Absence of Opioid Withdrawal Symptoms in Patients Receiving Methadone and the Protease Inhibitor Lopinavir-Ritonavir

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A study was designed to determine the interactions, both clinical and pharmacokinetic, between methadone and lopinavir-ritonavir. Results demonstrated a 36% reduction in the methadone area under the plasma concentration-time curve after the introduction *of* lopinavir-ritonavir, with no coincident symptoms of opioid withdrawal and no requirement for methadone dose adjustment.

Combination antiretroviral therapy is the standard treatment for HIV infection [1]. Previous studies have described the significant interaction between methadone and the nonnucleoside reverse-transcriptase inhibitors efavirenz and nevirapine, which results in symptoms of opioid withdrawal and, thus, requires methadone dose adjustment [2, 3]. Lopinavir (Lpv) is a protease inhibitor that is coformulated with ritonavir (Rtv) [4]. The coforinulation results in pharmacokinetic enhancement by Rtv and subsequent increased Lpv exposure. In vitro and in vivo studies have demonstrated that Lpv-Rtv is a potent inhibitor of the cytochrome enzymes P-450 3A4 (CYP3A4) and 2D6 (CYP2D6), which are primarily Rtv mediated. Agents that are extensively metabolized by CYP3A4 and that have high first-pass metabolism appear to be most susceptible to large increases in the area under the plasma concentration-time curve (AUC) when they are coadministered with Lpv-Rtv. However, interactions can be complex, and Lpv-Rtv both induces its own metabolism and increases the biotransformation of some drugs that are metabolized by CYP450 enzymes and by glucuroni-dation. Thus, in a study of healthy volunteers, there was a 47% reduction in the methadone AUC when methadone was co-administered with Lpv-Rtv [5].

A recent unpublished review of all injection drug users (IDUs) who were receiving Lpv-Rtv at the Genito Urinary Medicine and Infectious Diseases (GUIDE) Clinic in St. James's Hospital (Dublin, Ireland) demonstrated that none of the 14 patients who were evaluated complained of having any symptoms of methadone withdrawal (S.C., L McCullough, C.B., and P.M., unpublished data). This unexpected result prompted us to design a pharmacokinetic study to determine the pharmacokinetic interaction between Lpv-Rtv and methadone.

Patients and methods. Patients who fulfilled standard criteria to begin receiving antiretroviral therapy and who were also receiving methadone maintenance therapy on a regular basis were recruited to participate in the study. The study was approved by the local ethics committee {the joint research and ethics committee of Adelaide and Meath Hospital, incorporating the National Children's Hospital, in Dublin).

The pharmacokinetics of methadone were determined when the medication was administered alone (on day 1 of the study) and in combination with the presence of antiretroviral therapy (on day 1 of the study). After 3 days of receiving standardized directly observed methadone therapy in their drug treatment clinic, the patients were seen in the day ward at 8:30 A.M. on study day 1, at which time an intravenous cannula was inserted to facilitate blood sampling. The patients were then administered their daily methadone dose under supervision, and blood samples were obtained for methadone analysis at 0, 1, 2, 3, 4, 5, 6, 7, 8, and 24 h after dosing.

The blood samples underwent centrifugation without delay, and the separated plasma was heated to 58°C for 30 min to inactivate HIV. Plasma was stored at -70°C until drug analysis could be performed by HPLC. Patients then commenced receiving antiretroviral therapy that included 2 nucleoside reverse-transcriptase inhibitors plus Lpv-Rtv (Kaletra; Abbott Pharmaceutical). On the morning of day 14 of the study, the patients returned to the day ward, and a pharmacokinetic profile was repeated. The procedure was identical to that followed on day 1, except for the addition of antiretroviral therapy (including Lpv-Rtv) to the medication administered in the morning. Any adjustment in methadone dose did not occur until after the second day of the pharmacokinetic study.

At each clinic visit, urine samples for toxicology screening were obtained under supervision, and patients were assessed

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for evidence of methadone withdrawal (i.e., perspiration, agitation, sneezing, diarrhea, leg cramps, pupillary diameter, rhinorrhea, and yawning). None of the patients was prescribed any additional drugs that would be expected to interfere with the metabolism-of methadone.

Plasma concentrations of methadone were determined as described elsewhere [2, 3]. The limit of quantification was 2 ng/mL. Interassay variability was determined with 3 different control samples that contained nominal methadone concentrations of 50, 200, and 400 ng/mL and that had coefficients of variation that were 9.9%, 4.8%, and 4.2%, respectively. Intra-assay precision was determined with samples that contained 50 and 400 ng/mL.

The pharmacokinetic parameters that were determined for methadone included the maximum plasma concentration (C_{max}) and the AUC to 24 h (AUC_{0-24h}). C_{max} was determined by inspection of the data. AUC values were determined by noncompartmental analysis done with the use of TOPFIT computer software (Gustav Fischer Verlag). Differences in pharmacokinetic parameters were compared by paired Student's f test. $P < .05$ was considered statistically significant.

