mixed crania",[4] and he presented this work to a meeting of the Anatomical Society at Queen's in 1931 (Figure 1).

MacConaill was awarded the Queen's University Medical Travelling Studentship for 1929-30 to visit University College, London where he continued his work on statistical anthropology. From there he went to the University of Sheffield, initially as a Senior Demonstrator, but he was promoted to Lecturer by mid-1930. In 1942, MacConaill returned to Ireland to take up the Chair of Anatomy in University College, Cork. He revitalised the Department's teaching and research, collaborating with Edward Gurr to develop tissue staining methods, with Eric Scher on the geometry of the dental arcades,[5] and applied Boolean algebra to neuronal networks. He was elected a Member of the Royal Irish Academy in 1945 and awarded a DSc by the Queen's University of Belfast in 1950 and an MA by the National University of Ireland in 1964[1]. In 1950 he took on the role Officer Commanding the Army's First Field Medical Company,[6] from which he retired in 1967 with the rank of Commandant.[2] Michael MacConaill retired from UCC in 1973 and died in 1987.

MacConaill was one of the most prolific scientists in mid 20th Century Ireland. He published a great number of scientific articles and invited book chapters, and co-authored two highly regarded books: *Synovial Joints: Their Structure and Mechanics*[7] and *Muscles and Movements: A Basis for Human Kinesiology*[8] (Figure 2); this latter book also appearing in a second edition.[9] Besides these two books, MacConaill published two comprehensive series of papers on the mechanics of synovial joints, one series in the *Irish Journal of Medical Science*[10,11,12,13,14,15] and another series in the *Journal of Bone and Joint Surgery*.[16,17,18,19,20] His work on the mode of lubrication in synovial joints is still widely cited and his research into generalised methods for describing and analysing the motion of joints is well known as part of the science of kinesology which is central to medical specialities from orthopaedics and physiotherapy to rheumatology and rehabilitation. It is perhaps an indication of his reputation that was asked to contribute the chapter on human joints to the 15th Edition of the *Encyclopaedia Britannica*.[21] MacConaill can be justly seen as one of the pioneering contributors to biomechanics and it is appropriate to

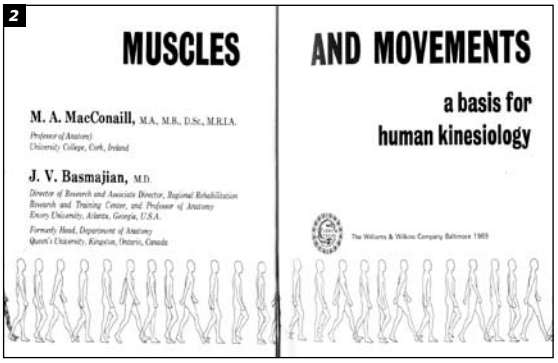


Figure 2 — Title page of the 1st Edition

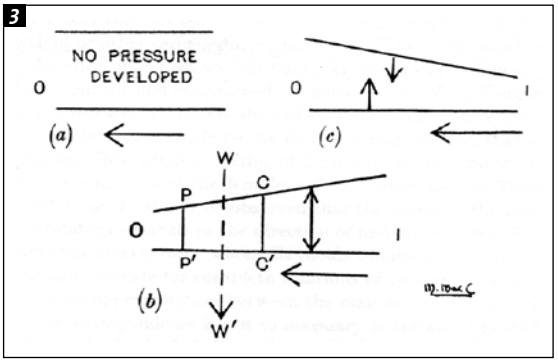


Figure 3 — (a) when two parallel surfaces move no pressure is developed, (b) when inclined surfaces undergo a relative movement the line CC' is shortened to PP' generating a pressure to support a load along WW', and (c) this generates a pressure between the opposing surfaces (after MacConaill)[22]

revisit and reinterpret his original work in the context of present research. Our aim is not only to draw some conclusions about the importance of his work for the development of the field but also to comment on the inter-relationship between anatomy, biomechanics, and rehabilitation in the wider sense.

RESEARCH IN BIOMECHANICS

SYNOVIAL JOINT LUBRICATION

According to MacConaill's own recollections[3] he was skimming through a physics textbook in a Sheffield bookshop when he noticed an account of the lubricating mechanism in engineering bearings that reminded him of synovial joints. This led him to theorize on the lubrication of mammalian joints, and develop the concept of 'hydrodynamic' lubrication of synovial joints; hydrodynamic lubrication occurs when one surface is slightly inclined relative to another so that, when the surfaces move, a wedge of fluid is trapped and pressurized between them, see Figure 3.

MacConaill claimed that the slight incongruence in the surfaces in synovial joints allows the synovial fluid to be trapped between the cartilage layers as the bones rotate relative to each other. Furthermore, he contended[22] that the menisci of joints did *not* exist, as had been usually assumed, to "abolish the effects of incongruity between male and female surfaces", but rather to provide a flexible wedge to allow the joint

surfaces to maintain the correct relative inclination for hydrodynamic lubrication (Figure 4). This was an ingenious hypothesis and involved a completely new way of thinking about diarthrodial joints and the role of menisci. Later MacConaill followed-up his study of the knee and inferior radio-ulnar joints with an analysis of the acromio-clavicular joint,[23] and of the foot[24] and carpus.[25]

MacConaill's contribution is acknowledged by Duncan Dowson, the world's foremost authority on tribology when he states[26] "MacConaill (1932) studied the structure of joints... ...and concluded that the mode of lubrication must be hydrodynamic". MacConaill's analysis of synovial joint lubrication stood unchallenged for some time. His contribution is often referred to in biomechanics textbooks, and is still widely cited. However, several explanations have now supplanted it, one of which is 'weeping lubrication' whereby synovial fluid is exuded by the spongy cartilage to form the fluid layer separating the cartilages – therefore according to 'weeping lubrication' the synovial fluid is not dragged between the layers by the relative movement of the surfaces as MacConaill had theorized. MacConaill had a spat with the proponents of weeping lubrication in the journal *Nature;*[27,28] he maintained that the source of the fluid layer, though interesting, was a "physiological problem" and that weeping lubrication "appears to complete the existing theory rather than supplant it, and is a valuable addition to our knowledge of biomechanics".[27] In a subsequent paper, MacConaill[29] presents further arguments in favour of hydrodynamic lubrication. One argument was that the incongruency of the joint surfaces will always permit a layer of synovial fluid to be present except in one localised contact area. However, recent research has made it clear that the relative motion between cartilage layers at human joints is simply not fast enough for hydrodynamic lubrication to act alone. More recently, a theory of *elasto*hydrodynamic lubrication has shown that the pressures generated are sufficient to deform the cartilage layers and therefore exude fluid.[30] Furthermore, even more recently, a theory of 'boosted lubrication' proposes that when the joint is unloaded the cartilage expands again imbibing fluid and leaving the large hylauronic acid molecules on the cartilage surface to act as a lubricating gel.[31]

