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Methadone, Buprenorphine, and Street Drug Interactions with Antiretroviral Medications

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Abstract While street drugs appear unlikely to alter the metabolism of antiretroviral (ARV) medications, several ARVs may induce or inhibit metabolism of various street drugs. However, research on these interactions is limited. Case reports have documented life-threatening overdoses of ecstasy and gamma-hydroxybutyrate after starting ritonavir, an ARV that inhibits several metabolic enzymes. For opioid addiction, methadone or buprenorphine are the treatments of choice. Because a number of ARVs decrease or increase methadone levels, patients should be monitored for methadone withdrawal or toxicity when they start or stop ARVs. Most ARVs do not cause buprenorphine withdrawal or toxicity, even if they alter buprenorphine levels, with rare exceptions to date including atazanavir/ritonavir associated with significant increases in buprenorphine and adverse events related to sedation and mental status changes in some cases. There are newer medications yet to be studied with methadone or buprenorphine. Further, there are many frequently used medications in treatment of complications of HIV disease that have not been studied. There is need for continuing research to define these drug interactions and their clinical significance.

Keywords Drug interactions · Street drugs · Methadone · Buprenorphine · Anti-HIV agents

Introduction

Many people with HIV use street drugs [1]. People who use street drugs (eg, heroin, cocaine, methamphetamine, club drugs) are at high risk for contracting HIV, hepatitis C, and other infections from used needles, syringes, or pipes, or from unprotected sex with high-risk partners, group sexual encounters, or exchanging sex for drugs for sex. Drug use also predicts progression of HIV disease, even when controlling for associated risk factors such as medication nonadherence [2]. As a result, many drug users with HIV will require treatment with antiretroviral medications (ARVs). Thus, it is essential for HIV clinicians to know their patients’ street drug use, and to convey to them how their reactions to street drugs may change when they start or stop ARVs. Clinicians also need to know how street drug use may affect patients’ response to ARVs, so that they can advise patients to stop using certain drugs, assist the patient with obtaining substance abuse treatment, or can select effective ARVs that do not interact with the specific street drugs used.

Many street drug users with HIV have developed addictions requiring treatment with medications. Many heroin-addicted patients need long-term maintenance with opioid therapy such as methadone or buprenorphine to prevent relapse, illness, and early death [3]. Medications for cocaine and methamphetamine addiction are in development. In this article, we review existing literature on clinically relevant drug interactions of ARVs with street drugs and opioids used in the treatment of opioid addiction.

ARV Metabolism

Adverse drug interactions can occur through several mechanisms, either pharmacodynamic (between drugs with
similar effects) or pharmacokinetic (between drugs that alter or are substrates of the same metabolic enzyme[s] or other drug disposition pathways). Most pharmacokinetic interactions occur when a drug increases or decreases metabolism of other drugs in the liver (cytochrome P450 [CYP] enzymes or glucuronidation). Other causes of pharmacokinetic interactions occur with changes in drug transport by P-glycoprotein, or in drug absorption.

Most ARVs used in the treatment of HIV are metabolized by the CYP450 enzymes [4], as are most drugs of abuse and the opioid medications methadone and buprenorphine. Alteration in the CYP450 system is the basis of most of the interactions between these substances. Specifically, the nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), which form the backbone of highly active antiretroviral therapy, are all metabolized by (ie, are substrates of) the CYP450 enzymes, most by CYP3A4. In addition, each of the NNRTIs and PIs induce and/or inhibit specific CYP450 enzymes. Among the NNRTIs, efavirenz and nevirapine induce CYP3A4, while delavirdine inhibits CYP3A4, and etravirine induces CYP3A4 while inhibiting CYP2C9 and CYP2C19. In vitro studies show most of the PIs are CYP3A4 inhibitors (atazanavir, darunavir/ritonavir, lopinavir/ritonavir, saquinavir, tipranavir/ritonavir), or strong CYP3A4 inhibitors (indinavir/ritonavir, nelfinavir, ritonavir). Some PIs both inhibit and induce CYP3A4 (amprenavir, fosamprenavir). Ritonavir also inhibits CYP2D6. The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), the fusion inhibitor enfuvirtide, and the integrase inhibitor raltegravir are not metabolized by the CYP450 system.

