defect is not important for the elimination of alfentanil, since the drug is not metabolized by the human cytochrome P-450 form that catalyzes debrisoquine 4-hydroxylation. This is further substantiated by *in vivo* findings described in two recent publications,[4,5] which show that the metabolism of alfentanil in poor metabolizers of debrisoquine was not deficient.

Finally, we wish to emphasize that, in order to draw valid conclusions, extrapolations from *in vitro* to *in vivo* should be based on a thorough investigation and characterization of the *in vitro* system.

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In Reply:—Drs. Lavrijsen and Heykants, using their recent data[2] make a valid analysis as to an extended interpretation of our data.[1] They point out that the K_i[1] of alfentanil being nearly eightfold higher than the K_m[2] represents additional evidence of the unimportance of debrisoquin hydroxylase in the metabolism of alfentanil. We agree that this is a valuable argument that deserves to be raised.

The letter also correctly points out that we ignored this relationship by deliberately confining ourselves to studying only inhibition. By restricting our investigation to inhibition, we were able to screen nine opioid analgesics. It is a matter of opinion whether this widely used technique, meant only to screen for presence of *in vitro* competitive inhibition, actually overemphasizes competitive inhibition. Such a study[1] can "be used as screening tests to identify drugs that interact with the debrisoquin hydroxylase," that *in vivo* studies performed in response to these results "found alfentanil clearance to be unaffected by the debrisoquin hydroxylase," and that the "importance of this polymorphism to the metabolism of fentanyl and dextropropoxyphene deserves investigation." These conclusions[1] are conservative and completely consistent with the use for which this test was originally designed.[3]

For these reasons we agree with the concluding two paragraphs of the letter, outlining further investigations about the metabolism of alfentanil and amplifying the necessity of a complete characterization of the *in vitro* metabolic system before extrapolating to *in vivo* circumstances.

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