KINESIOLOGY AND THE MECHANICS OF JOINT MOTION

The motion of one bone relative to another at a joint may seem straightforward – it is not. In the most general case we can assume that one bone moves relative to another by translation in three directions and rotation in three directions, *i.e.* has six degrees-of-freedom. MacConaill begins his analysis by recapitulating the seemingly obvious fact that all motions of one limb relative to another are either *spins* or a *swings*. However, a thought-experiment will make it clear that, say, flexion-extension of the lower limb (what one might think of as a swing) involves also spin at the ball-and-socket joint of the hip. Therefore, most motions of joints are composite motions of swings and spins. The next step in the analysis is to define a pure swing; to do this MacConaill draws on the concept of the 'ovoid-of-motion'; if a bone is rotated into every possible position then the locus of a point on the bone would describe a closed surface – this surface is the ovoid -of-motion (Figure 5). The shape of the ovoid-of-motion depends on the geometry of the articulating surfaces and their degree of congruency.

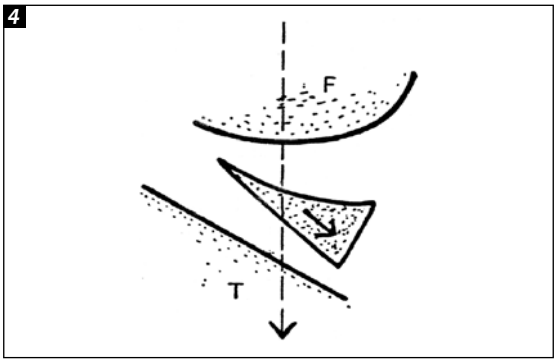


Figure 4 — The femur (F) is and the tibia (T) are separated by a meniscus which creates an incline in the surfaces needed for hydrodynamic lubrication (after MacConaill)[22]

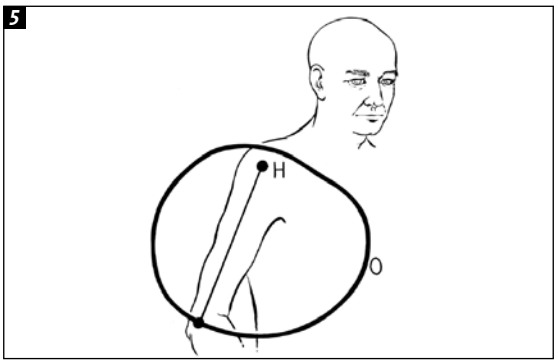


Figure 5 — An 'ovoid of motion' can be imagined for a joint by rotating the bone (about H in the Figure) and letting any point on the bone describe a loop (O in the Figure). All possible loops constitute a surface (like an 'eggshell') around the point H. [If the centre of rotation was constant, the ovoid of motion would be a sphere.]

Any swing that describes a line that is the shortest possible distance between two points on the ovoid of motion (the line would be a 'great circle' if the ovoid of motion was a sphere) is defined as a *cardinal* swing. MacConaill's insight came from an analysis of a succession of cardinal swings.[10,16] Consider making, say, three cardinal swings of the upper limb as follows: (i) hold the upper limb by the side, elbow straight,

palm facing the thigh; (ii) flex the shoulder through 90 degrees in the AP plane (the palm faces medially), (iii) swing the upper limb through 90 degrees (the palm faces forward), (iv) lower the upper limb through 90 degrees towards the body (the palm remains facing forward). This succession of three cardinal swings will not have returned the arm to the same position; a *consequential* motion of external rotation of the arm will have occurred. Naming the closed loop of cardinal swings as *diadochal* motion (Gr. *diadochos*, successive), MacConaill noted that any set of three swings that form a closed loop (not just 90 degree swings as in the foregoing example) on the ovoid of motion would result in a net rotation of some magnitude, which he termed a *conjunct* rotation.

MacConaill worked out the magnitude of the conjunct rotation from first principles[32] and computed the relationship between the degree of conjunct rotation consequent on a diadochal motion. He examined how the articular kinematics depends on the shape of the articulating surface[32]. Furthermore, "the arrangement of articular ligaments... must allow the conjunct rotation imposed on the moving part by the shape of the fixed surface"[20]. If several diadochal motions are carried out in succession, eventually the ligaments will restrain conjunct rotation at the joint. The only way to avoid this is to apply counter-rotations, and this requires counter-rotatory muscle actions. Therefore rotary muscles are brought into play even in pure (i.e. cardinal) swings. MacConaill emphasised the importance of understanding this for rehabilitation[33] and physiotherapy.[34] These concepts, while not generally common knowledge in biomechanics, are invoked as the theoretical foundation of various therapies. Zatsiorsky, a leading biomechanician of the former USSR and now working in Penn State University describes MacConaill's contribution to articular kimematics in his textbook *Kinematics of Human Motion,*[35] and a recent editorial by Di Fabio[36] concludes "The conceptual and intuitive framework provided by MacConaill many years ago still provides a wonderful anatomical and mechanical conceptualisation for justifying [....] treatments in the clinic".