It can be difficult to determine which mechanisms are responsible for drug interactions. Although in vitro studies reliably show induction or inhibition of specific CYP enzymes, these do not predict drug interactions when the compounds inhibit some and induce other enzymes, and do not predict responses in humans who ingest these medications. In this article, we review research on pharmacokinetic interactions of ARVs with street drugs, methadone, and buprenorphine.

Street Drug Interactions with Antiretrovirals

Street drugs, or drugs of abuse, are drugs that are obtained and often manufactured illegally, and taken for the subjective effects they produce. They often contain impurities and may cause unexpected toxicity. Fortunately, street drugs do not significantly induce or inhibit the CYP450 enzymes that metabolize many ARVs. However, many street drugs are substrates of one or more CYP450 enzymes, and their effects may be decreased or increased by ARVs that induce or inhibit these enzymes. Although there is almost no research in this area, a number of interactions are likely given their known metabolic pathways.

Heroin and Other Opiates

Commonly abused derivatives of the opium poppy include heroin (metabolized by plasma esterases to morphine), morphine (metabolized by glucuronidation), and codeine (metabolized by glucuronidation). Although ARVs are also metabolized by glucuronidation, no interactions between them and heroin, morphine, and codeine have been reported.

Commonly abused semisynthetics include oxycodone and hydrocodone, commonly prescribed for pain and widely available on the street. Both are metabolized by CYP2D6, and hydrocodone is also metabolized by CYP3A4 [5]. The effects of oxycodone may be increased and decreased when strong CYP2D6 inhibitors such as ritonavir are started and stopped, respectively. Hydrocodone is metabolized by CYP2D6 to a more potent metabolite, hydromorphone; as a result, the CYP2D6 inhibitor ritonavir may decrease rather than increase the effects of hydrocodone [5], resulting in opiate withdrawal symptoms and requests for dose increases.

Cocaine

Cocaine is a known immunotoxic agent, decreasing CD4 production threefold and increasing HIV reproduction up to 20-fold [6]. Cocaine is metabolized by plasma and hepatic esterases. However, about 10% is metabolized by CYP450 enzymes, including CYP3A4. Chronic cocaine administration has been shown to induce CYP3A4 in rodents [7]. If cocaine induces CYP3A4 in humans as well, it may decrease levels and effectiveness of the many ARVs that are CYP3A4 substrates, including most NNRTIs and PIs. P-glycoprotein, an efflux transporter, is increased both by HIV disease and chronic cocaine use [8]. For ARVs that are transported by p-glycoprotein, such as abacavir [9] or indinavir [10], this may result in increased excretion, and subtherapeutic ARV levels.

Ecstasy and Amphetamines

Amphetamines and ecstasy are primarily metabolized by CYP2D6 [5]. Combining even a small dose of ecstasy with the CYP2D6 inhibitor ritonavir has increased and prolonged the effects of ecstasy. In one report, a man died after drinking beer and taking ecstasy after ritonavir was added to his ARV regimen; he had had no adverse effects from ecstasy previously [11]. Another case report [12] described a near-fatal reaction (unresponsive, shallow respirations) in a 29-year-old man who took his usual dose of ecstasy and gamma-hydroxybutyrate (GHB) after having a change in ARVs to saquinavir/ritonavir. This individual reported...
taking two tablets of ecstasy, but became more agitated than usual, and this effect continued for longer than when he had taken similar doses of ecstasy before. A day later he took \( \frac{1}{2} \) teaspoonful of GHB to calm himself, similar to the quantity he had taken as a sleep aid on many occasions without adverse reactions. His friends were taking similar amounts of the same preparation of GHB every 2 to 3 h without adverse effects. Several hours later, he took another such dose of GHB, but this time became unconscious. The authors noted how drug users are often falsely reassured by the reactions of other people they are using drugs with, and recommended that clinicians caution patients that interactions between street drugs and medications can be unpredictable, sometimes dangerous, and differ widely between individuals.

