Interactions Between Recreational Drugs and Antiretroviral Agents

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OBJECTIVE: To summarize existing data regarding potential interactions between recreational drugs and drugs commonly used in the management of HIV-positive patients.

DATA SOURCES: Information was obtained via a MEDLINE search (1966–August 2002) using the MeSH headings human immunodeficiency virus, drug interactions, cytochrome P450, medication names commonly prescribed for the management of HIV and related opportunistic infections, and names of commonly used recreational drugs. Abstracts of national and international conferences, review articles, textbooks, and references of all articles were also reviewed.

STUDY SELECTION AND DATA EXTRACTION: Literature on pharmacokinetic interactions was considered for inclusion. Pertinent information was selected and summarized for discussion. In the absence of specific data, prediction of potential clinically significant interactions was based on pharmacokinetic and pharmacodynamic properties.

RESULTS: All protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors are substrates and potent inhibitors or inducers of the cytochrome P450 system. Many classes of recreational drugs, including benzodiazepines, amphetamines, and opioids, are also metabolized by the liver and can potentially interact with antiretrovirals. Controlled interaction studies are often not available, but clinically significant interactions have been observed in a number of case reports. Overdoses secondary to interactions between the "rave" drugs methylenedioxymethamphetamine (MDMA) or γ-hydroxybutyrate (GHB) and PIs have been reported. PIs, particularly ritonavir, may also inhibit metabolism of amphetamines, ketamine, lysergic acid diethylmide (LSD), and phencyclidine (PCP). Case series and pharmacokinetic studies suggest that nevirapine and efavirenz induce methadone metabolism, which may lead to symptoms of opiate withdrawal. A similar interaction may exist between methadone and the PIs ritonavir and nelfinavir, although the data are less consistent. Opiate metabolism can be inhibited or induced by concomitant PIs, and patients should be monitored for signs of toxicity and/or loss of analgesia. PIs should not be coadministered with midazolam and triazolam, since prolonged sedation may occur.

CONCLUSIONS: Interactions between agents commonly prescribed for patients with HIV and recreational drugs can occur, and may be associated with serious clinical consequences. Clinicians should encourage open dialog with their patients on this topic, to avoid compromising antiretroviral efficacy and increasing the risk of drug toxicity.

KEY WORDS: cytochrome P450, drug interactions, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, recreational drugs, street drugs.

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The advent of potent new therapies for HIV has seemingly turned the tide in the battle against this disease. Specifically, combinations of antiretroviral drugs that include a member of the protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) family offer new hope that the progression of the disease and death can be delayed.[1-3] However, the addition of combination therapies to already complex medication regimens dramatically increases the likelihood of drug interactions.[4-7] PIs and NNRTIs, in particular, have a propensity for causing drug interactions as a result of their ability to either inhibit or induce the cytochrome P450 (CYP450) enzyme system.[8-13] The effects of medications commonly used by patients with HIV/AIDS on the body's various drug-metabolizing pathways are summarized in Table 1.[8-13]

Author information provided at the end of the text.

While numerous interactions of varying clinical significance have been well described[10-12] with these antiretrovirals, less is known about the potential for drug interactions with recreational drugs. This is an issue of concern, since drug use by injection remains a significant risk factor for the acquisition of HIV infection.[14,15] According to the Centers for Disease Control and Prevention,[16] the proportion of AIDS cases in the US associated with injection drug use has increased from 12% in 1981 to 25% of all new cases through June 2001. In Canada, the proportion of new HIV infections attributable to injection drug use increased from 24% in 1987–1990 to 34% in 1999.[17]

A report[18] of a suspected fatal interaction between ritonavir and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) has sparked demands for increased awareness and research in this area. Realistically, however, it is unlikely that pharmacokinetic interactions between drugs used in HIV pharmacotherapy and most recreational agents will be formally studied, due to legal and ethical constraints. However, it is often possible to predict potential interactions using in vitro and in vivo drug metabolism data.[19] Since many recreational drugs are metabolized to some degree by the CYP450 system, it is reasonable to anticipate that concomitant use with PIs and delavirdine could possibly result in drug accumulation and/or toxicity. Similarly, treatment with enzyme inducers such as the NNRTI nevirapine may precipitate withdrawal reactions to recreational agents metabolized by the CYP450 system. Interactions between the NNRTI efavirenz and recreational drugs may be more difficult to predict, given that efavirenz can both inhibit (3A4, 2C9/19) and induce (3A4) selected isoenzymes of the CYP450 system, although induction of CYP3A4 appears to predominate over inhibition of this particular isoenzyme.[7,13]

The purpose of this review is to summarize data on drug interactions between recreational drugs and antiretrovirals. In the absence of such data, the potential for an interaction is addressed based on the metabolic fate of the recreational drug. General information regarding the steps involved in drug metabolism has been reviewed elsewhere.[19]

Table 1. Metabolic Characteristics of Antiretrovirals[8-13]

Class	Enzyme Inhibitors	Enzyme Inducers
NNRTI	delavirdine CYP3A4 efavirenz CYP2B6, 3A4, 2C9/19	nevirapine CYP3A4 efavirenz CYP3A4
PI	all inhibit CYP3A4 ritonavir (in descending order of potency of inhibition) 3A4>2D6>2C9>2C19>>2A6>2E1 CYP2B6 amprenavir CYP2C19 nelfinavir CYP2B6	ritonavir GCT CYP1A2 CYP3A4 (possible) nelfinavir GCT

GCT = glucuronyltransferase; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Methods

Information was collected on documented or suspected interactions and metabolic pathways of both commonly prescribed HIV medications and commonly used recreational drugs. Information was retrieved via a MEDLINE search (1966–August 2002) using the MeSH headings human immunodeficiency virus, drug interactions, cytochrome P450, names of antiretrovirals, and chemical and common names of frequently used recreational drugs including methylenedioxymethamphetamine (MDMA), methamphetamine, γ-hydroxybutyrate (GHB), ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), cocaine, heroin, methadone, meperidine, codeine, morphine, oxycodone, benzodiazepines, marijuana, and alcohol. Abstracts of international and national conferences, review articles, textbooks, and references of all articles were also searched. All literature on pharmacokinetic or pharmacodynamic interactions was considered for inclusion. When data on a particular combination were unavailable, a possible or potential interaction was predicted based on the metabolic fate of the involved agents.

Results

Many prescription, nonprescription, and recreational drugs undergo extensive hepatic metabolism via CYP450 isoenzymes and/or glucuronidation. Thus, there is potential for significant interactions between these agents and antiretrovirals, particularly PIs and NNRTIs. Concentrations of many recreational drugs may be significantly increased or decreased in the presence of these antiretrovirals and may be associated with serious adverse outcomes.

Rave Drugs

AMPHETAMINES

MDMA, also known as ecstasy, XTC, Adam, and Essence, is a commonly used substance at all-night dance parties known as raves and is also increasingly being used recreationally by young professionals. When MDMA is taken orally as a capsule or tablet at average doses of 75–100 mg,[20] users cite enhanced feelings of empathy for others, anxiolysis, and strong feelings of euphoria. MDMA is an amphetamine-like compound that undergoes demethylenation principally by CYP2D6.[21-23] Concomitant administration with CYP2D6 inhibitors could lead to significant increases in MDMA exposure with potentially dangerous and even fatal consequences, as illustrated by a case report.[18] Within a few hours of taking 180 mg of MDMA, a 32-year-old man with AIDS experienced symptoms suggestive of a heightened serotonergic state including tachypnea, tachycardia, cyanosis, and profuse sweating. He then experienced an apparent tonic–clonic seizure, tachypnea, and tachycardia (carotid pulse ~ 200 beats/min), and subsequently died from cardiorespiratory arrest. This patient had previously taken similar amounts of MDMA on several occasions without adverse effects,

but this was the first time he had taken MDMA since adding ritonavir 600 mg twice daily to his antiretroviral regimen. At autopsy, the patient's blood concentrations of MDMA were approximately tenfold higher than expected given the amount ingested. Since ritonavir is a well-known potent inhibitor of many hepatic isoenzymes including CYP2D6, the clinicians concluded that the patient likely experienced a fatal serotonergic reaction to MDMA as a result of an interaction with ritonavir.