SPURT AND SHUNT MUSCLES

In an article published in the *Irish Journal of Medical Science* in 1946, MacConaill[12] introduced the concept of spurt and shunt muscles (Figure 6a). The biomechanical basis for the classification may be summarized using the following notation:

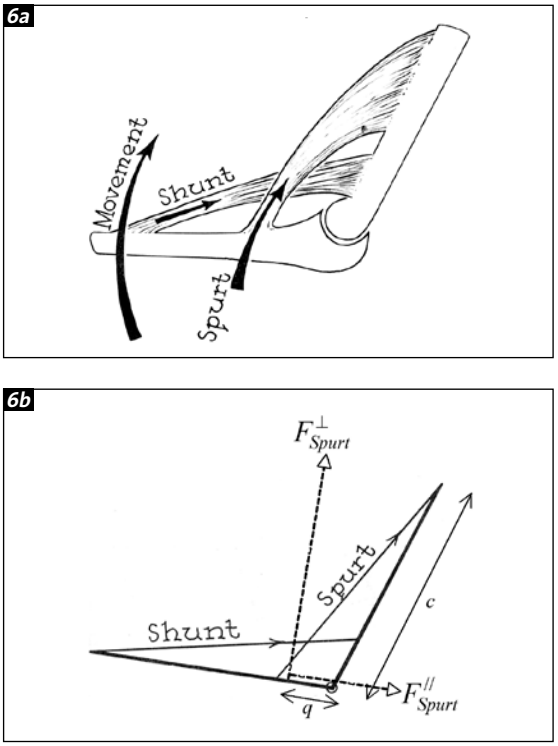


Figure 6 — Spurt and shunt muscles. (a) shows the direction of movement of the bone. The spurt muscle pulls more directly across the bone in most positions other than full extension whereas the shunt muscle pulls more directly along the moving bone, (b) biomechanical analysis (see text).

- let *c* be the distance along the stable bone between a muscle's attachment site and the joint (called the cisarticular length).
- let *q* be the distance between the joint and the attachment site on the moving bone (called the transarticular length).

Figure 6b shows *c* and *q* for the spurt muscle. Taking the spurt muscle and resolving its force into a component perpendicular to the moving bone (denoted $F^{\perp}_{Spurt}$) and a component parallel to the moving bone (denoted $F^{//}_{Spurt}$), simple mechanics shows that, when $c / q > 1$ as it is for spurt muscles, then $F^{\perp}_{Spurt}$ will be greater than $F^{//}_{Spurt}$ (for all but extreme extension) whereas the opposite would be the case for shunt muscles with greater component of the force (a centripedal force) being towards the joint which tends to 'shunt' the bones together. Spurt muscles need an antagonist but shunt muscles do not. (A complete mathematical treatment is given in MacConaill).[37] Based on the argument that shunt muscles will be required in rapid limb rotations to provide a ceptripedal force, Basmajian[38] performed electromyographic experiments to confirm the spurt/shunt classification system.

The concept of spurt and shunt muscles is not without its critics, even though it is treated as

settled knowledge in reference works such as Gray's Anatomy.[39] The modern treatment of this subject focuses on calculation of forces exerted by muscles by assuming an optimization function such as a minimization of muscle stresses.[40,41]

DISCUSSION

Michael MacConaill was a notably original thinker in biomechanics and an interdisciplinary researcher *avant-la-lettre*. Though discussion of his personality is, of course, not within our remit yet we note Professor John A. Murphy, in his history of UCC,[42] describes him as: learned, idiosyncratic, redoubtable, erudite. Not only could MacConaill make the fundamental contributions to biomechanics, but he could turn his hand to publishing a *rann* in the *Irish Times*[43] to the memory of the Lecky Professor of History in another University.

> IN MEMORIAM: EDMUND CURTIS, M.A.
>
> *A mhic dhílis d'Eirinn, a chara do cháirdibh Shasana,*
>
> *A ghiolla na h-éigse do neartuigh le mórshaothar staire,*
>
> *A ghaisce na nGaodhal: ba chathbhuilleach láidir do bhearta,*
>
> *'S ag caoineadh do dhéidh-se le géar-ghol atámuid, a Eamuinn.**

MacConaill's scientific papers have proved to be enduring contributions to several problems in biomechanics, particularly understanding of the lubrication of synovial joints.[22] However, his more widely published work on the movement of joints has been eclipsed by more rigorous treatments based on control systems theory incorporating the central nervous system as the controller.[40] Nonetheless the concept of consequential movements is still used, it seems, particularly among practitioners. The theory of spurt and shunt muscles has been the subject of some criticism, and rightly so in our opinion. A robust defence is given by MacConaill in the *Journal of Anatomy*[44] but, from a biomechanical point of view, it is unclear why the moving (i.e. distal) bone should be distinguished from the stationary (i.e. proximal) bone when all movements are relative.

MacConaill was also prepared to make some futuristic speculations in his papers. For example, in his classic 1932 paper[22] referred to above, he studied how collagen fibres are aligned in a stress field; he hypothesised as follows: "as iron filings are to a magnetic field so are collagen fibres to a tension field". This was a function/form relationship for cartilage, and it anticipated current research on the relationship between the microstructure of tissues and stresses to which they are exposed during growth, a subject that is now seen as central to tissue engineering and regenerative medicine.[45] His theoretical paper on myomechanics concludes with the statement that our neuromuscular circuits are geared to gravity.[37]

It is interesting to note that MacConaill's early research had been in ethnology. In fact, it seems MacConaill's first paper was published (when MacConaill was only 21 years of age) on the subject of the ethnology of the people of Rathlin Island.[46] He continued to study ethnology while in Sheffield where he published several papers reporting correlations between hair and eye colour, and stature.[47,48,49] However, this kind of research was discontinued in the early 1940s, perhaps because, to quote a modern historian, "it [became] virtually unthinkable for liberal intellectuals (which included most scientists) to operate with this concept [of race]. Indeed many doubted that it was legitimate to enquire systematically into the genetically determined differences between human groups, for fear that the results might provide encouragement for racist opinions".[50] In this respect it is interesting to note the renewed interest in genotype variations in human populations.

From the early 1930s onwards, MacConaill maintained a research interest in the biomechanics of the locomotor system. He applied a rigorous mathematical approach for each problem he tackled. In this we can see similarities with the work of the Trinity polymath of an earlier generation, the Rev. Samuel Haughton, MD. Haughton also used mathematics to analyse the musculoskeletal system.[51,52] For both Haughton and MacConaill, mathematics (and particularly geometry) had pride of place among the approaches for understanding the behaviour of biological systems – this was, and is, rather unusual.[53] (However it was not an Irish trait; another Irish anatomist, Abraham Colles declared: "Mathematics applied to the human body is altogether impractical".[54]

* O loyal son of Erin, O friend of the friends of England,
O servant of learning fortified by great works of history,
O valiant Gael, great and powerful thy deeds,
And, Edmund, 'tis keening with bitter tears after you we are.

Figure 7 — During the International Congress of Anatomy in Wiesbaden, Germany in the Summer of 1965, "several anatomists gathered for a luncheon to discuss the organization of a small society in electrophysiological kinesiology. They were J.V. Basmajian of Canada, S. Carlsøø and B. Jonsson of Sweden, M.A. MacConaill of Ireland, and J. Pauly and L. Scheving of the USA. On that date, on August 13,1965, this group agreed to found ISEK, the International Society of Electrophysiological Kinesiology. There and then Dr. Scheving took a photograph of the birth of ISEK which appeared on the cover of the June 1973 Newsletter" (see http://www.isek-online.org/history.html). MacConaill is in the centre.

