

## Letters to the Editor

### Indinavir-Fluconazole Interaction

In a recent article (1), De Wit et al. concluded that indinavir and fluconazole can be administered concomitantly to human immunodeficiency virus (HIV)-seropositive patients without adjustment of the dose of either drug, based on their results showing no significant pharmacokinetic interaction between the two drugs. I feel obliged to comment, as I am concerned about the acceptability of these results by health care providers in charge of the care of HIV-seropositive patients.

First of all, the authors do not clarify which antiretroviral drugs other than indinavir were used for managing these patients. Monotherapy with indinavir increases the risk for viral resistance. Further, if additional anti-HIV drugs were coadministered, the authors should have considered the possibility of drug interactions involving these compounds.

In order to exclude the possibility of physical incompatibility of these drugs in the gastrointestinal tract, these agents should have been administered with a time delay. There is no information in the article addressing this issue.

As mentioned in the article, fluconazole is a well-known CYP3A4 inhibitor (4), which may be expected to increase the areas under the curve of CYP3A substrates such as indinavir. Inhibition by fluconazole has been reported for numerous drugs such as phenytoin, cyclosporine, and anticoagulants (5). One of the most crucial issues in assessing such potential metabolic interactions is the half-life and time to steady state of the inhibitor drug. Given the long and variable half-life of fluconazole, 20 to 50 h (5), it is difficult to conclude that no significant interaction exists for these two drugs based on the duration of fluconazole exposure in this study. As stated in Results, fluconazole concentrations could not have reached steady state based on trough measurements carried out on day 8. Additionally, for the same reason, a 7-day washout period is not sufficient to ensure complete elimination from the body.

Keeping in mind the use of fluconazole for treatment of opportunistic candida infections in HIV-seropositive patients for at least 2 weeks and in many cases for an indefinite period for long-term maintenance therapy, the results of this study do not rule out the possibility of a pharmacokinetic interaction in the context of clinical practice. Maintaining optimal drug levels of protease inhibitors such as indinavir to delay antiviral resistance and avoid side effects has been shown to be important (2, 3). Therefore, adjustment of indinavir dosage for coadministration with fluconazole may be necessary in HIV therapy.

S. E. Bellibas is a recipient of a Merck Sharp & Dohme International Fellowship in Clinical Pharmacology.

#### REFERENCES

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#### Authors' Reply

Dr. Bellibas raises several interesting questions. With regard to other antiviral therapies used, it should be noted that this study was designed to be a study of pharmacokinetic interactions, not of antiviral efficacy. The patients enrolled in the trial did not have advanced HIV disease and were not on any other antiretroviral medications. When the study was carried out, in 1995, it was presumed that there would be negligible risk of the acquisition of resistance in patients receiving 1-week courses of indinavir.

Regarding the question of physical incompatibility of these drugs in the gastrointestinal tract, all doses of fluconazole were administered at the same time as the a.m. dose of indinavir. Therefore, the lack of significant pharmacokinetic effects on either drug, also indicates that physical incompatibility of these drugs in the gastrointestinal tract was not an issue.

It is true that fluconazole is a CYP3A inhibitor, but it is not as potent an inhibitor as other azoles (1). In fact, coadministration of fluconazole with indinavir led to small decreases in indinavir pharmacokinetic parameters, not the increase that would have resulted from potent CYP3A inhibition. We do not understand the mechanism responsible for this small decrease, but it does not appear that a dose adjustment is required.

With regard to the duration of fluconazole therapy, data indicated that fluconazole levels were close to steady state on day 8. If the half-life was as high as 50 h, a 90% approximation of steady state would be expected on day 8. The concentrations of fluconazole achieved, although not quite at steady state, would almost certainly be adequate to investigate the effects of commonly used doses of fluconazole on the pharmacokinetics of indinavir, especially since a relatively high (400 mg daily) dose of fluconazole was employed. Additionally, the lack of any detectable effect of indinavir on the pharmacokinetics of fluconazole would not likely be altered if a longer dosing period was employed and is consistent with the minor role of hepatic metabolism in the clearance of fluconazole.

Statistical analyses of the data with respect to different sequences of the treatments address the issue of whether the 7-day washout period was sufficient. These analyses do not suggest any clinically meaningful sequence effect.

Thus, we conclude that the study design was adequate to indicate that there is no clinically meaningful pharmacokinetic interaction between fluconazole and indinavir.

**REFERENCE**

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