Antiretroviral Drugs And Opioids Interact

BY DAMIAN McNAMARA
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SAN JUAN, P.R. — Better understanding of interactions between opioids and antiretroviral agents can improve clinical care and patient outcomes, said Elinore McCance-Katz, M.D.

"It may be that methadone is not the best opiate therapy for everyone with HIV who is opioid dependent," Dr. McCance-Katz said at the annual meeting of the American Academy of Addiction Psychiatry.

"These drug interactions are so potent, it is important to know if there are optimal combinations of opiate therapies and HIV medications," she added.

Through the cytochrome P-450 system, many antiretroviral agents interact with opioids, including methadone (see box), levomethadyl acetate (LAAM), and buprenorphine.

HIV drugs that induce metabolism of methadone can cause symptoms of opiate withdrawal between doses, whereas HIV drugs that inhibit such metabolism can cause opiate toxicity.

Such interactions can lead to nonadherence to antiretroviral regimens, viral resistance, and illicit drug use "in an attempt to self-medicate some of these noxious drug interactions that often go unrecognized," said Dr. McCance-Katz, chair of the division of addiction psychiatry, Virginia Commonwealth University, Richmond.

Drug toxicities that are additive can be a risk to patients. Because of the clinically significant interactions, the Food and Drug Administration now requires methadone interaction data before approval of a new antiretroviral agent.

Researchers are assessing alternatives to methadone for HIV patients. Buprenorphine, for example, may not have the same liabilities as methadone in combination with antiretroviral therapy, she said. "I'm still looking at the data, but we don't see the toxicities with buprenorphine and LAAM that we see with methadone."

Methadone-maintained patients using efavirenz as part of highly active antiretroviral therapy need a 50% increase in methadone level, from 80 mg/dL at baseline to 120 mg/dL, according to research by Dr. McCance-Katz. With buprenorphine, the mean 17.2-mg/dL dosage did not change when efavirenz was added. "We did not have to increase the opiate dose for anyone, and we did not have to restabilize people as a result."

Not all of methadone's effects on HIV drugs are via cytochrome P-450 metabolism. For example, didanosine and stavudine concentrations drop to subtherapeutic levels when these drugs are taken with methadone. Methadone decreases gastrointestinal motility, and didanosine and stavudine are particularly sensitive to stomach acid.

Dr. McCance-Katz highlighted some specific interactions between methadone and agents that combat HIV:

► Delavirdine mesylate inhibits cytochrome P-450, leading to a significant increase in methadone concentrations—the half-life is extended by almost 50%. "We would worry about accumulation," she said. "With LAAM, we see even more dramatic effects and LAAM metabolites, which have implications for cardiac toxicity."

► Nevirapine is similar to delavirdine, causing a decrease of about 50% in methadone area-under-the-curve concentrations. Withdrawal symptoms can occur if methadone dosages are not increased.

► Nelfinavir mesylate shows a "dramatic drop" in 7-day plasma levels when given with methadone. "Interestingly, we did not see withdrawal in these patients. We think that is because nelfinavir is a very good competitor for protein binding—so there was more free methadone available to protect them from opiate withdrawal," she said.

► Kaletra, a combination of lopinavir and ritonavir, causes methadone levels to become subtherapeutic. Dr. McCance-Katz observed withdrawal symptoms in these patients. "But we did not know if it was an effect of lopinavir, ritonavir, or both." When ritonavir was studied alone, the nonsignificant increase in methadone level implicated lopinavir as the component interacting with methadone. ■

Interactions

These antiretroviral drugs were found to interact with methadone:

- Abacavir
- Combivir
- Delavirdine
- Didanosine
- Efavirenz
- Lopinavir
- Nelfinavir
- Nevirapine
- Ritonavir
- Saquinavir
- Stavudine
- Zidovudine

Source: Dr. McCance-Katz

THE EFFECTIVE PHYSICIAN

Nonoccupational Postexposure HIV Prophylaxis

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Although the most effective method of preventing HIV infection is avoidance of exposure, questions arise as to the effectiveness of and strategy for antiviral prophylaxis following nonoccupational exposure. The CDC recently released guidelines for this complex clinical presentation.