Herries Davies suggests that the relative lack of success of science in "Free State Ireland" was because the people were "too introspective to display much enthusiasm for the thoroughgoing internationalism basic to science – too concerned with Irish language revival and literary censorship to be aware of the momentous developments taking place elsewhere".[55] It is interesting that Herries Davies would make such a speculation and the impetus for him to do so is perhaps worthy of investigation in itself; but, in the one case we have before us, MacConaill was both a language enthusiast and an internationalist – his books were translated into several languages,[2] and he was a founding member of the International Society of Electrophysiology and Kinesiology (see Figure 7) – a society which is very active today. Perhaps the explanation does not lie in the introspection of the people, but in the lack of funding for research prevented the continuity essential to building up research strength within the universities. Today research in biomechanics is inter-institutional, inter-disciplinary, and international in a way that was not possible in MacConaill's time. It is inspiring to have Irish names of the reputation of Michael MacConaill to number among the founders of the field.

ACKNOWLEDGEMENTS

The authors' scientific collaborations are funded by the Programme for Research in Third Level Institutions (PRTLI), administered by the Higher Education Authority. We thank Dr Sean Duffy FTCD for his translation of MacConaill's poem, and Prof.dr. Jan Pieter Clarijs of the Vrije Universiteit Brussel for Figure 7.

REFERENCES

1 Fraher JP. In Memoriam. M.A. MacConaill. J Anat 1987; 155: 209-211.

2 Obituary, Cork Examiner, 29 January, 1987

3 MacConaill MA. Odd Ulsterman Out. Leaves from a Scientist's Life-book. 1976 (unpublished)

4 Student Records Office, The Queen's University of Belfast, 27 May, 1999 (pers. comm.)

5 MacConaill MA, Scher E. The ideal form of the human dental arcade. Dent Rec 1949;69:285-302.

6 Obituary, Irish Times, 20 January 1987

7 Barnett CH, Davies DV, MacConaill MA. Synovial Joints: Their Structure and Mechanics. Longmans & Co: London, 1961

8 MacConaill MA, Basmajian JV. Muscles and Movements: A Basis for Human Kinesiology. The Williams & Wilkins Co.: Baltimore, 1969

9 MacConaill MA, Basmajian JV. Muscles and Movements: A Basis for Human Kinesiology. Robert E. Krieger Publishing Co., Huntingdon: N.Y., 1977

10 MacConaill MA. Studies in the mechanics of synovial joints. I Fundamental principles and diadochal movements, Ir J Med Sci (June) 1946;246:190-199.

11 MacConaill MA. Studies in the mechanics of synovial joints. II Displacements on articular surfaces and the significance of saddle joints. Ir J Med Sci (July) 1946; 247:223-235.

12 MacConaill MA. Some anatomical factors affecting the stabilising function of muscles. Ir J Med Sci 1946; Nr. 115, 160-164

13 MacConaill MA. Studies in the mechanics of synovial joints. IV The transarticular force: its magnitude and consequences. Ir J Med Sci (May) 1956, No. 365, pp. 193-203.

14 MacConaill MA. Studies in the mechanics of synovial joints. V The statics of single joints. Ir J Med Sci (August) 1956, No. 365, pp. 353-364,

15 MacConaill MA. Studies in the mechanics of synovial joints. VI Motion at one joint. Ir J Med Sci (March) 1957, pp. 99-113,.

16 MacConaill MA. The movements of bones and joints: 1. Fundamental principles with particular reference to rotation movement. J Bone Jt Surg 1948;30B:322-326.

17 MacConaill MA. The movements of bones and joints: 2. Function of the musculature. J Bone Jt Surg 1949; 31B:100-104.

18 MacConaill MA. The movements of bones and joints: 3. The synovial fluid and its assistants. J Bone Jt Surg 1950; 32B:244-252.

19 MacConaill MA. The movements of bones and joints: 4. Mechanical structure of articulating cartilage. J Bone Jt Surg 1951;33B:251-257.

20 MacConaill MA. The movements of bones and joints: 5. The significance of shape. J Bone Jt Surg 1953; 35B; 290-297.

21 MacConaill MA. Joints. In: The New Encyclopaedia Britannica (15th Ed.), Encyclopaedia Britannica Inc, Chicago, Vol. 28, pp. 296-303, 1974.

22 MacConaill MA. The function of intra-articular fibro-cartilages, with special reference to the knee and inferior radio-ulnar joints. J Anat 1932; 66: 210-227.

23 MacConaill MA. The mechanical anatomy of the acromio-clavicular joint of man. Proc R. Ir Acad Sect. B, Vol. 50: pp 159-166, 1944

24 MacConaill MA. The postural mechanism of the human foot. Proc R. Ir Acad Sect. B, 1945; 50: 265-298.

25 MacConaill MA. The mechanical anatomy of the carpus and its bearings on some surgical problems. J Anat 1941; 166-175

26 Dowson D. History of Tribology, Professional Engineering Publishing: London, p. 508, 1989.

27 MacConaill MA. Nature, (March) 1960, 105: 920

28 Lewis PR, McCutchen CW. Nature (March) 1960, 185: 920-921.

29 MacConaill MA. The synovial fluid. Laboratory Practice 1966; 15:60-70.

30 Dowson D. Natural joints. In: An Introduction to the Bio-mechanics of Joints and Joint Replacement. (Eds.: D. Dowson, V. Wright), Mechanical Engineering Publications Ltd.: London, pp. 120-133, 1981

31 Martin RB, Burr DB, Sharkey NA. Skeletal Tissue Mechanics, Springer, New York, 1998, pp. 291-300.

32 MacConaill MA. The geometry and algebra of articular kinematics. Bio-Medical Engineering 1966; 1; 205-211.

33 MacConaill MA. Rotary movements and functional décalage, with some reference to rehabilitation. Brit J Phys Med (March) 1950: 50-56.

