Treatment of Opioid Dependence and Coinfection with HIV and Hepatitis C Virus in Opioid-Dependent Patients: The Importance of Drug Interactions between Opioids and Antiretroviral Agents

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The occurrence of human immunodeficiency virus (HIV) disease and hepatitis C is common in injection drug users, most of whom are opioid dependent. Methadone pharmacotherapy has been the most widely used treatment for opioid addiction in this population. Methadone has significant, adverse drug-drug interactions with many antiretroviral therapeutic agents that can contribute to nonadherence and poor clinical outcomes in this high-risk population. The present article summarizes current knowledge about interactions between methadone and antiretroviral medications. Buprenorphine is the newest agent available for the treatment of opioid dependence and may have fewer adverse interactions with antiretroviral agents. Buprenorphine has a significant pharmacokinetic interaction with efavirenz but no pharmacodynamic interaction; therefore, simultaneous administration of these drugs is not associated with opioid withdrawal, as has been observed with methadone. This promising finding may simplify the treatment of opioid-dependent patients with HIV disease and should also improve clinical outcomes for persons coinfected with HIV and hepatitis C virus.

The prevalence of HIV disease and hepatitis C in North and South America, Europe, and parts of Asia is, to a large extent, driven by injection drug use. There is a high comorbidity of these diseases in injection drug users, with a reported rate in the United States of ~33% [1]. The increasing prevalence of these diseases is a consequence of opioid (e.g., heroin and opium) dependence and high-risk behaviors often associated with injection drug use, including sharing of contaminated syringes and unprotected sexual contact [2]. The treatment of choice for these patients is opioid maintenance therapy, available principally as either methadone or the newer agent for treatment of opioid dependence, buprenorphine [3].

Early preclinical studies elucidating the clinical pharmacology of antiretroviral medications and opioids indicated that drug interactions were likely to occur [4, 5]. Methadone and buprenorphine are primarily metabolized by hepatic cytochrome P_{450} (CYP_{450}) enzymes, specifically CYP_{450} 3A4 [6, 7]. A number of antiretroviral medications are substrates of CYP_{450} 3A4 and, in preclinical studies, were shown to inhibit the activity of CYP_{450} 3A4, which led to speculation that opioid toxicity and/or toxicity related to increased exposure to HIV medications could occur in patients receiving maintenance therapies. Conversely, if an antiretroviral agent induced production of CYP_{450} enzymes, an opioid abstinence syndrome could result, which would place the patient at risk for relapse to illicit drug use. Here, identified drug interactions known to occur in persons receiving both treatment for opioid dependence and antiretroviral therapy, focusing on methadone in combination with HIV therapies are discussed. In addition, methadone in combination with efavirenz, a frequent component of HAART, and in combination with buprenorphine are compared.

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DRUG-DRUG INTERACTION STUDIES

The emergence of several classes of antiretroviral therapeutics has transformed HIV disease from a uniformly progressive, fatal illness to a chronic disease. Potent HIV medications administered in combinations (HAART) are routinely used in the long-term treatment of HIV disease. HAART consists of either a protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor (NNRTI) in combination with 2 nucleoside reverse-transcriptase inhibitors (NRTIs) [8, 9]; the specific combination of drugs often is determined through testing of the infecting strain for drug resistance. One approach to identifying drug interactions of importance in patients undergoing opioid maintenance therapy receiving HAART would be to examine specific HAART regimens in combination with opioid therapies in HIV-infected patients. The large number of possible drug combinations in HAART and the growing number of antiretroviral agents available make it difficult to predict the most important combinations to study. Furthermore, recruitment of an adequate sample size of patients with HIV disease undergoing opioid maintenance therapy who are receiving any specific HAART regimen would be challenging and probably not feasible. To obtain an understanding of drug-drug interactions between opioids and antiretroviral medications in general, single antiretroviral agents have been studied in combination with opioids of interest. The underlying premise of these studies is that knowledge of the interaction of single antiretroviral agents with specific opioids is necessary to understanding interactions that might be identified in the course of HAART in patients undergoing opioid maintenance therapy.

