Life-Threatening Interactions Between HIV-1 Protease Inhibitors and the Illicit Drugs MDMA and [Gamma]-Hydroxybutyrate.

by Robert D. Harrington, Jane A. Woodward, Thomas M. Hooton and John R. Horn

Human immunodeficiency virus 1 (HIV-1) protease inhibitors have dramatically reduced the morbidity and mortality due to HIV-1 infection. However, most of these antiretrovirals are also potent inhibitors (and occasionally inducers) of hepatic and intestinal cytochrome P450 systems and, therefore, have the potential to alter the elimination of any substance that utilizes these metabolic pathways. We describe a patient infected with HIV-1 who was treated with ritonavir and saquinavir and then experienced a prolonged effect from a small dose of methylenedioxymetamphetamine (MDMA or ecstasy) and a nearly fatal reaction from a small dose of [Gamma]-hydroxybutyrate (GHB). We also discuss the potential for HIV-1 protease inhibitors to alter the metabolism of other abusable prescribed and illicit substances.

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Inhibitors of the human immunodeficiency virus 1 (HIV-1) protease have become a cornerstone of antiretroviral therapy and are recommended for most HIV infected individuals.[1] These agents block HIV-1 replication by preventing the proteolytic cleavage of HIV-1 precursor proteins into subunits that assemble into capsids within infectious virions. When used in combination with HIV-1 reverse transcriptase inhibitors or with each other, protease inhibitors lead to dramatic, sustained reductions in plasma HIV RNA levels, increases in [CD4.sup.+] T-cell counts, delayed HIV disease progression, and prolonged survival.[2-7]

Protease inhibitors are metabolized primarily by the hepatic cytochrome P450 system (isoenzyme CYP3A4) and also inhibit (and in some cases induce) this enzyme in varying degrees. The HIV-1 protease inhibitor ritonavir can also affect 3 other P450 cytochrome enzymes, CYP2D6, CYP2C9 and CYP2C19.[8] The effect of protease inhibitors on hepatic and intestinal drug metabolizing enzymes may dramatically alter the elimination of concurrently administered drugs, including illicit drugs often used by patients infected with HIV. We describe one such patient infected with HIV-1 who was treated with ritonavir and saquinavir. He then experienced prolonged and exaggerated effects from small doses of 2 recreational drugs, ecstasy (methylenedioxymetamphetamine [MDMA]) and [Gamma]-hydroxybutyrate (GHB), both of which he had previously used without adverse reactions. The administration of protease inhibitors to this patient likely interfered with the metabolism of ecstasy, leading to a sustained drug effect, and may also have altered the metabolism of GHB. We also discuss the potential of protease inhibitors to interact with other abusable prescribed and illicit drugs.

REPORT OF A CASE

A 29-year-old man with AIDS ingested a small quantity (approximately 1/2 teaspoonful) of GHB and within 20 minutes, became unresponsive and exhibited a brief episode of repetitive, clonic contractions of both legs and then the left side of his body. Emergency medical personnel found the patient responsive only to painful stimuli, with shallow respirations and a heart rate of 40/min. Atropine sulfate and pancuronium bromide (Pavulon; Organon Inc, West Orange, NJ) were administered before the patient was endotracheally intubated and transferred to a local hospital. Upon admission, vital signs revealed a blood pressure of 159/120 mm Hg, a heart rate of 117/min, ventilated respirations of 14 per minute and a temperature of 35.3 [degrees] C. Physical examination findings were normal except for flaccid paralysis due to pavulon. Chest x-ray and computed axial tomography scan of the head were within normal limits. Laboratory test results revealed normal serum electrolytes, blood urea nitrogen of 6.783 mmol/L (19 mg/dL), serum creatinine of 91.5 [micro]mol/L (1.2 mg/dL), and serum glucose of 5.61 mmol/L (101 mg/dL). Initial complete blood cell count showed hemoglobin of .148 g/L, hematocrit of .44, total white blood cell count of 1500 per ul, and absolute neutrophil count of 180 per ul. Initial arterial blood gases showed a pH of 7.45, [PCO.sub.2] of 38 mm Hg, and [PO.sub.2] of 501 mm Hg on 100% inspired oxygen. Urinary toxin immunochemical screen detected amphetamine and tetrahydrocannabinol, and urinary toxin screen using gas chromatography detected methamphetamine, atropine, MDMA, and prochlorperazine. Urinary toxin screen was negative for cocaine, opiates, barbiturates, benzodiazepines, ethanol, or salicylates.