34 MacConaill MA. Joint movement. Physiotherapy (Nov.) 1964, pp. 359-367.

35 Zatsiorsky VM, Kinematics of Human Motion, Human Kinetics Publishers, Leeds, 1998.

36 Di Fabio RP. Passion and manipulation. Journal of Orthopaedic and Sports Physical Therapy. 2000; 30:442-443.

37 MacConaill MA. Some minimal principles applicable in myomechanics. Bio-Medical Engineering 1966;1:498-503.

38 Basmajian JV. 'Spurt' and 'shunt' muscles: an electromyographic confirmation. J Anat 1959; 93: 551-553.

39 Williams PL. Gray's Anatomy 38th Edition, 1995, pp. 786-787.

40 Prendergast PJ, van der Helm F, Duda G. Analysis of muscle and joint loads. In Basic Orthopaedic Biomechanics and Mechanobiology, (Eds., V.C. Mow & R. Huiskes), Lippincott Williams & Wilkins: New York, pp. 29-89, 2005

41 FitzPatrick D, Commins E, Doheny E, O'Malley F, O'Malley M, Nolan P. Simulation of the neuro-muscular system: steps towards pre-clinical testing in orthopaedics and rehabilitation. In Topics in Bio-Mechanical Engineering, TCBE & NCBES: Dublin & Galway (Eds., P.J. Prendergast, P.E. McHugh), pp. 235-248, 2004. [available at www.biomechanics.ie]

42 Murphy JA. The College. A History of Queen's/University College Cork. Cork University Press, 1995.

43 Irish Times, 3 April, 1943

44 MacConaill MA. Anatomical Note: Spurt and shunt muscles. J Anat 1978; 126: 619-621

45 Prendergast PJ. Mechanics applied to skeletal ontogeny and phylogeny. Meccanica 37, 317-334, 2002.

46 MacConaill MA. Contributions to Irish Ethnology. "The people of Rachrai" (Rathlin Island, Co. Antrim). Proc Belfast Nat Hist Phil Soc 1922-1923; pp.4-7.

47 MacConaill MA, Ralphs FL. Post-natal development of hair and eye colour, with special reference to some ethnological problems, Annals of Eugenics 1936;7: 218-225.

48 MacConaill MA. The stature of male schoolchildren in relation to hair and eye colour, Annals of Eugenics 1937;8:117-125.

49 MacConaill MA. The classification of hair and eye colour upon developmental and genetic basis, Annals of Eugenics 1941;11:173-178.

50 Hobsbawm E. The Age of Extremes (1914-1991), Abaqus: London, 1995, p. 553

51 Haughton S. Principles of Animal Mechanics. Longmans & Co. London, 1872.

52 Prendergast PJ, Lee TC. On a wing and a prayer: the biomechanics of the Rev. Dr. Samuel Haughton, J Ir Coll Phys Surg 1999;28:38-43.

53 Prendergast PJ. Biomechanics in Ireland and Europe, In Proceedings of the 12th Conference of the European Society of Biomechanics (Eds.: PJ Prendergast, TC Lee, AJ Carr), Royal Academy of Medicine in Ireland: Dublin, pp. 1-4, 2000 (available at www.biomechanics.ie)

54 Lee TC. Bioengineering - past, present, and future. Ir J Med Sci 168, p. 208, 2001

55 Herries Davies GL. Irish thought in science. In The Irish Mind: Exploring Intellectual Traditions. (Ed., R. Kearney), Wolfhound Press, Dublin, pp. 294-362, 1985

Correspondence to: Patrick Prendergast, School of Engineering, Parsons Building, Trinity College, Dublin 2
Tel.: (01) 608 2061; Fax.: (01) 679 5554
Email: pprender@tcd.ie
Internet: www.biomechanics.ie

The burning of Bridget Cleary: Psychiatric aspects of a tragic tale

ABSTRACT

Background Bridget Cleary was brutally burned to death by her husband in the presence of her father and several close relatives in rural Ireland in 1895. The story has attracted public attention for more than a century now, for numerous reasons.

Aims The issue of psychiatric illness in this tragedy, and the role of fairy mythology in belief systems in 19th Century rural Ireland are reviewed, particularly in relation to providing explanations for physical and psychiatric illness, along with learning disability.

Methods Reference was made to a wide range of sources featuring the burning of Bridget Cleary.

Results There is some evidence to suggest that the actions of Michael Cleary and other key protagonists were influenced by Capgras syndrome and folie a plusiers.

Conclusions Delusional belief in fairy mythology may have coloured the psychological make-up, motivations and behaviour of some of the people involved in the killing of Bridget Cleary.

H O'Connell, PG Doyle

Limerick Mental Health Services, Tevere Day Hospital, Shelbourne Road, Limerick

'Are you a witch or are you a fairy,
Or are you the wife of Michael Cleary?'
(Childrens' nursery rhyme)

Bridget Cleary (nee Boland) was brutally burned to death by her husband, in the presence of her father and several other close relatives, in the kitchen of her small cottage in rural Tipperary in 1895. She was twenty-six years old at the time of her death and worked as a dress-maker. Her husband was thirty-five and worked as a cooper; they had been married for seven years and had no children.

The story of Bridget Cleary's death, sometimes mistakenly referred to as the last witch-burning in Ireland, has from the outset excited both scholarly interest and the interest of the general public in this country and further afield. A recent RTE documentary[1] and a feature film proposed for 2006 has again brought this story to public attention.

Bridget Cleary had been unwell, possibly with bronchitis or pneumonia and an associated delirium, for the two weeks prior to her death. Testimony in court from the key witnesses to her killing suggested that Michael Cleary became convinced during her illness and, possibly, in the months beforehand, that his wife had been abducted by the fairies, and that they had left a changeling in her place. He seems to have been supported in this view by Jack Dunne, a local storyteller or seanchai and cousin of Bridget Cleary. Dunne was an expert in fairy mythology and some locals believed that he had himself 'spent time with the fairies' in the past. Other members of Bridget Cleary's family also appear to have colluded with the story of fairy possession to a greater or lesser extent, and cooperated with Michael Cleary in performing several rituals and administration of herbal medication to his wife in the days leading up to her death.

Michael Cleary consulted a priest, doctor and two local herbal medicine experts in the days prior to killing his wife, in efforts to help her. Several days of ritualised cruelty, involving forced administration of herbal medicines, threatened burning and interrogation as to her true identity ended when Michael Cleary doused his wife with paraffin oil and burned her to death. Bridget's father, aunt and three of her first cousins were present in the small house at the time of her death but later claimed they were so intimidated by Michael Cleary that they could not intervene to stop the worsening violence in the days leading up to this. After killing his wife, Michael Cleary claimed that he had killed only a fairy changeling and, as a result, his real wife would be returned to him within three days. Following her death and burial by himself in a shallow grave near their home, he waited for three consecutive nights at a nearby ancient ring-fort or 'fairy-fort', apparently in wait for her return to him.