It appears that, in terms of drug disposition, persons without HIV disease do not differ significantly from those with HIV disease. This allows for pharmacokinetic study designs in which single-drug interactions between an opioid therapy and one antiretroviral medication are undertaken. For example, in early studies of zidovudine disposition in combination with opioid therapies (i.e., methadone, L-acetyl methadol [LAAM], buprenorphine, and naltrexone) [10, 11], zidovudine monotherapy was the standard of care when the study was initiated, and opioid-dependent persons with HIV disease who qualified for zidovudine treatment were routinely recruited for study participation. The advent of HAART occurred while these studies were being conducted, resulting in a change in study protocol such that only HIV-negative persons could be enrolled in single-drug interaction studies. A comparison of zidovudine pharmacokinetics in patients with and without HIV disease showed no significant differences [11]. In the present review, studies that describe significant drug interactions attributed to a single antiretroviral agent but studied in HIV-infected patients undergoing HAART are also summarized.

By preventing the onset of withdrawal symptoms and alleviating opioid craving, opioid therapy assists in stabilizing the day-to-day life of an opioid-dependent person. Without substance abuse treatment, opioid-dependent persons spend significant time using illicit opioids or engaging in activities necessary to obtain opioids (often activities placing them at high risk for contracting or transmitting viral infections). Their physical state fluctuates between intoxication and withdrawal. These realities make it difficult to adhere to the requirements of complex antiretroviral therapies for HIV disease or for hepatitis C. Failure to effectively treat opioid dependence is associated with poor treatment outcomes among patients with HIV disease [12, 13]. Similarly, treatment guidelines for hepatitis C recommend that the physician assist patients with addiction in undergoing treatment for substance use disorders and that the physician consider carefully the ability of the patient to comply with treatment with IFN plus ribavirin for hepatitis C if untreated substance abuse is a problem for the patient [14]. Other consequences of nonadherence to antiretroviral therapy include the emergence of virus resistant to current therapeutics, increased illicit drug use, lack of efficacy of both treatments, and toxicities associated with opioids and/or antiretroviral agents.

INTERACTIONS OF NRTI DRUGS WITH METHADONE

NRTI drugs were the first class of medications developed for the treatment of HIV disease and the first medications to be examined for interactions with methadone. These studies showed that NRTIs (e.g., zidovudine) were unlikely to affect methadone concentrations and, therefore, would probably not be associated with opioid abstinence symptoms or toxicity [10].

However, the first study of the effect of methadone on zidovudine was undertaken originally during the era of HIV monotherapy when patients undergoing methadone maintenance treatment complained of symptoms that appeared to be consistent with opioid withdrawal, but methadone levels were found to be therapeutic [15]. A study of zidovudine administered intravenously and orally before and after methadone stabilization of opioid-dependent persons with HIV disease showed that methadone was associated with inhibition of the glucuronidation of zidovudine. The resulting 41% increase in plasma concentrations of zidovudine produced zidovudine toxicity in some patients [10]. A subsequent study examining the interaction of LAAM, buprenorphine, or naltrexone—3 additional pharmacotherapies approved for the treatment of opioid dependence in the United States—showed no clinically significant effect on plasma concentrations of zidovudine [11]. No effect of zidovudine on the opioid pharmacotherapies was observed [10, 11]. This finding led to speculation that matching treatments for opioid dependence and HIV disease in patients with comorbid substance dependence and HIV disease would lead to improved clinical outcomes.