The danger associated with this interaction may be magnified due to the large variability in the actual amount of MDMA between tablets and the presence of other chemicals (e.g., amphetamines, ephedrine) in some MDMA tablets whose metabolism can also be inhibited by ritonavir, leading to a life-threatening consequence.[24] Thus, the combination of MDMA and ritonavir should be avoided. Other isoforms of the CYP450 system may also be involved in the metabolism of MDMA, notably 1A2, 2B6, and 3A4.[23] All PIs can inhibit CYP3A4 activity to varying degrees, and ritonavir, nelfinavir, and the NNRTI efavirenz also demonstrate inhibitory activity against 2B6[25]; therefore, individuals using MDMA should be warned about the potential for an interaction with these agents and advised to take appropriate precautions (e.g., use ~25% of the usual amount of MDMA, take breaks from dancing, ensure rave or party has medical team on site, maintain adequate hydration by avoiding alcohol and replenishing fluids regularly).

Other amphetamines, particularly methamphetamine (crystal meth, speed), may be used at raves. These drugs are also mainly metabolized by CYP2D6.[26-28] Thus, potentially dangerous interactions with ritonavir may occur, and the combination should be avoided if possible.

GHB

GHB, also known as liquid ecstasy, grievous bodily harm, or G, is a naturally occurring metabolite of the neurotransmitter γ-aminobutyric acid (GABA) that is used at raves for its euphoric effects. Colorless, odorless, and tasteless, GHB has also been used in the context of date rape when slipped into beverages. The pharmacokinetics of GHB have not been well characterized. The major route of elimination is expired breath as carbon dioxide, although animal data[29,30] suggest that first-pass metabolism may also play a large role in GHB clearance. Since first-pass metabolism is often mediated by the CYP450 system, it is possible that inhibitors of this system could predispose patients to GHB-related toxicity. As the precise metabolic pathway involved in the metabolism of GHB is unknown, patients who use this substance should be warned about the potential dangers of a drug interaction with PIs (especially ritonavir) and the NNRTIs delavirdine and, possibly, efavirenz.

The potential for an interaction is highlighted by a report[31] of an HIV-positive patient taking ritonavir and saquinavir who developed symptoms consistent with GHB toxicity shortly after ingesting a small amount of GHB (~10 mg/kg). The patient had taken GHB to counter the agitating effects of 2 MDMA tablets, which had lasted much longer (29 h) than when he had used MDMA prior to initiating antiretroviral therapy. Since the man had taken similar doses of both MDMA and GHB without incident prior to initiating therapy with ritonavir and saquinavir, the authors concluded that PI-mediated inhibition of MDMA and GHB was responsible for the adverse reactions.

KETAMINE

Ketamine, also known as special K or kit kat, may be used at raves for its dissociative, intoxicating, and amnesic properties. Users may inhale the powder form, while ketamine liquid is usually added to drinks and ingested orally. The main route of ketamine metabolism is *N*-demethylation to norketamine, a metabolite with approximately one-third the anesthetic activity of its parent compound. Norketamine is then hydroxylated and conjugated to water-soluble conjugates that are excreted in the urine.[32] CYP2B6 appears to be the main enzyme involved in ketamine metabolism, with 3A4 and 2C9 involved to a lesser extent.[33] There are no studies or case reports describing interactions between ketamine and antiretroviral agents. However, since ritonavir, nelfinavir, and efavirenz are potent inhibitors of CYP2B6, patients who use ketamine recreationally may be at risk for ketamine toxicity due to drug accumulation. Animal studies[34,35] suggest that ketamine may be a weak inhibitor of CYP3A4, although the clinical significance of this is unclear in the absence of human data. Still, until such results can be confirmed, it may be prudent to avoid recreational ketamine use while taking drugs that are CYP3A4 substrates and have narrow safety thresholds (e.g., cisapride, terfenadine, astemizole).

PCP

PCP, known on the street as angel dust, rocket fuel, or killer weed, may be used at raves for its hallucinogenic or dissociative properties. Users may also report feelings of empowerment and invulnerability with PCP use. PCP is metabolized in the liver through oxidative hydroxylation, with up to 5 metabolites being formed. CYP3A4 appears to play a major role in the hydroxylation of PCP.[36] Results from rat model studies also suggest that CYP2C11 may be involved in PCP metabolism[37] and that CYP2B1 may be inhibited in vitro.[38] Thus, it would be expected that concurrent use of PCP with PIs, delavirdine, and possibly efavirenz may result in elevated PCP concentrations and resultant toxicity. Patients using PCP who are also receiving treatment with antiretrovirals should be cautioned to use less than what they would normally use given the potential for a drug interaction.

LSD

LSD is also known popularly as acid or blotters, since it may be used in the form of paper microdots for its hallucinogenic and mild euphoric properties. Although the

CYP450 system may be involved in the metabolism of LSD, the exact contribution of this system in overall LSD clearance and the isoenzymes involved have not been detailed.[39,40] Thus, anticipating drug interactions with LSD is extremely difficult. Patients who use LSD recreationally and who receive treatment with antiretrovirals should be cautioned about the possibility of an interaction and to be familiar with signs of LSD toxicity, and perhaps consider using a smaller amount than normal. Table 2[18,21-23,26-40] summarizes the interactions between rave drugs and antiretrovirals.

Methadone

Since methadone is metabolized primarily by CYP3A4, with additional contributions by 2D6, 2C19, and 2B6, the likelihood of interactions with NNRTIs and PIs is high.[41-44] Several such interactions have been described in the literature and are summarized in Table 3.[45-72]

As expected, patients maintained on methadone who are subsequently treated with either efavirenz or nevirapine are at risk of developing opiate withdrawal symptoms due to NNRTI-mediated enzyme induction. Such patients may require an increase in their methadone dose, although the magnitude of the dose increase may not always parallel the reduction in total methadone exposure. For example, data reported by Clarke et al.[45] suggest that, despite a decrease of >50% in methadone AUC seen with the addition of efavirenz, a mean increase in methadone dose of only 22% (in 10-mg increments) was required to counteract symptoms consistent with opiate withdrawal. A similar interaction has been described[68] between nevirapine and methadone, in that a mean increase in methadone dose of 16% was required to compensate for a 50% reduction in methadone AUC.

Interactions between PIs and methadone have been even less predictable. In vitro, the AUC for methadone increased twofold when the drug was administered with ritonavir and 30% when administered with indinavir.[73] A later study[74] in healthy volunteers did not confirm these findings, noting a decrease in the AUC of methadone of 36% with concomitant ritonavir. However, these results are somewhat limited since only a single 5-mg dose of methadone was studied. Similarly, reduced methadone concentrations have been noted in the presence of lopinavir/ritonavir[70] and nelfinavir.[53] These observations suggest that ritonavir, nelfinavir, and possibly lopinavir may be inducing an alternative route of methadone metabolism.[52,57,58]

Reduced methadone concentrations have not always been accompanied by symptoms of opiate withdrawal. This lack of correlation between concentrations and clinical withdrawal may be related to a disproportionately larger induction in the metabolism of methadone's inactive *S*(+)-enantiomer as opposed to the *R*(–)-enantiomer, which harbors essentially all opiate activity.[54] Further studies need

Table 2. Interactions Between Antiretrovirals and Rave Drugs[18,21-23,26-40]