In the subsequent trial he was found guilty of manslaughter and served fifteen years of a twenty-year prison sentence before emigrating to Canada. Bridget Cleary's father, Patrick Boland, and her cousins Jack Dunne, Patrick and Michael Kennedy were found guilty of lesser crimes for their roles in her death and the concealment of her body.

PSYCHIATRIC ASPECTS

Michael Cleary was undoubtedly sleep deprived, agitated and distressed in the days prior to killing his wife. In a petition to the Lord Lieutenant written by him in 1905, appealing for part of his sentence to be remitted, he wrote: 'Petitioner (i.e. Michael Cleary) attended to the wants of his wife during her illness both night and day until he was in a manner just as bad as deceased'.[2]

He went to considerable lengths to arrange that Mass be said in his cottage to help his wife. He also arranged for the local doctor to call and assess his wife. Most controversially of all the aid he sought, he acquired herbs from a local 'herb doctor' and went to considerable lengths to make his wife take them, along with boiled 'new' milk or 'beestings' (i.e. the milk first produced by a cow after calving, thought to have curative properties). Micheal Cleary's father also died during this time and he did not leave tending his sick wife to attend the wake or funeral.

In this stressful context, it is possible that Michael Cleary may have developed a brief psychotic episode around the time he killed his wife. There is no evidence to suggest that he had a history of psychiatric illness prior to or subsequent to killing his wife, but his mental state and psychiatric history was not formally assessed as part of the investigation into her death.

The particular phenomenology of such a psychotic state may be described as the Capgras syndrome. First described by Capgras and Reboul-Lachaux in 1923,[3] the Capgras syndrome involves delusional misidentification of a person or people, usually someone who has close emotional ties to the patient. While the form of this phenomenon is a delusion, the content is culture-dependent.[4] For example, a present day manifestation may involve the development of a delusion that an extraterrestrial impostor has replaced the person in question. The patient will often acknowledge the similarities in physical appearance between their loved one and the impostor, but they may perceive minor and telling differences.

For Michael Cleary, the cultural context was that of 19th Century working-class rural Ireland where belief in fairy mythology and a plethora of associated superstitions was still strong in many places. Therefore (assuming that he *was* psychotic), for Michael Cleary to become convinced that his wife was actually a changeling left by the fairies would not have been a surprising manifestation of Capgras syndrome.

It has also been suggested that Michael Cleary, who was a stronger and more dominant character than the others involved, may have induced some of them to share in his delusional beliefs. This phenomenon has been described as 'folie a deux' or, when more than two people are involved as in this case, 'folie a plusiers. It may in part explain the actions of Bridget Cleary's father and male cousins who cooperated with her husband in holding her down, forcibly giving her herbs and milk and interrogating her as to her true identity in the days leading up to her death.

Furthermore, it is possible that delusional misidentification and fairy possession may have been suggested to Michael Cleary by the comments of Jack Dunne ('That is not Bridgie Boland'), whose expertise in the area of fairy mythology was acknowledged in the local community.

A less likely possibility is that Michael Cleary was fabricating psychiatric symptoms both before and after killing his wife, in an effort to avoid the charges of murder or manslaughter.

The possibility that the some of the key protagonists in this tragedy may have had learning disabilities has never been explored. The presence of learning disability might explain in part why fairy mythology was invoked so readily by some of them to explain events. Michael and Bridget Cleary were both literate and had their own trades, so they were unlikely to be disabled. Jack Dunne, however, who was illiterate and whose limp and short stature were likely to be vestiges of childhood polio, may have had a learning disability and this may have been a factor in his enthusiasm for fairy mythology.

Angela Bourke's masterly review of this case also raises other psychiatric aspects relating to the treatment of people with both psychiatric illness and learning disabilities in 19th Century Ireland.[2] Bourke cites other examples of perceived fairy possession and burning in rural Ireland, involving children with physical deformities or mental retardation. She argues

that fairy mythology may have been used to provide a rationale for such conditions, which may have been puzzling and difficult to accept for parents and other family members. At a more sinister level, fairy mythology may have been consciously used to justify both ambivalent feelings towards and cruel treatment of people who were different from the norm.

Bourke also highlights the stark contrast between the rapid advances in science, technology, literacy and the organization of society that was taking place in 1895 (a year that saw the discovery of X-rays and the first cinema shows) and the more traditional society of the Clearys and their relatives, based as it was on oral history and traditions such as fairy mythology. Transcultural psychiatry did not then exist as a discipline, but if it had it might have shed some light on the sociocultural context of Michael Cleary's beliefs about his wife's fairy possession.

CONCLUSIONS

The burning of Bridget Cleary was undoubtedly a gruesome tragedy, yet it has fascinated people for over a century now, for different reasons. Political opponents of the Home Rule movement in Ireland at the time used the story to suggest that the Irish were incapable of self-government. Writers and folklorists such as Lady Gregory and William Butler Yeats were drawn to the fairy-mythology aspects of the story. Only in more recent years has the story attracted the attention of psychiatrists.[5]

As Michael Cleary and the other people involved in Bridget Cleary's killing were never formally psychiatrically assessed, an article such as this can only speculate on their psychological make-up and the role, if any, of psychiatric illness on their actions. Nevertheless, this story is useful in highlighting how a distinctly Irish sociocultural context may have coloured psychological make-up, motivations and behaviour in a time not long before the increasingly globalized Ireland of today.

REFERENCES

1. RTE 'Hidden History' series, first broadcast November 2005.
2. Bourke A. The Burning of Bridget Cleary. Pimlico, London, 1999.
3. Capgras JML and Reboul-Lachaux J: *L'illusion des sosies dans un délire systématisé chronique*. Bulletin de la Société clinique de médecine mentale, 1923, 11: 6-16.
4. Sims A. Symptoms in the Mind. Harcourt Publishers Ltd., 2000.
5. Walsh D. The Burning of Bridget Cleary. The Irish Times. 1999.