A study examining the effect of methadone administration on pharmacokinetics of didanosine (ddI) and stavudine (d4T) showed significant decreases in exposure to both drugs (reduction in area under the concentration-time curve [AUC] for ddI of 63% [$P = .04$] and for d4T of 25% [$P = .005$]) when each was administered at its standard clinical dose for treatment of HIV infection [16]. The explanation for this phenomenon was a reduction in bioavailability, which was postulated to be due to slowed gastrointestinal transit time, with decreased absorption related to increased exposure to drug-metabolizing enzymes lining the intestine and/or to acid-catalyzed degradation in the stomach. The decrement in plasma concentration was most marked for ddI; therefore, an enteric-coated formulation was developed that can be given once daily and lacks the interaction described with methadone for the ddI tablet formulation [17]. Neither ddI or d4T appears to have a significant effect on the pharmacokinetics of methadone [16]. In another study, the combination tablet lamivudine plus zidovudine has been shown to have no effect on methadone concentrations in persons undergoing opioid maintenance therapy [18]. This finding is also of relevance to the treatment of hepatitis B in patients undergoing methadone maintenance therapy, because lamivudine is an approved treatment for hepatitis B. Abacavir in combination with methadone is associated with an increase in methadone clearance that did not require alteration of methadone dose and with little effect on pharmacokinetics of abacavir [19]. Notably, the effect of methadone on the NRTIs is not mediated by CYP_{450} enzymes and, thus, is not readily studied in vitro, underscoring the need to conduct drug interaction studies in human volunteers.

PROTEASE INHIBITORS WITH METHADONE

The protease inhibitors have also been studied in combination with methadone because of the potential for adverse drug interactions to occur with opioids. In vitro studies showed that protease inhibitors, specifically saquinavir, indinavir, ritonavir, and nelfinavir, were inhibitors of CYP_{450} 3A enzyme activity [5], which led the manufacturers of antiretroviral medications to include warnings about the potential for methadone-associated opioid toxicity with simultaneous administration, because the question of whether drug interactions occurred had not been studied in humans at the time of approval by the US Food and Drug Administration (FDA). However, in vivo studies showed the opposite to be true; in fact, concomitant administration of several of the protease inhibitors with methadone showed decreases in serum concentrations of methadone [20–26].

Studies of drug interactions between methadone and nelfinavir in humans have been reported [20, 21]. A significant decrease in methadone levels relative to pre-nelfinavir baseline methadone pharmacokinetics occurs with concomitant administration of these drugs (42% decrease in methadone AUC after administration of nelfinavir) [21]. It appears that in most persons, the decrease in methadone exposure is offset by competition between methadone and nelfinavir for protein binding, with a resulting increase in free methadone levels. This relative increase in free methadone is sufficient to prevent the onset of opioid abstinence symptoms in most patients.

The effect of ritonavir plus saquinavir on methadone disposition has also been studied. Ritonavir plus saquinavir was associated with induction of methadone metabolism, but this effect was greater for the inactive form (*S*-methadone [40%]), whereas the active form (*R*-methadone) was decreased by only 32%. The reduced effect of ritonavir plus saquinavir on *R*-methadone was not associated with opioid abstinence symptoms or a need for a change in methadone dosage for study participants [22]. Amprenavir has been associated with a reduction in methadone exposure and opioid withdrawal symptoms when administered in combination with abacavir, an NRTI that can also reduce plasma concentrations of methadone [23]. Similarly to the effect of saquinavir on methadone, amprenavir administered over the course of 10 days reduced both *R*- and *S*-methadone, but the predominant effect was on *S*-methadone [24].

Lopinavir plus ritonavir (Kaletra; Abbott Laboratories) is the first combination protease inhibitor to be approved by the FDA and has been studied in combination with methadone, to determine whether adverse pharmacokinetic or pharmacodynamic interactions might occur in persons receiving both drugs. Lopinavir plus ritonavir was associated with significant reductions in methadone AUC ($P < .001$), maximum concentration in serum (C_{max}) ($P < .001$), minimum concentration in serum (C_{min}) ($P < .001$), increased oral clearance ($P < .001$), and increased opiate withdrawal symptoms ($P = .013$) [25]. However, ritonavir alone modestly and nonsignificantly increased methadone concentrations, as might be predicted given that ritonavir is an inhibitor of CYP_{450} 3A4 and is used in subtherapeutic doses in the lopinavir-ritonavir combination drug. For example, each lopinavir-ritonavir dose contains 100 mg of ritonavir, which is administered twice daily to a patient receiving Kaletra. A therapeutic dose of ritonavir alone for the treatment of HIV disease is 600 mg twice daily. Because of its ability to inhibit CYP_{450} 3A4, ritonavir has been used to increase concentrations of other antiretroviral agents also metabolized by CYP_{450} 3A4. Lopinavir, a known inducer of CYP_{450} 3A4, is a potent inducer of methadone metabolism. In that study [25], some participants, particularly those with trough methadone concentrations at the lower end of the therapeutic range, experienced symptoms consistent with an opioid abstinence syndrome. Other studies have reported similar decreases in methadone exposure in patients treated with lopinavir plus ritonavir but found no evidence for opioid withdrawal symptoms [26]. Those findings