Drug	Metabolism	Actual/Theoretical Interaction	Potential Significance	Recommendation
Amphetamines	CYP2D6[26-28]	possible ↑ concentrations with ritonavir	hypertension, hyperthermia, seizures, arrhythmias, tachycardia, tachypnea	avoid combination with ritonavir if possible; alternatively, start with $^1/_4$–$^1/_2$ of initial amount of amphetamine used
GHB	expired breath as CO_2; first-pass metabolism[29,30]	possible ↑ concentrations/ prolonged effect with antiretrovirals, especially ritonavir	1 case[31] of GHB toxicity with ritonavir/saquinavir; myoclonic or seizure activity, bradycardia, respiratory depression, loss of consciousness	use cautiously with CYP450 inhibitors (i.e., PIs, delavirdine, efavirenz); become aware of signs/symptoms of GHB toxicity
Ketamine	CYP2B6 (main), 3A, 2C9 (both to lesser extent)[32-35]	possible ↑ concentrations with antiretrovirals, especially, ritonavir, nelfinavir, and efavirenz	respiratory depression, loss of consciousness, hallucinations	use cautiously with CYP450 inhibitors, especially ritonavir, nelfinavir, and efavirenz; become aware of signs/ symptoms of ketamine toxicity
LSD	unknown[39,40]	possible ↑ LSD concentrations	hallucinations, agitation, psychosis, flashbacks	use cautiously with CYP450 inhibitors (i.e., PIs, delavirdine, efavirenz); become aware of signs/symptoms of LSD toxicity
MDMA, Ecstasy	CYP2D6[21-23] (main), 1A2, 2B6, 3A4 (to lesser extent)[23]	possible ↑ concentrations with ritonavir, other PIs, efavirenz	1 death reported[18]; hyponatremia, hyperthermia, arrhythmias, tremor, hyperreflexia, sweating, seizures, tachycardia, rhabdomyolysis	avoid combining with ritonavir if possible; alternatively use ~$^1/_4$–$^1/_2$ of usual amount and watch for signs of MDMA toxicity; stay well hydrated at party, avoid alcohol, take breaks from dancing
PCP	CYP3A,[36] CYP2C11,[37] inhibits CYP2B1[38]	possible ↑ concentrations with antiretrovirals	seizures, hypertension, rhabdomyolysis, hyperthermia	use cautiously with CYP450 inhibitors (i.e., PIs, delavirdine, efavirenz); become aware of signs/symptoms of PCP toxicity

GHB = γ-hydroxybutyrate; LSD = lysergic acid diethylamide; MDMA = methylenedioxymethamphetamine; PCP = phencyclidine; PI = protease inhibitor.

Table 3. Interactions Between Antiretrovirals and Methadone[45-72]

Antiretroviral	Study Type	Patients	Interaction	Recommendation
NRTIs				
abacavir[62]	pharmacokinetic	19 pts. titrated to constant methadone dose (≥40 mg/d) over 14 d; days 15–28, received concomitant methadone and abacavir	slight ↑ in methadone clearance by abacavir; no statistically significant change in C_{max}, half-life, or renal clearance of methadone; methadone causes slight delay in rate but not extent of abacavir absorption	combination appears safe
didanosine/ stavudine[59]	pharmacokinetic	17 pts. on methadone maintenance and 10 control pts.; 2 pharmacokinetic studies completed for each subject and control (1 each for both drugs)	stavudine AUC 23%; didanosine AUC ↓ 57%; effect primarily related to reduced bioavailability	no data to guide dose adjustments; monitor for virologic failure
didanosine EC capsule[72]	pharmacokinetic	HIV-negative patients (n = 17) on stable methadone dose; randomized to EC or tablet formulation, and crossed-over to alternative regimen after pharmacokinetic monitoring over 24 h; comparisons made to historical data in nonmethadone pts.	EC formulation provided didanosine plasma AUC concentrations comparable to historical controls in nonmethadone patients	combination of EC capsule of didanosine appears safe
zidovudine[60]	pharmacokinetic	14 HIV-positive pts. on methadone maintenance for at least 6 mo and 5 control pts.; all pts. were receiving zidovudine 200 mg po q4h	zidovudine AUC ↑ 43% vs. control; no effect on methadone maintenance	monitor for zidovudine-related toxicities (e.g., nausea, vomiting, bone marrow suppression)
zidovudine[61]	pharmacokinetic within subject	8 pts. started on acute methadone therapy as inpatients; both po and iv zidovudine pharmacokinetics determined before starting methadone, following acute methadone treatment, and after 2 mo of daily methadone	zidovudine AUC ↑ 41% during acute methadone treatment and 29% during chronic treatment	
NNRTIs				
delavirdine[63]	pharmacokinetic	16 HIV-negative volunteers maintained on methadone and 15 controls, each treated with delavirdine 600 mg bid for 5 d	methadone did not alter pharmacokinetics of delavirdine or *N*-delavirdine; effect of delavirdine on methadone not studied	since delavirdine inhibits 3A4, monitor for symptoms of opiate toxicity (e.g., miosis, drowsiness, ↓rate and depth of respiration, nausea, vomiting, constipation, bradycardia, hypotension) until further data available
efavirenz[45]	pharmacokinetic	11 pts. on stable methadone maintenance, due to begin antiretroviral therapy with 2 NRTIs and efavirenz	efavirenz ↓ methadone C_{max} (p = 0.007) and AUC by mean of 60%; pts. developed symptoms of methadone withdrawal 8–10 d after starting efavirenz and received ↑ methadone dose (10-mg increments) until symptoms resolved (22% mean ↑ in methadone dose required)	monitor for symptoms of opiate withdrawal (e.g., lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection); adjust methadone dose if necessary
efavirenz[47]	case report	1 pt. on methadone 100 mg/d for >1 y; switched from nelfinavir/lamivudine/ stavudine to efavirenz-containing regimen	4 wk after introduction of efavirenz, pt. reported tiredness, headache, cold sweats, shivering; concentrations of (*R*)-methadone (active enantiomer of methadone) before and after introduction of efavirenz were 168 and 90 ng/mL, respectively; methodone dose ↑ to 180 mg/d before symptoms disappeared	

C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; EC = enteric coating; EC_{50} = 50% effective concentration; HAART = highly active antiretroviral therapy; HCV = hepatitis C virus; HGC = hard-gel capsule; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft-gel capsule.

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Table 3. Interactions Between Antiretrovirals and Methadone[45-72] (continued)