During the next 3 hours, the patient’s vital signs normalized, and he woke up and extubated himself. Upon questioning, he...
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admitted to ingesting 2 tablets of MDMA approximately 29 hours prior to admission (PTA), about 1/2 teaspoonful of GHB 6 hours PTA, and a similar dose of GHB immediately before becoming unconscious. The patient stated that he took GHB to counter the agitating effects of MDMA, which had persisted for more than 1 day after ingestion. The patient also admitted to smoking a small quantity of marijuana 3 days PTA, and ingesting 5 mg of prochlorperazine maleate for nausea 17 hours PTA. The patient claimed that, prior to his use of protease inhibitors, he had taken a similar quantity of GHB as a sleep aide on many occasions and had never experienced adverse reactions. Furthermore, during the 24 hours PTA, his friends had consumed similar amounts of the same preparation of GHB every 2 to 3 hours without adverse effects.

The patient had a history of Pneumocystis carinii pneumonia, cutaneous Kaposi's sarcoma, thrush, and neutropenia. A recent [CD4.sup.+] T-cell count was 0.024 x [10.sup.9]/L (24/uL). He had been treated with stavudine, lamivudine, and indinavir sulfate, but was switched to ritonavir (400 mg twice daily) and saquinavir (400 mg twice daily) 5 days PTA because of rising plasma HIV RNA levels. Other medications he had taken included granulocytecolony stimulating factor (300 [micro]g three times weekly), azithromycin (1200 mg once weekly), acyclovir (400 mg three times daily as needed), aerosolized pentamidine (monthly), and multivitamins (daily).

Analysis of a sample of the GHB solution ingested by the patient was performed at the Washington State Toxicology Laboratory, Seattle, which confirmed that the liquid was GHB at a concentration of 420 mg/mL.

COMMENT

Although protease inhibitors have dramatically improved the prognosis for many HIV-infected patients, they are associated with numerous adverse effects, including hyperglycemia, hypertglyceridemia, lipodystrophy, hepatitis, nephrolithiasis, and a variety of gastrointestinal symptoms.[9] In addition, HIV protease inhibitors can cause serious adverse reactions when administered with other substances in which the metabolism is altered due to the inhibitory effect of protease inhibitors on the cytochrome P450 system. Much has been written[10-12] regarding hazardous interactions between protease inhibitors and other prescribed medications, but we are aware of no published scientific reports regarding the added dangers of using recreational drugs while taking HIV-1 protease inhibitors. Our report describes a patient treated with HIV-1 protease inhibitors who suffered significant adverse reactions from 2 commonly used illicit drugs. This account highlights the need to warn patients who may use recreational drugs while taking potent anti-HIV therapy of the potential for life-threatening drug interactions.

Our patient maintained that the duration ([is greater than] 29 hours) of the stimulatory effect of the MDMA he ingested was much longer than when he had taken similar doses of ecstasy--prior to his use of ritonavir and saquinavir. In fact, he stated that the sustained effects of MDMA are what prompted him to take GHB, given its sedating qualities.

Amphetamines and their hallucinogenic derivatives are mostly metabolized to active metabolites, which are further metabolized or eliminated via renal excretion. Three commonly used amphetamines (amphetamine, MDMA, and methamphetamine [crystal meth]), are metabolized by the CYP2D6 isofrm of the cytochrome P450 system. All 4 commercially available HIV protease inhibitors can block the CYP3A4 isofrm of the P450 system to varying degrees, but ritonavir can also inhibit the CYP2D6, CYP2C9, and CYP2C19 isozymes. Since our patient was taking both ritonavir and saquinavir when he ingested MDMA, it is plausible that the sustained clinical effects of MDMA were due to a ritonavir-mediated delay in its metabolism. Unfortunately, no plasma levels of MDMA were obtained to confirm this speculation.