Gamma-Hydroxybutyrate

This depressant is believed to be metabolized by CYP2D6. In combination with saquinavir/ritonavir, a CYP2D6 inhibitor, the combination of GHB and ecstasy has been near-fatal [12].

Benzodiazepines

Several commonly abused benzodiazepines are metabolized by CYP3A4. These include alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), and flunitrazepam (Rohypnol). CYP3A4 inhibitors cause their levels to rise, resulting in possible toxicities such as oversedation. For example, ritonavir has been shown to decrease clearance and increase effects of alprazolam [13]. Conversely, when CYP3A4 inhibitors are stopped, patients may have benzodiazepine withdrawal symptoms. Likewise, CYP3A4 inducers may cause withdrawal symptoms and dose escalation (eg, medication seeking) to avoid withdrawal.

Marijuana

The active ingredients of marijuana, THC and its metabolites, are metabolized via CYP3A4 and to a lesser extent by CYP2C9 [5]. Strong CYP3A4 inhibitors such as the PIs indinavir, nelfinavir, and ritonavir may interfere with marijuana metabolism and increase the risk of marijuana toxicity, such as paranoia. Users can adjust to this by smoking smaller amounts at a time to see how it affects them. Fortunately, several studies showed no effects of smoked marijuana on ARV metabolism [14, 15].

Dissociative Anesthetics

Although phencyclidine (PCP) is metabolized by CYP3A4, and its derivative ketamine is metabolized by CYP3A4 and CYP2B6, there are no reports of toxicity related to CYP3A4 inhibitors [5].

LSD

LSD is metabolized by the liver, but little is known about how this occurs. Patients should be advised about the possibility of unknown interactions [5].

Summary

As described above, ritonavir, a CYP2D6 and CYP3A4 inhibitor, has been associated with life-threatening overdoses from CYP2D6 substrates ecstasy and GHB, and has been shown to increase blood levels and effects of the benzodiazepine and CYP3A4 substrate alprazolam (Xanax). For other street drugs, there is no published research on interactions with ARVs, only knowledge of how they are metabolized, and thus what interactions are likely. Street drug toxicities might be expected with medications that inhibit the enzymes metabolizing street drugs, such as CYP2D6 (eg, ritonavir) for oxycodone, ecstasy, and GHB, and CYP3A4 (eg, delavirdine, ritonavir, PIs) for marijuana, certain benzodiazepines, PCP, and ketamine. Drug users need to be advised that different people react differently to street drugs, and that caution is needed after starting medications that inhibit drug metabolism.

Methadone and Buprenorphine

Because adherence to medication regimens among people with heroin addiction is often poor, effective treatment for HIV in this population requires successful treatment for opioid addiction, usually with opioid therapy. This can prevent withdrawal symptoms and reduce craving that leads opioid-addicted people to spend much of their time in activities aimed at obtaining heroin or other opioids. Interactions between methadone or buprenorphine and other medications can result in suboptimal or excessive levels of the opiate therapy or of the other medication. Subtherapeutic levels of ARVs increase the risk of viral resistance, viral replication, and treatment failure. Similarly, inadequately treated opioid withdrawal symptoms are a primary reason why patients resume illicit drug use and drop out of opioid treatment. This increases risk of nonadherence, development of viral resistance to ARVs, and of return to unsafe drug use and sexual practices that spread HIV to others [16]. Conversely, excessive concentrations of either therapy may cause unwanted side effects leading to treatment nonadherence, treatment discontinuation, or overdose. Methadone, a long-acting \( \mu \)-opioid receptor agonist, is especially helpful with opioid-addicted patients who can...
benefit from daily observed methadone dosing and a structured treatment program. It is also the first choice for heroin-addicted patients who have chronic pain needing to be managed with opioid analgesics. In the United States, methadone treatment for addiction is allowed only in specialty methadone clinics that are regulated by the Substance Abuse and Mental Health Services Administration (SAMHSA) [17].