Results. Eight patients (4 men and 4 women) were enrolled in the study. The mean patient age was 34 years (range, 23-38 years). All patients were found to be positive for hepatitis C antibody and PCR positive for hepatitis C virus, and all had normal biochemical hepatic function. Of the 8 patients, 2 *(25%)* had not previously received antiretroviral therapy, and 6 (75%) had previously received antiretroviral therapy. The mean baseline CD4 cell count was 148 X 10^6 cells/L (range, 65-282 X 10^6 cells/ L), and the mean HIV RNA level was 115,492 copies/mL (5-06 log; range, 8000 copies/mL [3.09 log] to 250,000 copies/mL [5.4 log]). All patients received combination therapy that consisted of 3 antiretrovirals: stavudine, didanosine, and Lpv-Rtv (for 4 patients) or zidovudine, lamivudine, and Lpv-Rtv (for 4 patients). Antiretroviral drugs were chosen on the basis of previous patient exposure to antiretrovirals and the resistance profiles of the drugs, when available. The mean pretreatment methadone dose was 74 mg (range, 40-100 mg; median, 80 mg).

All a patients who were recruited completed the study. The mean methadone AUC_{0-24h} data for the 8 patients, both before and after Lpv-Rtv therapy, are illustrated in figure 1. The mean AUC_{0-24h} for methadone was significantly reduced from 10,835 ng/h/mL (range, 3829-12,638 ng/h/mL) to 6943 ng/h/mL (range, 3949-13,692 ng/h/mL) when Lpv-Rtv was coadministered (95% CI, 436-7892; P = .01). There was also a 44% reduction in the mean C_{max} for methadone when Lpv-Rtv was coadministered. None of the patients experienced symptoms of methadone withdrawal during the study period or during the extended 6-week follow-up.

Discussion. A small study has reported conflicting findings of enhancement of both methadone effects and withdrawal

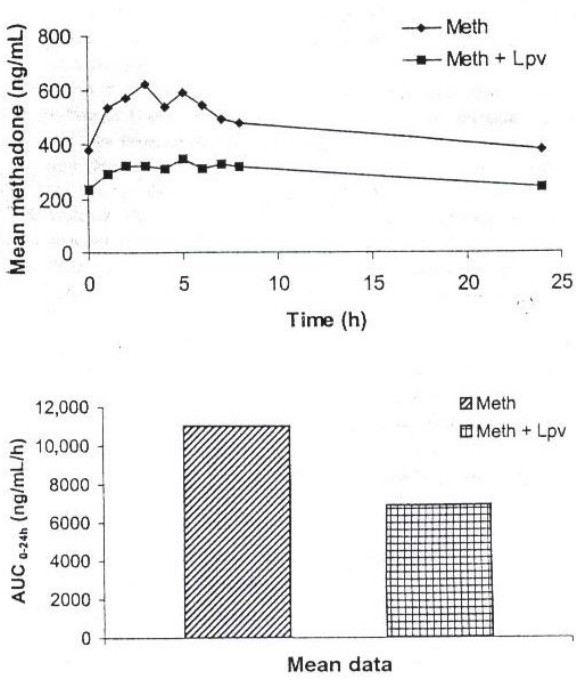

Figure 1. Mean methadone (Meth) profiles before and after lopinavir (Lpv) and ritonavir cotherapy. AUC_{0-24h}, area under the plasma concentration–time curve to 24 h.

symptoms when the drug is received in combination with Rtv, indinavir, and saquinavir (Sqv) [6]. Coformulation of Lpv with Rtv results in pharmacokinetic enhancement by Rtv and a subsequent increase in Lpv exposure [4]. In vitro and in vivo studies have demonstrated that Lpv-Rtv is a potent inhibitor of CYP3A4 and CYP2D6, which are primarily Rtv mediated [5]. In contrast, in a study of healthy volunteers, there was a 47% reduction in the methadone AUC when methadone was coadministered with Lpv-Rtv [5]. It has therefore been suggested that patients who receive methadone and Lpv-Rtv concurrently may require an increased methadone dose as a result of in vivo induction of CYP450 enzymes and glucuronyltransferase [5].

The results of our clinical experience with GUIDE Clinic patients who received both Lpv-Rtv and methadone are not consistent with *a* pharmacokinetic interaction that affects individual methadone dose requirements. Since Lpv-Rtv became available on an expanded-access program, data have been prospectively collected on all IDUs who have received this drug as part of combination therapy. Lpv-Rtv was prescribed to 14 IDUs who concurrently received methadone. After receiving, therapy for 8 weeks, none of the patients experienced symptoms, consistent with methadone withdrawal. Maximum induction of hepatic enzymes occurs within 7-10 days of commencing; therapy with an enzyme inducer, so it is therefore unlikely that

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any of these patients will experience methadone withdrawal at a later stage [7]. A retrospective study of patients *who* received Lpv-Rtv suggested that, contrary to the implications from the heal thy volunteer data, there is no need to adjust the methadone dose for patients who receive Lpv-Rrv (S.C., L. McCuIlough, C.B., and EM., unpublished data).