Antiretroviral	Study Type	Patients	Interaction	Recommendation
efavirenz[64]	case report	3 HIV-infected iv drug users on methadone	opiate withdrawal symptoms emerged 4–7 d following introduction of efavirenz; methadone concentrations in 1 pt. were 65% lower with efavirenz than at baseline; pts. required 66-133% ↑ in methadone dose	
nevirapine, then efavirenz[48]	case report	pt. stabilized on methadone 40 mg/d; antiretroviral therapy changed from zidovudine/lamivudine to stavudine/didanosine/nevirapine and, later, efavirenz	2 d following change, pt. experienced symptoms compatible with opiate withdrawal (e.g., cramps, tremor, rhinorrhea); symptoms stopped with discontinuation of nevirapine and recurred with nevirapine rechallenge; symptoms recurred following change to efavirenz in spite of dose ↑ to 80 mg/d; methadone concentrations stable despite dose increase	
nevirapine[46]	case report	1 pt. on methadone 80 mg/d for 3 y; switched from stavudine/didanosine/saquinavir-HGC nelfinavir after 1 mo (because of didanosine intolerance) to stavudine/nelfinavir/saquinavir-SGC/nevirapine	1 wk following the change to a nevirapine-containing regimen, the pt. experienced symptoms of methadone withdrawal (e.g., total body pain, nausea, vomiting, insomnia, sweats, sense of impending doom); the dose ↑ over 4 wk to 130 mg/d and symptoms resolved	monitor for symptoms of opiate withdrawal (see Efavirenz); adjust methadone dose if necessary
nevirapine[50]	retrospective chart review	7 pts. on chronic methadone maintenance following initiation of treatment with nevirapine-containing regimens	methadone withdrawal precipitated in all pts. within 4–8 d of initiating nevirapine; methadone concentrations subtherapeutic in 3 pts.; dose ↑ necessary; 4 pts. discontinued nevirapine therapy	
nevirapine[51]	case series	5 pts. in methadone maintenance program starting nevirapine-based HAART	4 pts. exhibited symptoms of opiate withdrawal 6–15 d after beginning nevirapine therapy; 2 pts. discontinued nevirapine; 2 pts. remained on therapy but required ↑ methadone dose (33% and 100%)	
nevirapine[49]	prospective	45 iv drug users stabilized on methadone and treated with nevirapine, didanosine, and lamivudine, all once daily	30% of the pts. required ↑ methadone dose due to withdrawal symptoms	
nevirapine[68]	pharmacokinetic	8 pts. on stable daily doses of methadone beginning treatment with nevirapine-based HAART	nevirapine ↓ methadone AUC by a mean of 50%; 6 pts. reported symptoms of methadone withdrawal 8–10 d after starting nevirapine; methadone dose ↑ in increments of 10 mg (mean ↑ 16%)	
PIs				
amprenavir[55]	pharmacokinetic	16 opiate-dependent, HIV-negative pts. on at least 30 d of stable methadone doses; methadone concentrations reassessed after 10 d of amprenavir 1200 mg bid	preliminary data for 12 subjects: AUC of *R*-methadone ↓ 12%, AUC of *S*-methadone ↓ 24%; no change in opiate pharmacodynamics	combination appears safe based on preliminary data
indinavir[69]	pharmacokinetic	12 HIV-positive pts. on methadone 20–60 mg/d; indinavir 800 mg po q8h added	no significant effect of indinavir on methadone AUC vs. historical controls; no significant effect of methadone on indinavir AUC, but ↑ indinavir C_{min} 50–100% and ↓ indinavir C_{max} 16–36%, all vs. historical controls	combination appears safe
indinavir, nelfinavir, ritonavir, saquinavir[58]	case series	methadone concentrations measured prior to and at least 1 wk after addition of a PI to stable dual NRTI therapy in 10 pts. in methadone maintenance program	methadone concentrations unchanged in 6 pts. switched to indinavir and 1 pt. switched to saquinavir; methadone steady-state concentrations ↓ 40–50% in 1 pt. switched to ritonavir and 2 pts. switched to nelfinavir	monitor for symptoms of opiate withdrawal (see Efavirenz) with nelfinavir and ritonavir; adjust methadone dose if necessary

C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; EC = enteric coating; EC_{50} = 50% effective concentration; HAART = highly active antiretroviral therapy; HCV = hepatitis C virus; HGC = hard-gel capsule; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft-gel capsule.

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Table 3. Interactions Between Antiretrovirals and Methadone[45-72] (continued)

Antiretroviral	Study Type	Patients	Interaction	Recommendation
lopinavir/ ritonavir[70]	prospective pharmacokinetic	8 HIV/HCV coinfected pts. on methadone maintenance; methadone concentrations measured prior to and following 14 d of lopinavir/ritonavir in combination with 2 NRTIs	lopinavir/ritonavir ↓ methadone AUC 36% and ↓ methadone C_{max} 44%; no pt. exhibited symptoms of methadone withdrawal during the study or the 6-wk follow-up	combination appears safe; monitor for symptoms of opiate withdrawal (see Efavirenz) and adjust methadone dose if necessary
nelfinavir[53]	prospective pharmacokinetic	14 pts. stabilized on a fixed methadone dose for at least 1 mo before nelfinavir 1250 mg po bid for 8 d was added	concentrations of *S*(+)-methadone and *R*(-)- methadone ↓ by 47% and 39%, respectively; no pt. exhibited withdrawal symptoms; no dosage adjustments were necessary	monitor for symptoms of opiate withdrawal (see Efavirenz); adjust methadone dose if necessary
nelfinavir[56]	retrospective case series	75 pts. on stable methadone dose started on nelfinavir	2 of 75 pts. needed slight ↑ in methadone dose (10 mg/d); otherwise, no impact of nelfinavir on methadone activity	
nelfinavir[57]	case report	1 pt. on stable methadone dose of 100 mg/d, indinavir and zalcitabine; stavudine and nelfinavir added to regimen	within 6 wk of medication change, pt. developed opiate withdrawal symptoms, which ↑ in severity over 3 mo; methadone dose ↑ at 1 to 2-wk intervals; subtherapeutic methadone concentrations documented until dose of 285 mg/d attained	
nelfinavir[65]	pharmacokinetic	16 HIV-negative volunteers on stable methadone dose for 4 wk and 13 controls received nelfinavir 1250 mg po bid for 5 d	nonsignificant ↑ in median nelfinavir 12-h trough concentration with methadone; 12-h AUC of M8 53% lower than control	
nelfinavir[66]	multisite, retrospective	32 pts. on stable methadone dose receiving nelfinavir-based HAART; 84% of pts. coinfected with HCV	17% of pts. required methadone dose adjustments (mean 26 mg); otherwise, well-tolerated combination	
ritonavir/ saquinavir[52]	case report	1 pt. on methadone 90 mg/d for 2 y; antiretrovirals changed from indinavir/lamivudine/zidovudine to ritonavir/saquinavir/ stavudine because of virologic progression	1 wk following initiation of ritonavir-containing regimen, pt. was admitted to hospital with shakiness, diaphoresis, blurred vision, anxiety, and hypotension; methadone plasma concentration on admission was 210 ng/mL (within therapeutic range; however, no concentrations prior to initiation of ritonavir); methadone dose gradually ↑ to 130 mg/d	monitor for symptoms of opiate withdrawal (see Efavirenz); adjust methadone dose if necessary
ritonavir/ saquinavir[67]	pharmacokinetic	12 HIV-negative volunteers on stable methadone dose evaluated before and after 14 d of once-daily saquinavir/ ritonavir (1600 mg/100 mg)	clinically insignificant change in unbound methadone concentrations; 83% of subjects had C_{min} of saquinavir >EC_{50}	
ritonavir/ saquinavir[54]	24-h study before and after 15 d of antiretroviral therapy to examine effect of ritonavir/saquinavir on methadone kinetics	12 pts. receiving stable methadone dose for at least 2 wk	↓ *S*-methadone AUC 40% and ↓ *R*-methadone AUC 32%; however, when change in methadone AUC expressed in terms of unbound methadone, change in AUC no longer significant; no evidence of opiate withdrawal	
ritonavir/ saquinavir[71]	retrospective	18 HIV-positive pts. beginning once-daily therapy with ritonavir 100 mg, and saquinavir-SGC 1600 mg and 5 HIV-positive pts. beginning once-daily therapy with ritonavir 200 mg and indinavir 1200 mg; all pts. on methadone, 19 pts. coinfected with HCV	no pt. required methadone dose adjustment	

C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; EC = enteric coating; EC_{50} = 50% effective concentration; HAART = highly active antiretroviral therapy; HCV = hepatitis C virus; HGC = hard-gel capsule; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft-gel capsule.

to be conducted comparing methadone with PIs to better clarify the nature of these interactions. Clinicians should be prepared for the possibility that some patients stabilized on methadone might require a dose increase when nelfinavir or ritonavir is introduced.

Interactions between methadone and the nucleoside reverse transcriptase inhibitors zidovudine, didanosine, and stavudine have also been described.[59-61] Overall, methadone appears to increase total exposure to zidovudine. The mechanisms underlying this interaction appear to involve inhibition of zidovudine glucuronidation and, to a lesser extent, decreased renal clearance of zidovudine. Although the clinical implications of these findings are unclear, patients receiving the combination of methadone and zidovudine should be monitored for zidovudine-related toxicities such as nausea, vomiting, headaches, and myelosuppression.[60,61] Since many of these symptoms may mirror those of opiate withdrawal, patients may confuse the symptoms of zidovudine toxicity with a requirement for a higher methadone dose. However, methadone concentrations do not appear to be altered by concomitant zidovudine administration, thereby discounting the association of such symptoms with opiate withdrawal.