Buprenorphine, a µ-opioid receptor partial agonist with high affinity to opioid receptors, blocks other opioids’ access to the opioid receptors. As such, at doses used for treatment of opioid dependence, buprenorphine can block the effect of a full µ-agonist analgesic. Because buprenorphine is a Schedule III drug, in the United States it is available by prescription from physicians with a Drug Enforcement Administration waiver that can be obtained with 8 h of SAMHSA-approved training. Therefore, buprenorphine can be provided in any medical setting, such as HIV primary care. This allows patients with complex medical problems and opioid dependence to be treated by the same physician [18].

Buprenorphine has fewer possible drug interactions than methadone, for both pharmacokinetic and pharmacodynamic reasons. Buprenorphine is absorbed sublingually, thus competing less with ARVs for absorption in the gastrointestinal (GI) tract. Methadone is metabolized via CYP 2B6 and 2C19, with mixed literature on the involvement of CYP 3A4, and with minor 2C8 and 2D6 pathways [19, 20â€•, 21â€•]. Buprenorphine is primarily converted to an active metabolite, norbuprenorphine, via CYP3A4 and to a lesser extent by CYP2C8. Buprenorphine and its metabolite norbuprenorphine are further metabolized by glucuronidation, reducing the potential of competing with other drugs in the CYP system and therefore reducing the likelihood of clinically significant drug interactions when compared to methadone [22]. The naloxyone that buprenorphine is often formulated with to discourage misuse is also metabolized by glucuronidation. Neither methadone nor buprenorphine are major inducers or inhibitors of P450 enzymes (methadone is a moderate CYP2D6 inhibitor in vitro); however, they could compete with other medications metabolized by these same pathways.

Pharmacodynamically, as a partial agonist, buprenorphine has a ceiling effect at higher concentrations. Thus, when the metabolism of buprenorphine is inhibited, higher concentrations do not produce typical opioid toxicity effects such as respiratory depression [23]. On the other hand, when buprenorphine metabolism is induced, its high affinity for the µ-opioid receptors [18] may allow it to stay on the receptors despite falling plasma concentrations.

Effects of ARVs on Methadone

Table 1 shows the interactions of ARVs with methadone and buprenorphine. Most of the interactions are ARV effects on methadone metabolism. Several NNRTIs strongly induce CYP3A4 and have been shown to lower methadone plasma concentrations and cause methadone withdrawal symptoms such as anxiety, abdominal cramps, and muscle and joint pain. The NNRTI efavirenz decreased methadone area under the curved (AUC) 55% and required methadone dose increases on average by 52% [24â€•]. Similarly, when methadone maintenance patients were started on the NNRTI nevirapine, methadone AUC decreased by 63%, resulting in opioid withdrawal among 9 of 10 patients, and requiring an average 20% increase in methadone dose [25â€•].

The NNRTI etravirine induces CYP3A4 but inhibits CYP2C19, another route of methadone metabolism. A study of etravirine given over 14 days showed slightly increased methadone AUC, and no need for methadone dose adjustment [26â€•].

For the NNRTIs known to induce methadone metabolism, methadone dose increases are often needed. However, an immediate methadone dose increase could result in opioid toxicity since it cannot be predicted who will develop opioid withdrawal or severity. Therefore, a dose increase prior to onset of objective signs and symptoms of opiate withdrawal is not recommended. Moreover, CYP enzyme induction requires the synthesis of new enzymes, generally over 7 to 21 days, which is therefore the time frame for onset of opiate withdrawal and need for a methadone dose increase. Because methadone providers manage methadone dose in these patients, it is important for HIV providers to let methadone treatment providers know when a new ARV with inducing properties is initiated, so that they can monitor for opioid withdrawal symptoms and then adjust the methadone dose as needed.