Correspondence to: Henry O'Connell, Tel: 061-452971
Email: hpoconnell@yahoo.ie

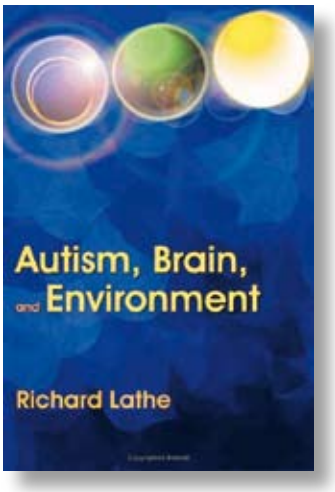
Autism, Brain, and Environment

Richard Lathe
Publishers: Jessica Kingsley Publishers, www.jkp.com
ISBN 1 84310 438 5.
Hardback Stg.£15.99/US$24.95

M Fitzgerald

Henry Marsh Professor Child & Adolescent Psychiatry, Trinity College Dublin

The author of this book Richard Lathe has a background in brain research, neuroscience research, as well as industrial research. In the book he moves from diagnostic issues to the genetic contributions to autism. Then he discusses prevalence of autism and proposes an additional element from the environment i.e. that the limbic brain is damaged by environmental toxins including heavy metals. Controversially he suggests that this accounts for the increasing diagnosis of autism are not just due to changes in diagnostic criteria or greater awareness of the condition which most of us believe. He discusses in considerable detail the physiological changes in the body, which affect the brain and behaviour. These matters are discussed in much greater detail and with much greater expertise than in other books on autism. For that very reason this is an original book on autism. Many books on autism don't cover or cover in minimal detail the material that he covers. For that reason this is a significant addition to anybody's autism library and would be of interest to all those professional and lay people with an interest in autism. For the lay person there are abbreviations and a glossary at the end which is most helpful. This glossary will considerably extend the targeted readership for the book. He deals with many issues which parents ask clinicians but clinicians wouldn't be in a position to answer because the majority of clinicians don't have his understanding of basic science. His hypotheses are of great importance because there is still much that we don't know about autism and autism is a condition with genetic and environmental inputs. Clearly the major strength of the book is on the environmental inputs to autism. There is no doubt that there are gastrointestinal tract problems in autism but these are given minimal attention in books on autism. This is corrected in this book. When I received this book to review I already had my copy of it and had read it in advance of the request to review it. I had already recognised the importance and the uniqueness of the book. The references in the book are exhaustive and indeed take up 59 pages. This makes the book very useful to postgraduate students, to researchers in autism, and anybody who wants to pursue their knowledge to a deeper level.



Clinical Practice, American College of Physicians Guidelines and US Preventative Services Task Force Recommendations

American College of Physicians
ISBN 1-930513-60-7
Edited by Vincenza Snow, MD

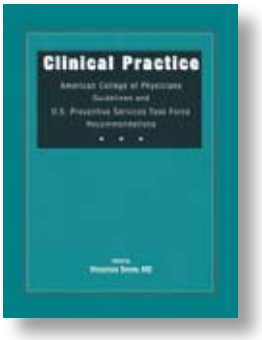
R Costello

RCSI Education & Research Centre, Smurfit Building, Beaumont Hospital, Dublin

The background to this book is that in 1981 the American College of Physicians received a three-year grant to develop a programme called the "Clinical Efficacy Assessment Project". This project aimed to review the clinical literature on specific topics so that they may best identify the best scientific papers, then reanalyse, reformulate and present information on these to practitioners so that they could readily determine the use of diagnostic tests, procedures and treatments. The latest outcome from this project which has continued through to the current time is a synopsis of clinical guidelines which cover the management of several chronic diseases and in a separate section appropriate use of antibiotics in respiratory tract infections and a further section of screening and prevention of several chronic conditions.

In general this evidence based practice guideline book has many valuable benefits which would make it an attractive proposition for any Physician in practice. The most important being that these are practical evidence based guidelines on important topics. The consensus printed is a joint opinion of several of the world leading authorities and thus is of a sound nature and maturely conceived. Another advantage to this book is that it is written in a uniform style with careful editing and in addition the papers whilst concise are quite pithy in nature. It is a particular aim of the clinical practice guidelines to take on difficult areas of management, for example, management of newly detected atrial fibrillation. I found this chapter and that on the management of Type II diabetes and the pharmacological treatment of acute major depression particularly valuable.

I would recommend this book whole-heartedly to anybody in clinical practice dealing with such common clinical issues.



***BuTrans*® matrix patches are Ireland's first patches designed to provide 7 days' continuous relief from severe osteoarthritis pain. Good news for doctors, good news for patients, good news for joints.**

Not suitable for the treatment of acute pain.