In contrast to zidovudine, methadone appears to decrease concentrations of both stavudine and didanosine (buffered tablet formulation), possibly by delaying absorption of these agents and thereby allowing enhanced time for enzymatic or acid-catalyzed degradation. Since didanosine is more prone to acid-catalyzed degradation than is stavudine, the impact of methadone on didanosine concentrations is more pronounced than for stavudine.[59] This theory is corroborated by recent evidence[72] which indicates that the impact of methadone on didanosine concentrations is negligible when didanosine is administered as an enteric-coated capsule preparation, as such a coating would be expected to protect the drug from degradation until it has cleared the stomach. As well, the significance of reductions in didanosine concentrations is unclear, since intracellular concentrations of dideoxyadenosine triphosphate were not measured, and neither virologic nor immunologic outcomes were addressed. Although an increase in the dose of didanosine may be necessary when the buffered tablet formulation is taken with methadone, there are currently no guidelines for dosage adjustment.

As well as being a substrate of the CYP450 system, methadone can also act as an inhibitor of the 2D6 and 3A isoforms.[75-77] It is therefore possible that concomitant use of methadone and PIs or NNRTIs may result in increased antiretroviral concentrations and predispose patients to drug-specific adverse events. However, methadone did not alter the pharmacokinetics of delavirdine, a CYP3A4 substrate.[63] In addition, aside from a reduction in concentrations of the pharmacologically active M8 metabolite, significant changes to the pharmacokinetics of nelfinavir were not observed with concomitant administration of methadone.[65] The metabolism of nelfinavir to its M8 metabolite is mediated by CYP2C19, suggesting that methadone may inhibit this isoenzyme as well. Although virologically active, a reduction in M8 concentrations does not appear to be clinically significant.[78] Thus, significant elevations in the concentrations of PIs and NNRTIs may not occur with methadone. Still, the impact of methadone on other members of these classes is unknown and, as with zidovudine, it may be difficult to discriminate between symptoms associated with PI toxicity (e.g., nausea, vomiting, diarrhea) and methadone withdrawal. However, since enzyme inhibition is an acute process, while enzyme induction occurs following several days of drug administration, it may be possible to distinguish the 2 interactions based on the time course of symptom development. Specifically, symptoms that develop within 2–3 days of concomitant administration may be due to PI toxicity, whereas those that develop after 6 days are more likely to be related to opiate withdrawal.

Meperidine and Other Opiates

Two pathways are involved in meperidine metabolism: hydrolysis to meperidinic acid by liver carboxylesterases and demethylation to normeperidine by microsomal enzymes. Demethylation to normeperidine may be mediated by the CYP450 system, although the exact isoenzyme involved is unknown.[79,80] In patients with renal failure or with frequent dosing, normeperidine can accumulate, leading to central nervous system (CNS) excitatory toxicity.

In an open-label study,[81] 8 HIV-negative volunteers received meperidine 50 mg prior to treatment and following 10 days of treatment with escalating doses of ritonavir. Meperidine AUC decreased 67% in the presence of ritonavir ($p < 0.005$), while normeperidine AUC increased 47%, suggesting that ritonavir induces the metabolism of meperidine to normeperidine. However, since normeperidine has some pharmacologic activity, the potential for decreased analgesic effect and risk of opiate withdrawal may be lessened. On the other hand, because normeperidine possesses CNS excitatory effects, patients who use meperidine and ritonavir concomitantly may be at increased risk for seizures. Patients with renal failure may also be at increased risk for CNS excitatory toxicity due to normeperidine accumulation.

Reports detailing interactions between antiretrovirals and commonly used opiate analgesics such as codeine, morphine, or oxycodone are lacking. Postulated interactions between these opiates and antiretrovirals are described in Table 4.[79-91]

Cocaine and Heroin

The significant role played by cocaine in the transmission of HIV cannot be underestimated. While injecting cocaine or heroin puts users at risk of acquiring HIV through contaminated syringes, smoking "crack" cocaine may independently be associated with acquisition of HIV infection through its association with high-risk sexual practices such as the exchange of drugs for sex.[92-94] Since patients who acquire HIV in the context of crack or cocaine use may con-

tinue their drug use practices, an understanding of the potential for interactions with antiretrovirals is important.

Cocaine is metabolized chiefly by 1 of 3 pathways.[95] Spontaneous hydrolysis of cocaine to benzoylecgonine accounts for approximately 39%, 30%, and 16% of a single dose of cocaine administered by the intravenous, intranasal, and smoked routes, respectively.[96] Degradation by serum and hepatic cholinesterases to ecgonine methyl ester can account for up to 32–49% of an administered cocaine dose.[95,97] Finally, *N*-demethylation to norcocaine, mediated by CYP3A4, makes up <10% of cocaine's biotransformation.[95,98,99] Other metabolites (e.g., anhydroecgonine methyl ester, p-hydroxy cocaine) are also produced in the metabolism of cocaine, although in smaller amounts.

Interactions between cocaine and antiretrovirals have not been described. Theoretically, inhibition of CYP3A4 may increase concentrations of the parent compound by blocking a route of cocaine metabolism. However, given that *N*-demethylation is a relatively small component of cocaine metabolism, such an interaction would not be expected to increase the risk of cocaine toxicity. An exception may occur in patients who are also cholinesterase deficient, since they lack the complementary enzymes necessary to metabolize the excess cocaine burden.[100]

Inhibition of the CYP3A4 isoform would consequently result in decreased production of norcocaine; norcocaine is thought to play a critical role in mediating the hepatotoxicity of cocaine.[101,102] In vitro studies[103] documenting the protective effect of 3A4 inhibitors against cocaine-elicited hepatotoxicity lend credence to this notion. Thus, it is possible that inhibition of CYP3A4 by some antiretrovirals may theoretically ameliorate the hepatotoxicity associated with cocaine, although it should be stressed that there are no clinical data to support this. Furthermore, such postulated effects may not be clinically significant in the context of other factors, such as concomitant hepatitis B or C infection.

However, if inhibition of CYP3A4 is theoretically protective against cocaine-mediated liver injury, the reverse may be true. That is, induction of CYP3A4 by nevirapine or efavirenz may lead to increasing amounts of norcocaine being formed, potentially increasing the risk of hepatotoxicity. Again, further research is necessary to clarify the nature and consequences of interactions between enzyme inducers and cocaine.