Conversely, when inducers are stopped (such as when primary providers decide to stop them, or when patients decide to stop or decrease the medication on their own, or when patients are unable to get a medication refilled due to financial issues), methadone levels increase, resulting in possible sedation, constipation, respiratory depression, cardiac arrhythmias, and other toxicities. When methadone patients receiving CYP3A4-inducing ARVs experience methadone toxicity, this may be due to cessation of or nonadherence to these ARVs. For example, efavirenz can cause dizziness, somnolence, insomnia, or confusion. If patients decrease or stop this medication to avoid these side effects, they may be at risk for opioid toxicity. Methadone patients who have had their dose increased to accommodate efavirenz or nevirapine need to be monitored closely for possible methadone toxicity in case they go off these medications unexpectedly.

Although in vitro studies indicate that the PIs inhibit CYP3A4, many have been found to decrease rather than increase methadone concentrations in humans, possibly due to other metabolic processes such as renal clearance or induction of other CYP enzymes. Several PIs are associated with reduced
methadone AUC as well as methadone withdrawal symptoms, including darunavir/ritonavir [27] and lopinavir/ritonavir [28*]. A case report described how a patient developed Torsades de Pointes (cardiac arrhythmia reported in association with methadone) after stopping lopinavir/ritonavir, due to failure to reduce the methadone dose that had been increased when lopinavir/ritonavir was started [29*]. Nelfinavir decreased methadone AUC, but no withdrawal was observed [30*]. In a study with healthy volunteers not on methadone maintenance, nelfinavir decreased methadone plasma concentrations 40% despite 50% CYP3A4 inhibition, by increasing renal clearance [20*]. Similarly, ritonavir decreased methadone concentrations despite CYP3A4 inhibition, also by increasing renal clearance [31*]. Tipranavir/ritonavir has been shown to reduce methadone serum concentration 50% [32], despite CYP3A4 inhibition. The mechanism may be its induction of CYP2C19 and intestinal p-glycoprotein [33*].

Fortunately, there are several PIs without significant effects on methadone AUC, including the CYP3A4 inhibitors atazanavir [34], indinavir/ritonavir [21*], saquinavir/ritonavir [35*], and the mixed CYP3A4 inhibitor and inducer fosamprenavir/ritonavir [36*].

In sum, studies of methadone maintenance patients starting efavirenz, nevirapine, and several PIs have evidenced decreased methadone concentrations and withdrawal symptoms requiring methadone dose increases when these medications are started and methadone dose decreases when they are stopped. For efavirenz and nevirapine, these drug interactions are consistent with their induction of CYP3A4. In contrast, for many PIs these drug interactions are opposite to their inhibition of CYP3A4 and thus most likely due to other mechanisms.

**Effects of ARVs on Buprenorphine**

To date, few of the effects of NNRTIs or PIs on methadone metabolism have been observed with buprenorphine. For
example, the NNRTIs, efavirenz and nevirapine, induce CYP3A4 and have been linked to opiate withdrawal symptoms in methadone-maintained patients [24•, 25•]. In contrast, when given to buprenorphine-maintained individuals, these medications were not associated with opioid withdrawal despite reductions in buprenorphine plasma concentrations. One of these, efavirenz, decreased buprenorphine AUC significantly, but this did not lead to withdrawal symptoms [37•]. Similarly, nevirapine did not significantly affect buprenorphine pharmacokinetics or lead to withdrawal symptoms [38•]. Research is needed on the effects of buprenorphine and methadone on drug interactions that might occur with new ARVs (substrates of) CYP450 enzymes (most often CYP3A4 or CYP2D6). Fortunately, the currently available street drugs are not known to significantly induce or inhibit the CYP450 enzymes. In contrast, many ARVs induce or inhibit CYP3A4 and/or CYP2D6, and may thereby alter metabolism of many street drugs. Although there is almost no research in this area, toxicities and withdrawal symptoms are likely when patients start or stop ARVs that inhibit CYP3A4 or CYP2D6. Ritonavir, a CYP2D6 and CYP3A4 inhibitor, has been shown to increase blood levels and effects of benzodiazepines metabolized by CYP3A4. Case reports document life-threatening ecstasy and GHB toxicity after starting ritonavir.