BuTrans*®** 5 µg/h, 10 µg/h and 20 µg/h Transdermal Patch. Prescribing Information Republic of Ireland. Presentation: Transdermal beige coloured patch with rounded corners, containing buprenorphine. 5 µg/h square patch marked: ***BuTrans 5 µg/h. 10 µg/h rectangular patch marked: ***BuTrans*** 10 µg/h. 20 µg/h square patch marked: ***BuTrans*** 20 µg/h. Indications: For the treatment of severe opioid responsive pain conditions which are not adequately responding to non-opioid analgesics. Dosage and Administration: ***BuTrans*** patches should be administered every 7 days and is not suitable for the treatment of acute pain. *Elderly and adults over 18 years:* Initially, the lowest dose (5 µg/h patch) should be used. The patient's previous opioid history and the medical status should be considered. Dose should not be increased before 3 days. Analgesia can be increased by increasing patch strength or by adding another patch. Do not use more than two patches at a time. Short acting supplemental analgesia may be used during initiation and titration until effective analgesia with ***BuTrans*** patches is achieved. *Children under 18 years:* Not recommended. Contra-indications: Known buprenorphine or excipient hypersensitivity, treatment of opioid dependency or narcotic withdrawal, respiratory depression, concurrent administration of monoamine oxidase inhibitors or within 2 weeks discontinuation of their use, myasthenia gravis, delirium tremens or pregnancy. Precautions and Warnings: Convulsive disorders, head injury, shock, reduced consciousness of uncertain origin, intracranial lesions or increased intracranial pressure, hepatic impairment, history of drug abuse. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. As with all opioids, chronic use of bupenorphine can result in the development of physical dependence. Withdrawal symptoms include agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastrointestinal disorders. Not recommended immediately post operatively or for situations characterised by a narrow therapeutic index, or a rapidly varying analgesic requirement. The ability to drive and operate machinery may be impaired especially during treatment initiation or titration to a higher dose. Patients affected should not drive or use machines while wearing a patch and for at least 24 hours after the patch has been removed. A general restriction is not necessary in cases where a stable dose is used. Interactions: ***BuTrans*** patches interact with benzodiazepines (this combination can potentiate respiratory depression of central origin, with risk of death), other CNS depressants, other opioid derivatives, certain antidepressants, sedatives, alcohol, anxiolytics, neuroleptics, clonidine and related substances. Effects may be intensified with inhibitors of CYP 3A4 and weakened by inducers. Pregnancy and Lactation: Contraindicated in pregnancy. Avoid during lactation. Side Effects: Serious adverse reactions that may be associated with ***BuTrans*** patches are similar to those observed with other opioid analgesics including respiratory depression and hypotension. Common side effects are anorexia, confusion, depression, insomnia, nervousness, anxiety, headache, dizziness, somnolence, paraesthesia, vasodilation, dyspnoea, constipation, (dry mouth, nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, pruritus (at site), erythema, rash, sweating, exanthema, tiredness, asthenia, pain, peripheral oedema, oedema, chest pain. Some side effects, that are not common, but may be serious, are respiratory depression, hypotension, psychotomimetic disorders, dependence, visual disturbances, circulatory disorders, serious allergic reaction, micturition disorders and withdrawal symptoms. Rare or very rare side effects include sedation, taste perversion, impaired concentration, numbness, speech disorder, mood swings, sleep disorders, restlessness, dysequilibrium, muscle fasciculation, miosis, ear pain, hot flushes, hyper-ventilation, hiccups, pyrosis, retching, pustules, vesicles, decreased erection, decreased libido and weariness. Legal Category: CD (Sch2) POM. Package Quantities: 5 µg/h transdermal patch: 2 individually sealed patches. 10 µg/h transdermal patch: 4 individually sealed patches. 20 µg/h transdermal patch: 4 individually sealed patches. Marketing Authorisation Numbers: PA 913/24/1-3. Marketing Authorisation Holder: Napp Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0GW, UK. Further information is available from Napp Laboratories, 54 Fitzwilliam Square, Dublin 2. Tel: Dublin 6612115. Member of the Mundipharma/Napp independent associated companies. Date of Preparation: September 2005. ® ***BuTrans*** and the NAPP device are Registered Trade Marks. © Napp Pharmaceuticals Limited 2005.

Bu7rans®

Buprenorphine Matrix Patch 5µg/h, 10µg/h, 20µg/h

When non-opioid analgesics aren't enough

Nexium®
esomeprazole

AstraZeneca

NEXIUM TABLETS

Abridged prescribing information: (see summary of product characteristics for full prescribing information)

Presentation: Gastro-resistant tablets containing 20mg or 40mg esomeprazole. **Uses:** Treatment of erosive reflux oesophagitis; long term management of patients with healed oesophagitis and symptomatic treatment of gastroesophageal reflux disease. Healing of *Helicobacter pylori* associated duodenal ulcer. Prevention of *Helicobacter pylori* associated peptic ulcer relapse. In patients requiring continued NSAID therapy - healing of gastric ulcers associated with NSAID therapy, and prevention of gastric and duodenal ulcers associated with NSAID therapy in at risk patients. **Dosage and administration:** (Adults only) Erosive reflux oesophagitis: Nexium 40mg once daily for 4 weeks. Long term management of patients with healed oesophagitis: Nexium 20mg once daily. Symptomatic treatment of gastroesophageal reflux disease in patients without oesophagitis: Nexium 20mg once daily for up to 4 weeks. Following resolution of symptoms, subsequent symptom control can be achieved using an on demand regimen of 20mg once daily when required. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended. Healing of Helicobacter pylori associated duodenal ulcer and prevention of Helicobacter pylori associated peptic ulcer relapse: 20mg with 1g amoxycillin and 500mg clarithromycin, all twice daily for 7 days. NSAID therapy: Healing of gastric ulcers: 20mg once daily for 4-8 weeks. Prevention of gastric and duodenal ulcers; 20mg once daily. The Elderly: Dose adjustment is not required. Children: Not recommended. Renal and liver impairment: Dose adjustment is not required in patients with impaired renal function. For patients with severe liver impairment a dose of Nexium 20mg once daily should not be exceeded. **Contra-indications:** Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation. Esomeprazole, like other PPIs, should not be administered with atazanavir. **Special warnings and precautions:** In the presence of any alarm symptoms and when gastric ulcer is suspected, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis. Patients on long term maintenance should be kept under regular surveillance. Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. **Interactions:** Absorption of ketoconazole and itraconazole can decrease during treatment. When Nexium is combined with drugs metabolised by CYP2C19 (diazepam, citalopram, imipramine, clomipramine, phenytoin) a dose adjustment may be necessary (see summary of product characteristics). Concomitant administration of Nexium 40mg with cisapride resulted in an increase in the AUC and a prolongation of elimination half life. Monitoring is recommended when initiating and ending concomitant treatment with warfarin. **Pregnancy & lactation:** see summary of product characteristics. **Undesirable effects:** Refer to full SPC Common: Nausea/vomiting, headache, abdominal pain, diarrhoea, flatulence, and constipation. Uncommon: dermatitis, pruritus, urticaria, dizziness, dry mouth. Rare: hypersensitivity reactions e.g. angioedema, anaphylactic reaction, increased liver enzymes, Stevens Johnson syndrome, erythema multiforme, myalgia, or blurred vision. **Package quantities:** Nexium 20mg - Blister packs in wallets or cartons of 28 tablets. Nexium 40mg - Blister packs in wallets or cartons of 28 tablets. **Storage precautions:** Do not store above 30°C. Marketing authorisation number: PA970/27/1 - Nexium Tablets 20mg; PA970/27/2 - Nexium Tablets 40mg. **Legal classifications:** S1B. Prescription only medicine (POM) **Marketing Authorisation holder:** AstraZeneca UK Limited, 600 Capability Green, Luton, LU1 3LU. **Further information available from:** AstraZeneca Pharmaceuticals (Ireland) Ltd., College Park House, 20 Nassau Street, Dublin 2. Tel: (01) 609 7100; Fax: (01) 679 6650. **Abridged Prescribing Information prepared:** 06/06. **Item approval date:** June 2006. Nexium® is a trademark of the AstraZeneca Group of companies.

References: 1) Miner P et al. Am J Gastroenterol 2003;98:2616-20.

06/0049