Table 4. Postulated and Actual Interactions Between Commonly Used Opiate Drugs and Antiretrovirals[79-91]

Drug	Metabolism	Actual/Theoretical Interaction	Potential Significance	Recommendation
Codeine	3 pathways: glucuronidation to codeine-6-glucuronide (~70%); *N*-demethylation to norcodeine (3A4) (<10%); *O*-demethylation to morphine (2D6) (10–15%)[82-87]	↓ morphine concentrations: 2D6 inhibition (inhibit *O*-demethylation); 3A4/glucuronide induction (less substrate available for 2D6)	opiate withdrawal, loss of analgesia	monitor for signs/symptoms of opiate withdrawal (see Meperidine); reassess level of analgesia
		↑ morphine concentrations: 3A4 inhibition (shunting of substrate to 2D6 pathway)	opiate toxicity	monitor for signs/symptoms of opiate toxicity (e.g., miosis, drowsiness, ↓ rate and depth of respiration, nausea, vomiting, constipation, hypotension, bradycardia)
Meperidine	2 pathways: hydrolysis to meperidinic acid by liver carboxylesterases; demethylation by CYP450 system to normerperidine (exact isoenzyme unknown)[79,80]	AUC of meperidine ↓ 67% and AUC of normeperidine ↑ 47% in open-label study[81] of 8 volunteers receiving treatment with meperidine 50 mg prior to and following 10 d of treatment with ritonavir	possible opiate withdrawal, loss of analgesia; possible ↑ risk of seizures with normeperidine accumulation	monitor for signs/symptoms of opiate withdrawal (e.g., lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection); reassess level of analgesia; avoid combination of ritonavir and meperidine in pts. with renal failure and pts. who use meperidine regularly for analgesia or recreationally due to risk of neurotoxicity
Morphine	glucuronidated to M6G and M3G[89-91]	increase glucuronidation: accelerate morphine metabolism, ↓ concentrations of morphine,↑ concentrations of pharmacologically active M6G	possible opiate withdrawal, and loss of analgesia, although may be attenuated by ↑ formation of M6G	monitor for signs/symptoms of opiate withdrawal (see Meperidine); reassess level of analgesia
Oxycodone	3 pathways: CYP2D6 to oxymorphone; CYP3A4 to noroxycodone; ketoreductase[88]	↓ oxymorphone concentrations: inhibition of 2D6; 3A4 induction (less substrate for 2D6 pathway)	possible opiate withdrawal and loss of analgesia, although ↓ oxymorphone concentrations do not appear to alter pharmacodynamics of oxycodone; possible opiate toxicity	monitor for signs/symptoms of opiate withdrawal (see Meperidine); reassess level of analgesia
		↑ oxymorphone concentrations: 3A4 inhibition (shunting to 2D6 pathway)		monitor for signs/symptoms of opiate toxicity (see Codeine)

M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide.

Heroin is rapidly metabolized to 6-monoacetylmorphine and morphine by plasma and liver esterases, respectively. Maximal blood concentrations of heroin and 6-monoacetylmorphine are attained within minutes and are cleared rapidly, while morphine concentrations increase and decrease more slowly.[104-107] Thus, potential interactions of concern may be similar to those noted with morphine (Table 4).

Benzodiazepines

Benzodiazepines remain among the most commonly prescribed psychotropic drugs. In Canada, the overall prevalence of benzodiazepine use for anxiolysis in the 1990s was estimated at roughly 8% of the adult population, while about 2.5% of adults were prescribed this group of drugs for insomnia.[108] Benzodiazepines may be used recreationally either alone or, more commonly, in the setting of multiple drug abuse. Potential abuses of benzodiazepines include moderating the effects of stimulants, allaying withdrawal symptoms from other recreational substances, acting as disinhibitory agents, or augmenting the effects of other recreational drugs. As a class, benzodiazepines are extensively metabolized by the liver, with individual agents metabolized predominantly by either the CYP450 system or glucuronyltransferases.

Midazolam, triazolam, and alprazolam are metabolized mainly by CYP3A4.[109,110] Interactions with PIs, delavirdine, and, possibly, efavirenz are thus likely to produce increased concentrations of these compounds and place patients at risk of toxicity such as extreme sedation and respiratory depression. Pharmacokinetic studies and case reports documenting such interactions are summarized in Table 5.[111-115] It is interesting to note that conflicting data exist regarding the interaction between alprazolam and ritonavir. While Frye et al.[111] noted a reduction in alprazolam exposure and relatively little change in pharmacodynamic effect following 12 days of ritonavir, subsequent work by Greenblatt et al.[112] found that acute exposure to ritonavir reduced alprazolam clearance and enhanced alprazolam's pharmacodynamic properties. This discrepancy may be accounted for by the fact that ritonavir, over time, may induce as well as inhibit CYP3A4.[116] Thus, acute exposure to ritonavir may place patients at increased risk for alprazolam toxicity, while longer-term exposure to ritonavir may result in a loss of anxiolysis and possible withdrawal in patients who are using alprazolam recreationally. A longer-term study is necessary to further clarify the time course and nature of the interaction between alprazolam and ritonavir.

Additional information is also required to clarify the safety of using midazolam with PIs. Palkama et al.[113] concluded that, aside from the possibility of a longer sedative effect, the use of bolus doses of intravenous midazolam with saquinavir is likely safe. However, other investigators[114] reported on a patient who experienced prolonged sedation secondary to the combination of midazolam and saquinavir; their experience warrants that patients receiving the combination should be closely monitored. Data with other PIs are lacking. The use of midazolam with PIs and delavirdine should be avoided if possible, given the risk of prolonged sedation and respiratory depression associated with large increases in midazolam concentrations. Although formal pharmacokinetic studies are lacking, similar interactions between clonazepam and flunitrazepam and PIs are possible, since both agents are substrates of CYP3A4.[117,118] As well, caution should be exercised with diazepam, particularly in combination with ritonavir, since both the 3A4 and 2C19 systems appear to be important in its metabolism.[119,120] In contrast, nevirapine and efavirenz may put patients who are using midazolam, triazolam, alprazolam, clonazepam, and flunitrazepam at risk for loss of effect and/or withdrawal due to their 3A4 inductive potential.

Interactions between lorazepam, oxazepam, or temazepam and antiretrovirals differ from those described above, since these members of the benzodiazepine family are metabolized primarily by glucuronidation.[121,122] Thus, drugs that increase the activity of glucuronyltransferases (i.e., ritonavir, nelfinavir) may accelerate the metabolism of these compounds, resulting in lower drug exposure. Although reports are lacking, concomitant use of lorazepam, oxazepam, or temazepam with either ritonavir or nelfinavir may decrease the anxiolytic effect of these agents or precipitate symptoms consistent with benzodiazepine withdrawal reaction due to the aforementioned interaction. A higher dose of the benzodiazepine may be necessary to compensate for the interaction.

Tetrahydrocannabinol

Tetrahydrocannabinol (THC), the active ingredient of smoked marijuana, remains a commonly used recreational agent. In Canada, 23.1% of surveyed adults had used marijuana more than once in their lives, and current use was estimated at 7.4%.[123] In the context of HIV/AIDS, smoked marijuana or THC-containing preparations may also be used for antiemetic or appetite stimulation purposes.

THC is metabolized in humans by microsomal oxidation to several hydroxylated metabolites, among them 11-hydroxy-THC, which is pharmacologically active. Concentrations of 11-hydroxy-THC vary with the route of administration, with oral administration generally producing more of the active metabolite than inhaled THC due to significant first-pass effect. Limited data suggest that CYP3A and 2C9 isoenzymes are involved in microsomal oxidation of THC.[124-127] Although inhibition of CYP3A4 or 2C9 may decrease the formation of pharmacologically active metabolites, the effects of THC are unlikely to be significantly attenuated, as THC itself is active and will be more bioavailable. Increased THC concentrations may lead to dose-related effects including frank hallucinations, delusions, paranoid thinking, accentuation of altered time sense, anxiety, panic, depersonalization, loss of insight, orthostatic hypotension, and increased heart rate. Furthermore, inhibition of THC metabolism to 11-hydroxy-THC may be important only in the setting of oral administration, since just trace amounts of the active metabolite are present following smoking.