could be associated with higher trough plasma concentrations of methadone at baseline. Treatment with lopinavir plus ritonavir in patients undergoing methadone maintenance therapy will require clinical monitoring and increased methadone dosages for some patients, whereas ritonavir has no significant effect on methadone exposure.

NNRTI INTERACTIONS WITH METHADONE

There are currently 3 NNRTIs available for the treatment of HIV disease. Each has a significant interaction with methadone. Furthermore, a recent study has also shown that LAAM has a significant interaction with the NNRTI delavirdine [27]. Likewise, a significant pharmacokinetic interaction occurs with simultaneous administration of buprenorphine and efavirenz, but without concomitant pharmacodynamic interactions [28].

Nevirapine, an inducer of CYP_{450} 3A activity [29], was the first of the NNRTIs reported to be associated with an adverse interaction with methadone. A clinical report discussed the onset of significant and severe opioid abstinence syndromes after administration of this medication in several patients undergoing methadone maintenance therapy and with HIV disease [30], leading to discontinuation of nevirapine therapy in several instances or significant increases in daily methadone dose. A study of the interaction between nevirapine and methadone in 8 patients with HIV disease undergoing maintenance therapy with methadone who received a nevirapine-containing HAART regimen revealed a significant decrease in methadone exposure ($P = .0052$), resulting in opiate withdrawal symptoms and increases in methadone dosages in 6 of 8 participants [29].

Delavirdine is an inhibitor of CYP_{450} 3A [6]. As such, it might be less likely to be associated with symptoms of opioid withdrawal that can occur when HIV medications that increase the rate of methadone metabolism are administered. However, if delavirdine were to inhibit CYP_{450} 3A metabolism of opioids, its use could present a risk for opioid toxicity when administered in combination with opioid therapies. In a study examining the pharmacokinetic and pharmacodynamic interactions of concurrent delavirdine and opioid administration, delavirdine was found to significantly decrease methadone clearance ($P = .018$) and increase methadone elimination half-life ($P < .001$), with a resultant increase in AUC of 19% and C_{min} of 29% [27]. The effect of delavirdine on LAAM and its active metabolites, norLAAM and dinorLAAM, was to significantly increase AUC by 43% ($P < .001$), C_{max} by 30% ($P = .013$), and C_{min} by 59% ($P = .004$), while decreasing time to C_{max} ($P = .05$). No cognitive deficits or opioid withdrawal symptoms were observed with simultaneous administration of delavirdine and methadone or LAAM, but participants were administered delavirdine for only 7 days, a far shorter period than would be expected for treatment of HIV disease. Methadone and LAAM did not affect delavirdine concentrations, which remained in the therapeutic range. The findings from that study [27] showed that delavirdine treatment in persons undergoing maintenance therapy with methadone or LAAM resulted in altered opioid pharmacokinetics, with increased exposure and a potential risk for opioid toxicity. LAAM has been associated with prolongation of the QTc interval and potentially life-threatening cardiac arrhythmias [31, 32], underscoring the potential risk of concomitant LAAM and delavirdine administration.

Efavirenz is a newer NNRTI. This drug is known to be both an inducer and substrate of CYP_{450} 3A4. It has been shown in 2 studies to induce methadone metabolism and to be associated with the onset of an opioid abstinence syndrome in most persons receiving the 2 drugs concurrently [28, 33]. Efavirenz reduces methadone concentrations through its induction of CYP_{450} 3A4 enzyme activity.

THE FUTURE OF DRUG INTERACTION STUDIES

As a result of the identification of several serious adverse drug interactions between methadone and antiretroviral medications, the US FDA now requires pharmaceutical manufacturers to conduct drug interaction studies between methadone and their antiretroviral agents in development, a decision of real benefit to opioid-dependent patients with HIV disease. Several newer drugs have been studied, and results are available to clinicians by review of package insert material.