Our patient also experienced a life-threatening reaction to ingestion of GHB that may have been partly due to the coadministration of ritonavir and saquinavir. An endogenous compound produced as a metabolite of [Gamma]-aminobutyric acid, GHB is found in many tissues, including the brain, kidney, heart, muscle, and fat. It is approved for use in the United States only in research protocols, although it has been used in Europe as an anesthetic and to treat narcolepsy and ease alcohol withdrawal.[13] Illicit uses have been to promote sleep, control weight, enhance muscle mass (reportedly by increasing growth hormone levels), and to induce euphoria. One hundred twenty-six cases of GHB poisoning, including 1 death due to cardiac arrest, have been reported.[13,14] Manifestations of GHB poisoning include vomiting, respiratory depression and arrest, myoclonic or seizure activity, and a variety of alterations in mental status, from inebriation and agitation to stupor and coma.[13-15] Many patients in reported cases had also used ethanol.
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and other drugs besides GHB. Our patient exhibited features typical of GHB poisoning, with a rapid onset of loss of consciousness, seizurelike activity, respiratory depression, and then rapid and complete recovery. Although our patient admitted to taking small, similar doses of GHB 6 hours prior to and shortly before his collapse, the precise amount of GHB taken is unknown. Nevertheless, the estimated dose ingested immediately prior to his collapse was relatively small (approximately 10 mg/kg) and much less than the amount reported to cause respiratory depression, coma, and seizure ([is greater than] 50 mg/kg).[13] Furthermore, our patient claimed to have taken similar and larger doses of GHB on many occasions prior to using protease inhibitors without ill effects. In addition, acquaintances of the patient had ingested multiple doses of the same GHB preparation without adverse reactions. This suggests that the pharmacokinetics of GHB metabolism may have been altered in our patient due to the concomitant administration of ritonavir and saquinavir. Clearance of GHB from the systemic circulation is thought to occur rapidly by oxidation to succinic acid, which then enters the Krebs cycle.[15,16] However, while there are no human data, animal data suggest that a large portion of GHB is also degraded by first-pass metabolic pathways,[17] which usually involve the cytochrome P450 system. Since the plasma concentrations of drugs subject to high first-pass metabolism are markedly increased by inhibitors of these pathways, relatively small doses of high first-pass drugs taken with inhibitors of first-pass enzymes can lead to significantly increased drug levels. This may explain the dramatic response our patient had to the small quantity of GHB he ingested.

Some P450 isozymes are responsible for the metabolism of other commonly abused substances whose metabolism may be affected by HIV-1 protease inhibitors (Table). In most cases, the inhibitory effect of protease inhibitors on the cytochrome P450 system is thought to dominate, resulting in elevated levels and an enhanced effect of other substances also metabolized by this system. However, several recent reports[18-22] have demonstrated an apparent induction by ritonavir of the CYP3A4-mediated metabolism and glucuronidation of several drugs. These in vivo, multi-dose studies showed that ritonavir decreased the drug exposure (area under the curve) of methadone, alprazolam, and meperidine hydrochloride, all of which are metabolized primarily by CYP3A4.[18-20] Whether this effect is mediated by ritonavir or a metabolite of ritonavir is not clear. Similarly, nelfinavir mesylate can either inhibit or induce cytochrome P450-mediated drug metabolism, and is known to increase the degradation of ethinyl estradiol.[21] Furthermore, the metabolism of the drugs listed in the Table may also be affected by other P450-active medications commonly used in HIV-1 infected patients such as azole-antifungals, clarithromycin, and the non-nucleoside HIV-1 reverse transcriptase inhibitors delavirdine, efavirenz, and nevirapine. In fact, nevirapine was recently demonstrated to reduce plasma methadone levels and to precipitate opiate withdrawal in patients who were maintained on methadone for narcotics addiction.[22] Finally, given the variations in drug absorption and metabolism that exist between individuals, it is impossible to accurately predict the effect of drug combinations in any one person. This is particularly important with regard to the use of illicit drugs, which are often taken by groups of people; individuals may be falsely reassured by other members of the group of the apparent safety of drug combinations. Thus, a prudent approach for HIV providers would be to caution their patients that the known and potential drug interactions between abusable substances and HIV medications are complex, unpredictable and, occasionally dangerous. Furthermore, coadministration of these medications with illicit substances should be strongly discouraged and coadministration of HIV medications with other abusable drugs should take place only under the close scrutiny of their provider.
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<table>
<thead>
<tr>
<th>Substance</th>
<th>Metabolism/Mechanism</th>
</tr>
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<tbody>
<tr>
<td>Hydrocodone</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone, morphine, heroin</td>
<td>Glucuronidation?</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Marijuana, dronabinol, zolpidem</td>
<td>Cytochrome P450 (CYP3A4)</td>
</tr>
<tr>
<td>Sildenafil (Viagra)</td>
<td>Cytochrome P450 (CYP3A4)</td>
</tr>
<tr>
<td>Cocaine(*)</td>
<td>Hydrolysis by plasma cholinesterase</td>
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(*) Metabolism should not be affected by protease inhibitors.

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Corresponding author: Robert D. Harrington, MD, Harborview Medical Center, Campus Box 359930, 325 Ninth Ave, Seattle, WA 98104 (e-mail: rdh@u.washington.edu).

REFERENCES


[13.] Centers for Disease Control and Prevention. Multistate outbreak of poisonings associated with illicit use of gamma...
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From the Department of Medicine, School of Medicine (Drs Harrington and Hooton), and the Department of Pharmacy, School of Pharmacy (Drs Woodward and Horn), University of Washington, Seattle.