Induction of CYP3A4 may increase the formation of the pharmacologically active metabolite; however, the conversion of active metabolite to its inactive counterparts may also be accelerated, thereby decreasing the duration of THC effect. This action may be more clinically important with oral THC administration due to its large first-pass effect. The impact of THC on the pharmacokinetics of indinavir and nelfinavir has been evaluated in a small, randomized, placebo-controlled study.[128] Patients on stable indinavir or nelfinavir therapy were randomized to receive either THC 3.95% cigarettes, THC 2.5-mg capsules, or placebo, each administered 3 times a day. Nelfinavir and indinavir concentrations were determined prior to and on day 14 of THC use. A statistically significant 14% reduction in indinavir maximum concentration was observed with smoked THC. As well, smoked THC significantly reduced the ratio of M8 (active metabolite of nelfinavir) to nelfinavir by 18% ($p = 0.039$). However, as mentioned previously, reductions in M8 concentrations do not appear to be clinically important. Furthermore, a significant reduction ($p = 0.025$) in M8 concentrations relative to baseline was observed in patients receiving placebo. Other

Table 5. Interactions Between Antiretrovirals and Benzodiazepines[111-115]

Reference	Study Type	Patients	Nature of Interaction	Recommendation
Alprazolam				
Frye et al. (1997)[111]	pharmacokinetics of alprazolam 1.0 mg determined prior to ritonavir treatment and after 12 d of escalating ritonavir doses	healthy volunteers	alprazolam AUC ↓ 12%; ritonavir did not produce clinically important impairment and had no effect on peak sedation; combination appeared to prolong sedation	short-term PI administration: monitor for alprazolam toxicity (e.g., sedation, dizziness, ataxia, respiratory depression) with acute administration of ritonavir and, possibly, other PIs and delavirdine
Greenblatt et al. (2000)[112]	double-blind, randomized, 2-way crossover study of pharmacokinetics of alprazolam 1.0 mg with ritonavir or placebo	10 healthy volunteers	alprazolam $t_{1/2}$ ↑ from 13 to 30 h ($p < 0.005$); alprazolam clearance ↓ to 41% of control values with ritonavir ($p < 0.001$); ritonavir ↑ benzodiazepine agonist effects (e.g., sedation, performance impairment)	chronic ritonavir administration: monitor for alprazolam withdrawal (e.g., anxiety, dysphoria, nausea, muscle twitching, insomnia, panic/paranoia, convulsions) and loss of anxiolysis with chronic ritonavir use
Midazolam				
Palkama et al. (1999)[113]	randomized, double-blind, crossover study; pts. received treatment with saquinavir-SGC 1200 mg or placebo 3 times/d for 5 d; on day 3, received midazolam 7.5 mg po or 0.05 mg/kg iv over 2 min; on day 5, second dose of midazolam given, alternating routes of administration	12 healthy volunteers	po midazolam: saquinavir ↑ C_{max} 2.3-fold ($p < 0.001$); ↑ AUC 5-fold ($p < 0.01$), ↑$t_{1/2}$ from 4.3 to 10.9 h ($p < 0.01$), ↑ bioavailability from 41% to 90% ($p < 0.001$); sedative effects of po midazolam profoundly enhanced iv midazolam: saquinavir ↓ clearance; by 56% ($p < 0.001$), ↑ $t_{1/2}$ from 4.1 to 9.5 h ($p < 0.001$); authors suggest ↓ initial midazolam dose by 50% when given by infusion, followed by careful titration	midazolam contraindicated with PIs, delavirdine, and efavirenz; if necessary to use combination, consider dose ↓ of 50% with careful titration and monitoring for toxicity (e.g., extreme/prolonged sedation, respiratory depression, hypotension)
Merry et al. (1997)[114]	case report: pt. received midazolam 5.0 mg iv for bronchoscopy with no ill effect; 8 wk later, pt. received second dose for bone marrow aspirate and biopsy; between the first and second dose, pt. began saquinavir-HGC-based HAART regimen	32-y-old man with advanced HIV	following second dose, pt. did not wake spontaneously and required flumazenil due to prolonged sedation, possibly as a result of an interaction with saquinavir	
Triazolam				
Greenblatt et al. (2000)[115]	double-blind, randomized, crossover study of pharmacokinetics of triazolam 0.125 mg concurrent with ritonavir or placebo	6 healthy volunteers	ritonavir ↑ triazolam $t_{1/2}$ from 3 to 41 h ($p < 0.005$) and ↓ triazolam clearance to 4% of control values ($p < 0.005$); sedation and performance impairment magnified by ritonavir	avoid combination of triazolam and PIs, delavirdine, or efavirenz

C_{max} = maximum plasma concentration; HAART = highly active antiretroviral therapy; HGC = hard-gel capsule; PI = protease inhibitor; SGC = soft-gel capsule; $t_{1/2}$ = half life.

variables did not change significantly, nor did oral THC produce significant changes in indinavir or nelfinavir pharmacokinetics. The long-term clinical consequence of these changes is likely negligible, especially with the increasing use of boosted PI regimens. There are no reports documenting the impact of antiretrovirals on THC pharmacokinetics or pharmacodynamics. The nature of such an interaction would be difficult to predict, as several variables, including route of administration and the concentration of THC smoked, may confound the outcome.

Considering the widespread use of smoked and oral THC derivatives for appetite stimulation and control of nausea and vomiting, and the lack of reports documenting deleterious effects secondary to the combination of THC and PIs, a clinically significant drug interaction may not exist when THC is used in moderate amounts. Patients who use THC and are beginning antiretroviral therapy should be warned about possible accentuation of the effects of THC, and that they may need to use less THC for the same effect following treatment initiation.

Alcohol

Ethanol metabolism is mediated chiefly by the enzymes alcohol dehydrogenase (formation of acetaldehyde) and aldehyde dehydrogenase. Since 1 of the 2 main metabolites of abacavir is a carboxylate derivative, the formation of which is catalyzed by the alcohol dehydrogenase enzyme, an interaction between ethanol and abacavir is possible due to competition for metabolism. A randomized, open-label, crossover study[129] confirmed the existence of such an interaction. Twenty-five HIV-positive patients were randomized to receive either a single dose of abacavir 600 mg, ethanol 0.7 g/kg, or the combination of abacavir and ethanol, with a washout period of 7 days between treatments. Concomitant administration of ethanol and abacavir resulted in a statistically significant 41% increase in abacavir AUC (CI 1.35 to 1.48); no changes in ethanol blood concentrations were observed. The increase in abacavir AUC is unlikely to be clinically significant, as the concentrations were within the ranges observed in previous pharmacokinetic studies of abacavir that employed higher abacavir doses and did not demonstrate additional safety issues.[128]

Acute administration of alcohol may increase plasma concentrations of other substrates by inhibiting isoforms such as CYP2D6 and 2C19.[130] On the other hand, chronic administration may reduce plasma concentrations of drugs metabolized by CYP2E1 and 3A.[131,132] Thus, there is potential for induction of PI and NNRTI metabolism with chronic alcohol use. Such an interaction may result in subtherapeutic concentrations of these agents, predisposing to resistance and compromising antiretroviral efficacy over time. However, there are currently no data documenting such an interaction. Appropriately conducted pharmacokinetic studies are necessary to confirm the existence of an interaction between antiretrovirals and chronic alcohol use and to clarify appropriate management strategies.

Discussion

The increasing numbers of available PIs and NNRTIs and the identification of various isoforms of the CYP450 enzyme system have heightened awareness about the significance of drug interactions in the HIV population. However, recreational drugs are often not considered by both clinicians and patients when reviewing a particular medication regimen for potential interactions. One of the inherent concerns associated with recreational drug use is that the margin of safety for many of these substances is often poorly defined, and quality control is often highly variable. Thus, factors that may lead to unpredictable drug concentrations can further increase the risk of adverse outcomes. Given the increasing incidence of HIV infection among substance users and the increasing use of complex combination antiretroviral regimens, the risk of adverse drug interactions with possibly fatal consequences cannot be overlooked or ignored. Clinicians should, therefore, strive to gather information about recreational drug use as part of a comprehensive medication history. Reassuring the patient that confidentiality will be respected and the use of open-ended questions directed in a nonthreatening and nonjudgmental manner will facilitate the information-gathering process.