Pharmaceutical manufacturers are not, however, required to conduct drug interaction studies between their agents and other opioid therapies for the treatment of substance use disorders, perhaps the most important being buprenorphine. The concept of matching treatments to patients who are opioid dependent and who have HIV disease and, often, hepatitis C is of interest. Because of the several clinically significant adverse interactions between methadone and antiretroviral agents, it becomes important to determine whether there is an opioid therapy for treatment of opioid addiction that might confer an advantage over methadone. Two research studies that demonstrate the importance of understanding drug interactions between opioids and antiretroviral therapies, the potential effect on treatment outcomes, and the potential of buprenorphine as a pharmacotherapy for opioid dependence in patients who also are receiving treatment for HIV disease [28, 34] are summarized below.

MODIFIED DIRECTLY OBSERVED THERAPY IN OPIOID-DEPENDENT PATIENTS WITH HIV DISEASE

In this study, persons undergoing methadone maintenance who had AIDS and were eligible for HAART were prescribed a regimen containing once-daily efavirenz and enteric-coated didanosine with 1 additional NRTI that was administered twice

daily [34]. Participants received 1 daily dose of HAART at the methadone maintenance program and were given 1 unit dose of the twice-daily nucleoside as a take-home medication. This pilot study was undertaken to determine the feasibility of observed antiretroviral dosing in the substance abuse treatment program and to determine whether such an intervention was effective. All of the study participants had previously experienced failure of HAART because of nonadherence. With directly observed therapy, participants showed significant improvement over the first 8 weeks of treatment, as evidenced by substantial decreases in virus load (4 of 5 patients had a nondetectable virus load by week 8 of treatment) and nonsignificant increases in $CD4^+$ cell count. However, 4 of 5 study participants also developed rapid onset of opiate abstinence (within 2 weeks of initiation of HAART) and required significant increases in methadone dosage (on average, a 52% increase over the course of 5 weeks) in response to opiate withdrawal symptoms. With the onset of withdrawal symptoms, participants were admitted to the hospital, where a pharmacokinetics study was undertaken. This study revealed a significant decrease in methadone exposure associated with HAART [34]. Efavirenz was postulated to be responsible for the decrease in methadone concentrations through induction of CYP_{450} 3A4 enzyme activity, because didanosine and other NRTIs included in the antiretroviral regimens in this study were known not to have significant effects on methadone disposition. This pilot study showed that modified directly observed therapy for patients with HIV disease receiving methadone maintenance therapy can be a promising intervention for increasing adherence to HAART and improving clinical outcomes. However, the complexity of the required close monitoring of patients for withdrawal symptoms and rapid increases in methadone dose complicate this intervention.

INTERACTION OF BUPRENORPHINE AND EFAVIRENZ

Buprenorphine is an opioid partial agonist that has been shown to be equivalent in efficacy to methadone in the treatment of opioid dependence, as shown by reductions in positive results of drug screens of urine for opioids and retention in substance abuse treatment programs [35]. Buprenorphine confers advantages over methadone for patients with HIV disease in that it is the first opioid drug to be approved by the US FDA for treatment of opioid dependence that is available by prescription from a physician in office-based practice, thus enabling patients with serious medical illnesses to receive treatment for substance dependence and medical illness from the same physician. This is likely to assist patients in receiving treatment for comorbid conditions by simplifying the process of receiving medical care.

Given the potential for the use of buprenorphine as a treatment for opioid dependence in this group, a primary question becomes whether adverse drug interactions similar to those observed with methadone and several antiretroviral agents will occur between buprenorphine and HIV therapeutics. In an attempt to begin to answer this question, drug interaction studies between buprenorphine and antiretroviral medications are being undertaken.