Our prospective pharmacokinetic study, which was performed to more accurately define the interaction between Lpv-Rtv and methadone, provided surprising results. Consistent with the data for healthy volunteers, there was a significant reduction (36%) in the methadone $AUC_{0\text{-}24h}$ when our patients received methadone in combination with Lpv-Rtv. However, despite this reduction, none of the patients either presented with symptoms or signs of methadone withdrawal or required a methadone dose adjustment. Three of the patients actually suggested that they believed that their methadone therapy lasted longer after antiretroviral therapy was initiated. The present study therefore confirmed the previous clinical observation that there is no need for dose adjustments for patients who receive methadone and Lpv.

The mechanism .for the reduction in the methadone AUC is unclear but will be related to one or more of the following: induction of CYP450 isozymes and/or glucuronyltransferase in' the liver or gastrointestinal mucosa; induction of P-glycoprotein; altered plasma protein binding; and unequal effects of the drug on isomeric forms of methadone. Why a significant tie-' crease in the methadone AUC should not lead to opioid withdrawal symptoms is also unclear. In a study of the clinical and pharmacological effects of Rtv and Sqv on methadone metabolism, Gerber et al. [81 provided important new data on the impact of altered plasma protein binding on methadone pharmacokinetics. They demonstrated a significant discordant effect on R-isomers and S-isomers, with a 40% reduction in S-methadone levels, compared with a 32% reduction in R-methadone levels. Unlike other studies of methadone metabolism, the study by Gerber et al. [8| also corrected for changes in plasma protein binding associated with Rtv-Sqv therapy, and, of interest, it also demonstrated that the actual reduction in free methadone iso-mers was 24.6% for S-methadone and 19.6% for R-methadone. The implied hypothesis is that this less significant effect on free R-methadone levels is the reason why none of the 12 patients in their cohort experienced symptoms of opioid withdrawal during the study period. It is important to note, however, that 5 of their patients tested positive for either benzodiazepines or cocaine during the study, a finding that may have altered the severity of any withdrawal symptoms.

The study by Gerber et al. [8] further highlights the need for a consistent evaluation of opioid effects that uses both objective and subjective findings. Currently available questionnaires and examination techniques demonstrate the extremes of opioid withdrawal or overdose, and minor symptoms of withdrawal or overdose may be overlooked. Similarly, the possibility that patients involved in methadone pharmacokinetic studies are supplementing their methadone therapy with additional methadone or with other illicit drugs when they are not in the confines of the study institution must also be considered.

These data on the interaction between Lpv-Rtv and methadone demonstrate a significant reduction in the methadone AUC and C_{max}, but the absence of overt opioid withdrawal symptoms in these patients will have a positive impact on the clinical usefulness of this drug for IDUs. Future studies of methadone interactions should include measures of isomeric and plasma protein-bound methadone and a standardized measurement of opioid effects.

References

1. Carpenter CC. Cooper DA, Fischyl MA, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA panel. JAMA **2000;** 283: 3:381-90.
2. Clarke S, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. Br J Clin Pharmacol **2001;** 5 1:213-7.
3. Clarke S, Mulcahy FM, Tjia J, et al. Pharmacokinetic interactions of nevirapine and methadone and guidelines for the use of nevirapine to treat injecting drug users. Clin Infect Dis **2001;** 33: 1595-7.
4. Stryker R, Brun S, King M, et al. Kaletra in antiretroviral naive H1V-posittve patients: follow-up beyond two years and viral load suppression below 3 copies/mL [abstract 101]. In: Program and abstracts of the 7th Annual Conference on Retroviruses and Opportunistic Infections (San Francisco). Abbott Park, IL: Abbott Laboratories, **2000.**
5. Bertz R, Hsu A, Lam W, et al. Pharmacokinetic interactions between Kaletra and other non-HIV drugs [abstract 438]. In: Program and abstracts of the 5th International Congress on Drug Therapy in HIV Infection (Glasgow). Abbott Park, IL: Abbott Laboratories, **2000.**
6. Beauverie P, Taburet A-M, Dessalles M-C, Furlan V, Touzeau D. Therapeutic drug monitoring of methadone in HIV-infected patients reviving PIs. AIDS **1998;** 18:2510-1.
7. Barry MJ, Feely J. Enzyme induction and inhibition. Pharmacol Ther **1990;**48:781-94.
8. Gerber JG, Kosenkranz S, Segal Y, et al. Effect of ritonavir/saquinavir on stereoselective pharmacokinetics of methadone: results of A IDS Clinical Trials Croup (ACTG) 401. J Acquir Immune Defic Syndr **2001;**27: 153-60.

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