Much of the information presented in this article is largely extrapolated from in vitro pharmacokinetic experiments, case reports, or animal model studies. There are obviously many limitations in applying such data to clinical practice settings. With case reports, information is often anecdotal in nature. Patients' own recall bias is an obvious limitation, making direct causality difficult to establish. Even when in vitro or in vivo data are available, results often may not be directly extrapolated to clinical situations. For instance, much of the interaction information for ritonavir is based on full-dose (i.e., 600 mg twice daily) studies. However, ritonavir is now frequently used at lower doses (e.g., 100–200 mg twice daily) as a pharmacokinetic boosting agent. Ritonavir can inhibit CYP450 activity and increase protease trough concentrations in a dose-related manner.[133] Therefore, the frequency, extent, and/or clinical significance of interactions with ritonavir 100 mg twice daily may be lower compared with higher doses of ritonavir. As an example, when efavirenz was added to a combination of amprenavir 600 mg twice daily plus ritonavir 100 mg twice daily, amprenavir concentrations were decreased by almost 80%; however, when the ritonavir dose was increased to 200 mg twice daily, amprenavir concentrations remained stable in the presence of efavirenz.[134]

These confounding factors highlight the importance of designing interaction studies that accurately reflect situations encountered in clinical practice. However, due to legal and ethical constraints, it is highly unlikely that rigorous, prospective, controlled interaction studies between antiretrovirals and recreational drugs will ever be conducted. As such, these limited data may serve as a tool for clinicians in anticipating and hopefully averting potential detrimental interactions with recreational drugs.

Summary

Adverse interactions between agents commonly prescribed in HIV and recreational drugs can occur, and may possibly be associated with serious clinical consequences. This issue highlights the need for clinicians to obtain thorough patient histories on both prescription as well as recreational drug use and to counsel and/or adjust therapeutic regimens when required to minimize the risk of morbidity or mortality.

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EXTRACTO

OBJETIVO: Resumir los datos que existen sobre las interacciones potenciales entre las drogas recreativas y aquellas comúnmente usadas en el manejo de pacientes con VIH.

FUENTES DE DATOS: Se obtuvo información por medio de una búsqueda en el banco de datos de MEDLINE (años 1966—agosto 2002) usando los términos MESH tales como "virus de inmunodeficiencia humana", "interacciones", "citocromo P450". También se uso en la búsqueda nombres de medicamentos comúnmente prescritos en el manejo del VIH e infecciones oportunistas relacionadas y nombres de los medicamentos de recreación comúnmente usados. También se repaso extractos de conferencias nacionales e internacionales, artículos de repaso, textos y referencias de todos los artículos encontrados.

SELECION DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Literatura sobre interacciones farmacocinéticas fue considerada para inclusión. En la ausencia de datos específicos, la predicción de interacciones significativas clínicas potenciales fue basada en características farmacocinéticas y farmacodinámicas.

RESULTADOS: Todos los inhibidores de proteasa e inhibidores de la transcriptasa reversa no nucleósidos son sustratos y potentes inhibidores o inductores del sistema de encima citocromo P450. Muchas clases de drogas recreativas, incluyendo las benzodiacepinas, anfetaminas y opioides, también son metabolizados por el hígado y pueden interactuar potencialmente con los antirretrovirales. Frecuentemente no existen estudios de interacciones controlados, pero se ha observado interacciones clínicas significativas en un número de casos reportados. Se han reportado sobredosis secundarias entre drogas de "rave" como la MDMA y GHB e inhibidores de proteasa. Los inhibidores de proteasa, particularmente el ritonavir, también pueden inhibir el metabolismo de anfetaminas, ketamina, LSD, y PCP. Series de casos e estudios farmacocinéticos sugieren que la nevirapina y el efavirenz pueden inducir el metabolismo de metadona, lo cual puede resultar en síntomas de retiro de opioides. Una interacción similar puede existir entre metadona y los inhibidores de proteasa ritonavir y nelfinavir, aunque los datos de estas interacciones son menos consistentes. El metabolismo opiáceo se puede inhibir o inducir con el uso concomitante de inhibidores de proteasa y se debe monitorear estos pacientes para síntomas de toxicidad y/o pérdida de analgesia. No se debe de administrar los inhibidores de proteasa conjuntamente al midazolam y triazolam, ya que la combinación puede resultar en sedación prolongada.

CONCLUSIÓNES: Pueden ocurrir interacciones entre agentes comúnmente prescritos para pacientes con VIH y drogas recreativas, y estas combinaciones pueden tener serias consecuencias clínicas. Los clínicos deben de tener un dialogo abierto con sus pacientes en cuanto a este tópico para así poder evitar comprometer la eficacia o aumentar el riesgo de toxicidad a estos medicamentos.

Carlos C da Camara

RÉSUMÉ

OBJECTIF: Rassembler toutes les données disponibles concernant les interactions médicamenteuses possibles entre les agents antirétroviraux fréquemment utilisés pour le traitement de l'infection par le VIH et les médicaments consommés à des fins "récréationnelles" ou drogues de rue.

REVUE DE LITTÉRATURE: L'information a été obtenue par une recherche effectuée dans la banque informatisée Medline (1966—août 2002) en employant les mots-clé suivants : virus de l'immunodéficience humaine, interactions médicamenteuses, cytochrome P-450, les noms des médicaments utilisés fréquemment pour le traitement de l'infection par le VIH ainsi que des infections opportunistes l'accompagnant et le nom des drogues de rue les plus souvent consommées. Les abrégés de conférences nationales ou internationales, les articles de revue, les livres de base ainsi que les articles cités dans la bibliographie des documents consultés ont aussi été analysés.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Tous les articles sur les interactions de nature pharmacocinétique ont été inclus. L'information pertinente a été extraite et synthétisée pour faire l'objet de la discussion. En l'absence de données spécifiques, des prévisions d'interactions possibles cliniquement significatives ont été basées sur les propriétés pharmacocinétiques et pharmacodynamiques des médicaments.

RÉSULTATS: Tous les inhibiteurs de la protéase et les inhibiteurs non nucléosidiques de la transcriptase inverse sont des substrats et des inhibiteurs ou des inducteurs potentiels du système enzymatique du cytochrome P450. Plusieurs classes de drogues de rue, incluant les benzodiazépines, les amphétamines et les opiacés sont aussi métabolisées par le foie et peuvent possiblement interagir avec les agents antirétroviraux. Des données issues d'études contrôlées concernant les interactions médicamenteuses sont rarement disponibles mais des interactions cliniquement significatives ont été observées chez un bon nombre de patients. Des intoxications secondaires à la prise concomitante des médicaments "rave" 3,4-méthylènedioxymetamphétamine (MDMA, ectasy) et gamma hydroxybutyrate (GHB) avec les inhibiteurs de la protéase ont été rapportées. Les inhibiteurs de la protéase, particulièrement le ritonavir, peuvent aussi inhiber le métabolisme des amphétamines, de la kétamine, du LSD et du PCP. Des séries de cas et des études sur la pharmacocinétique suggèrent que la névirapine et l'éfavirenz induisent le métabolisme de la méthadone et peuvent provoquer des symptômes de sevrage aux opiacés. Une interaction semblable peut exister entre la méthadone et les inhibiteurs de la protéase ritonavir et nelfinavir, mais les données sont moins concluantes. Le métabolisme des opiacés peut être inhibé ou induit par l'administration concomitante des inhibiteurs de la protéase et les patients devraient être suivi afin de détecter des signes de toxicité ou une perte d'efficacité analgésique. Les inhibiteurs de la protéase ne devraient pas être co-administrés avec le midazolam ou le triazolam car une sédation prolongée pourrait apparaître.

CONCLUSIONS: Des interactions médicamenteuses entre les agents antirétroviraux utilisés pour le traitement de l'infection par le VIH et les drogues de rue peuvent survenir et peuvent présenter des effets cliniques indésirables importants. Les cliniciens devraient encourager des discussions franches avec leurs patients sur ce sujet afin d'éviter de compromettre l'efficacité antirétrovirale des divers agents et d'augmenter le risque de toxicité.

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