Similar to methadone, the principal route of clearance for buprenorphine is via *n*-demethylation to norbuprenorphine by CYP_{450} 3A4 [36]. In a study in which opioid-dependent participants stabilized by treatment with buprenorphine-naloxone (Suboxone) for at least 2 weeks were given standard clinical doses of efavirenz (600 mg daily) for 15 days, administration of efavirenz produced substantial and significant decreases in buprenorphine and nor-buprenorphine exposure [28], but plasma efavirenz concentrations remained in the therapeutic range with standard clinical doses of buprenorphine [37]. Interestingly, these study participants experienced no opioid abstinence symptoms (table 1) as measured by the Objective Opiate Withdrawal Scale [38], a clinician-administered rating scale measuring severity of opiate withdrawal symptoms, and required no buprenorphine dose adjustments, in contrast to patients with HIV disease undergoing maintenance therapy with methadone who received treatment with efavirenz-containing HAART in the study of modified directly observed therapy [34]. The results of these studies in total indicate that, compared with methadone, buprenorphine is less likely to be associated with adverse events when given with efavirenz-containing HAART. The reason for this lack of a significant pharmacodynamic interaction may be related to the high affinity and long duration of mu opioid receptor binding for buprenorphine [39, 40]. Buprenorphine is metabolized to nor-buprenorphine, an active metabolite that may prolong opioid effects. This is in contrast to methadone, which is metabolized to inactive compounds. These findings with buprenorphine will contribute to simplification of the treatment of opioid-dependent patients with HIV disease who require efavirenz. Buprenorphine treatment of opioid dependence offers a significant advantage for

Table 1. Comparison of the effect of efavirenz on opioid dependence pharmacotherapy treatment with either methadone or buprenorphine.

Factor	Methadone	Buprenorphine
Baseline opioid dose, mg/day	80 (28)	17.2 (1.9)
Post-efavirenz opioid dose, mg/day	120 (10)	17.2 (1.9)
Opioid dose increase, %	50	0
Time to opiate withdrawal, weeks	1 (.84)	Not applicable
Time to stable opioid dose, weeks	4 (4.2)	0
Baseline OOWS score	0.7 (1.1)	0
Post-efavirenz OOWS score[a]	5 (3.3)	0.10 (0.3)

NOTE. Data are mean (SD) except where noted. OOWS, Objective Opiate Withdrawal Scale.

[a] $P = .0005$.

HIV-infected patients who require an efavirenz-containing HAART, because patients will be less likely to experience opioid withdrawal when prescribed both treatments, thus increasing the likelihood of adherence to prescribed regimens with better clinical outcomes.

SUMMARY

Drug interactions are an important potential complication of opioid-assisted treatment for opioid dependence in patients with HIV disease. The consequences of adverse drug interactions are substantial and include opioid abstinence syndromes, as well as opioid and/or antiretroviral toxicity. Adverse drug interactions are also associated with nonadherence and poor clinical outcomes in this population with comorbid opioid addiction and HIV disease, as well as high rates of hepatitis C. Knowledge of drug interactions can also be used to "match" treatments to patients, thus minimizing toxicities and optimizing clinical response.

Buprenorphine represents a significant advance in the treatment of opioid dependence and may confer specific advantages to opioid-dependent patients with HIV disease. Efavirenz is associated with a significant and severe adverse interaction in combination with methadone, but it is an important pharmacotherapy for the treatment of AIDS because of its potent effect on HIV. The observed adverse pharmacodynamic interaction with simultaneous methadone and efavirenz administration is absent with buprenorphine and efavirenz therapy. This greatly simplifies treatment of both opioid dependence and HIV disease because standard clinical dosages of both medications can be administered without close monitoring or frequent medication titrations. If this finding extends to buprenorphine in combination with other antiretroviral therapies, it will represent an important advance in the treatment of HIV disease in patients with comorbid opioid dependence. Positive effects will include not only the absence of adverse drug interactions between buprenorphine and HIV therapeutics but also the efficiencies inherent in having a single physician provide care for both infectious disease and addiction, as well as decreased toxicities in patients who must also undergo treatment with IFN plus ribavirin for hepatitis C. Ongoing research studies are currently investigating the question of the presence and extent of drug interactions between buprenorphine and other antiretroviral agents, with planned studies to examine drug interactions between therapies for hepatitis C virus infection as well.

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