Methadone and buprenorphine are effective treatments for opioid addiction. Because some ARVs decrease or increase methadone levels, patients need to be monitored.

Effects of Methadone and Buprenorphine on ARVs

Methadone has been shown to interact with at least one ARV by reducing its absorption from the GI tract. As a full μ-opioid receptor agonist, methadone slows GI motility. This increases degradation of medications that are sensitive to the acidic environment of the stomach. This has been observed when methadone-maintained patients were administered the NRTI stavudine, resulting in subtherapeutic stavudine concentrations [43•]. For the NRTI didanosine, AUC was reduced by 63% when given in the early tablet form to methadone-maintained individuals [43•]. In contrast, the newer enteric-coated capsule formulation of didanosine designed to prevent degradation in the stomach remained at therapeutic plasma levels in methadone-maintained individuals [44] and buprenorphine-maintained individuals [45].

Several ARVs are metabolized by glucuronidation. Methadone inhibits glucuronidation of the NRTI zidovudine and had been associated with zidovudine toxicity in some cases; the symptoms of muscle and joint pain, dysphoria, and insomnia of zidovudine toxicity can easily be confused with opioid withdrawal symptoms [46•]. This increase in zidovudine levels was not found with buprenorphine [47•]. Similarly, although the NNRTI nevirapine is metabolized by glucuronidation, plasma levels are not affected by buprenorphine [38•]. Research is needed on how methadone and buprenorphine affect glucuronidation of ARVs.

Conclusions

Many street drugs as well as ARVs are metabolized by (substrates of) CYP450 enzymes (most often CYP3A4 or CYP2D6). Fortunately, the currently available street drugs are not known to significantly induce or inhibit the CYP450 enzymes. In contrast, many ARVs induce or inhibit CYP3A4 and/or CYP2D6, and may thereby alter metabolism of many street drugs. Although there is almost no research in this area, toxicities and withdrawal symptoms are likely when patients start or stop ARVs that inhibit CYP3A4 or CYP2D6. Ritonavir, a CYP2D6 and CYP3A4 inhibitor, has been shown to increase blood levels and effects of benzodiazepines metabolized by CYP3A4. Case reports document life-threatening ecstasy and GHB toxicity after starting ritonavir.

Methadone and buprenorphine are effective treatments for opioid addiction. Because some ARVs decrease or increase methadone levels, patients need to be monitored.
for methadone withdrawal or toxicity when they start or stop ARVs. Recent research shows that most ARVs do not cause buprenorphine withdrawal or toxicity, even if they affect buprenorphine levels. The one exception is the PI combination atazanavir/ritonavir. Research is needed on a number of other PIs that may have similar effects, such as amprenavir, indinavir/ritonavir, and saquinavir/ritonavir.

Although buprenorphine has fewer drug–drug interactions with ARVs than methadone, opioid-addicted patients who are stable on methadone maintenance should not necessarily be transferred to buprenorphine, because it can be clinically challenging to reduce the methadone dose to a point where transition to buprenorphine is possible. Rather, clinicians with HIV-positive patients on methadone maintenance should be aware of major drug interactions that may occur between ARVs and methadone and adjust methadone doses as clinically indicated. If a patient with HIV or at risk for HIV is new to opioid therapy or wishes to be readmitted to opioid therapy, buprenorphine may be preferable as it appears that it will have fewer clinically significant interactions with ARVs.

The findings to date on how ARVs affect the metabolism of street drugs, methadone, and buprenorphine, and how methadone affects the metabolism of a number of ARVs, are useful to clinicians who must treat both HIV disease and opioid dependence in the same patients. However, at this point it is not possible to predict who will experience a drug–drug interaction, as this relates to individual genetics that affect metabolism. Improvement in medication adherence and clinical outcomes can be enhanced by discussion with patients about possible interactions, clinical monitoring, and rapid intervention should a drug–drug interaction occur.

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