We read with interest the article by Wahidi et al1 in CHEST (November 2011). We are concerned that the section on midazolam did not provide up-to-date information on interactions between this drug and highly active antiretroviral therapy (ART) used in HIV-infected individuals.

The study that is quoted in the consensus statement suggests that higher doses of midazolam may be needed in certain HIV-infected populations.2 We believe this reflects the situation in IV-drug users who are HIV-positive (the main HIV study group) and are likely to have acquired a tolerance to benzodiazepines through prolonged use. There is no detail provided on ART usage; therefore, the conclusions should not be extrapolated to all patients with HIV.

The majority of current ART regimens contain either potent cytochrome P450 enzyme 3A4 (CYP3A4) inhibitors, such as the HIV protease inhibitor ritonavir, or enzyme inducers, such as the non-nucleoside reverse transcriptase inhibitors efavirenz or nevirapine. Midazolam is extensively metabolized by CYP3A4 and coadministration with, for example, lopinavir/ritonavir results in a fourfold increase in midazolam bioavailability (area under the curve) after parenteral administration.2 This may result in prolonged sedation and other adverse effects such as arrhythmias.

Diazepam at reduced doses has been used in clinical practice with ritonavir (100 to 200 mg daily), although at higher ritonavir doses, it is contraindicated.3 Alternatively, lorazepam has the least potential for interaction with ART of all the currently available benzodiazepines4 used in bronchoscopy. It may be considered in this scenario (where available) despite its disadvantage of a longer onset of action and duration of sedation. The use of benzodiazepines for other patient groups receiving CYP3A4 inhibitors such as macrolide antibiotics, itraconazole, and the new hepatitis C virus NS3 inhibitors (boceprevir and telaprevir) should also be undertaken with caution.

Conversely, the concomitant administration of CYP3A4 inducers such as efavirenz, or rifampin antibiotics may lead to therapeutic failure of standard-dose benzodiazepines. Dose escalation should be performed with careful clinical and physiologic monitoring.

The response to sedation in patients who are HIV-positive is unpredictable. The choice of sedative and its dosage results in a fourfold increase in midazolam bioavailability (area under the curve) after parenteral administration.2 This may result in prolonged sedation and other adverse effects such as arrhythmias.

Conversely, the concomitant administration of CYP3A4 inducers such as efavirenz, or rifampin antibiotics may lead to therapeutic failure of standard-dose benzodiazepines. Dose escalation should be performed with careful clinical and physiologic monitoring.

The response to sedation in patients who are HIV-positive is unpredictable. The choice of sedative and its dosage must be tailored to the individual’s history and most importantly his or her concurrent medication. Increased postprocedure monitoring is mandatory.

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Response

To the Editor:

We appreciate the comments of Dr José and colleagues about our recent consensus statement in CHEST7 and thank them for bringing attention to HIV disease, wherein great advances have been accomplished. Continuous attention to this patient population is indeed essential.

Our article attempted to address the major issues on the use of topical anesthesia, analgesia, and sedation during bronchoscopy. Therefore, it was beyond the scope of our effort to address all possible interactions of medications with various disease states.

Our segment on benzodiazepines specifically mentioned the need for higher doses of midazolam in “HIV-infected patients with history of drug dependence” and did not advocate it in all patients with HIV. We do agree that precautions should be taken when using benzodiazepines in patients with HIV receiving antiretroviral therapy, as these medications are known to inhibit the cytochrome P450 enzyme 3A4, potentially leading to excessive sedation.2,3

Our consensus statement can serve as a general platform to guide administration of sedation to patients undergoing bronchoscopy. Optimal and safe sedation requires physicians to tailor regimens to individual patients after careful assessment of comorbidities, medication profile, and procedural needs.

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