Conclusions

There are nearly 40,000 new HIV infections annually in the United States. At this time, few individuals seek care after nonoccupational exposure. In addition, some patients are not appropriate candidates for nonoccupational postexposure HIV prophylaxis (nPEP) because of recurring high-risk exposures.

Surveys indicate that 69% of HIV-discordant couples report unprotected intercourse in the previous 6 months, and 17% of bisexual or homosexual men report condom failure in the last 6 months.

In a national sample, 13% of women reported having been raped, and 60% of these rapes occurred before age 18. Male victims account for nearly 12% of reported rapes in the United States.

In animal studies, tenofovir blocked intravenous transmission of simian immunodeficiency virus if given within 24 hours of exposure and continued for 28 days. Delay until 48-72 hours and shorter duration of therapy diminished effectiveness.

In humans, it is estimated that prompt initiation of zidovudine after a needle stick reduces the risk of HIV transmission by 81%. Clinical trials indicate that single-dose therapy to laboring HIV-infected mothers coupled with a dose of antiviral agents to the neonate within 72 hours of birth substantially reduces peripartum transmission of the virus.

Studies of the cost effectiveness of nPEP endorse therapy only for patients exposed to a known source of HIV and those who have had repeated receptive anal intercourse with a homosexual or bisexual partner of unknown serostatus.

Implementation

► When counseling a patient post exposure, the following rates of transmission per 10,000 events may be of value: 9,000 infections after infected blood transfusion, 67 infections after sharing needles, 50 infections after receptive anal intercourse, 30 infections after a needle stick, 10 infections after receptive vaginal intercourse, 5-7 infections after insertive intercourse, and 0.5-1 infections after oral intercourse.

► Risk for transmission might be greatest if the source had been infected recently, which is associated with high viral loads in body fluids.

► The following signs and symptoms are present in acute retroviral infections: 96% of patients have fever, 74% have lymphadenopathy, 70% have pharyngitis, 70% have rash, 54% have myalgias/arthralgias, 33% have diarrhea or headache, and 27% have nausea and vomiting.

► In assessing a patient with high-risk behavior for nPEP, a physician should consider the patient's ongoing risk-reduction behavior in the context of the recent exposure. These patients should be offered counseling to help them change their lifestyles and thereby reduce the continued risk of infection.

► The CDC recommends prompt (within 72 hours) initiation of highly active antiretroviral therapy (HAART) and continuation for 28 days in patients with exposure to sources known to be HIV infected or when the event poses substantial risk for transmission. Patients with small exposure risks or those who are seen more than 72 hours after the event should not receive nPEP. Other circumstances warrant careful assessment of the benefits versus the risks of initiating therapy.

► Current data indicate that nPEP is less likely to be effective if started more than 72 hours after exposure. After such delays, the potential benefit may not outweigh the risks of taking antiviral medication.

► There are two preferred regimens. One is efavirenz and either lamivudine or emtricitabine with either zidovudine or tenofovir. The other is lopinavir/ritonavir (Kaletra) and zidovudine plus either lamivudine or emtricitabine.

► Prior to initiation of nPEP, patients should themselves be screened for HIV to avoid treatment of a patient with more remote infection.

► Frequent side effects of postexposure prophylaxis include nausea (57%) and fatigue or malaise (38%). Nevirapine has been associated with severe hepatotoxicity as well as pronounced skin reactions; it should not be used for postexposure prophylaxis.

► Patients seeking care after a potential exposure to HIV should be serotested at baseline, 3 months, and 6 months after the critical event. There have been reports of low viral load levels (fewer than 3,000 copies) after exposure in patients who do not subsequently seroconvert.

► Patients who seroconvert despite the use of combination antiretroviral therapy should be tested for resistance to guide ongoing therapy.

► In several studies it was found that most victims of sexual assault refuse or do not complete the 28-day course of antiviral prophylaxis. They should be offered supportive counseling, appropriate testing, prophylaxis for STDs, and emergency contraception.

► In one study, 72% of recipients decreased their risky behavior, and 14% increased such activity; 17% sought a second course of therapy within the year after treatment.

Reference

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