In reply—Dr. Kraft takes issue with my editorial, noting that monitoring standards in this country will soon be set by the legal profession rather than physicians. Actually, if such an unfortunate circumstance develops, it will occur only because physicians have not developed meaningful standards for themselves. Development of practice standards requires the same objectivity as we apply to the evaluation of drugs and other forms of medical technology, as I tried to emphasize.

He cites “three key points that neutralize” the validity of Dr. Eichhorn’s conclusions regarding the value of the monitoring standards, which he feels that I overlooked. Two points are related problems with the design of Dr. Eichhorn’s study, that it ignored the universe of anesthetic complications by considering only intraoperative catastrophes and immediate outcomes. Such a narrow focus was probably chosen intentionally because it would emphasize the circumstances in which many believe that monitoring standards would have their greatest impact. Despite this bias, however, the case was weak, at best, obviating the need to consider anesthetic complications more broadly. Yet, I did note that “risk management interest is now shifting appropriately to the postanesthetic recovery room.”

Dr. Kraft’s third point—that correction of inadequacies in supervision of residents and nurse anesthetists and in equipment maintenance would have prevented the adverse events, even in the absence of other actions, such as the imposition of monitoring standards—actually dovetails nicely with my emphasis on the diverse ways in which anesthesia safety may be enhanced, in addition to improved monitoring. He also highlights an important, unemphasized issue in discussions of sophisticated monitoring equipment. While the pulse oximeter, for example, is capable of detecting subtle changes in arterial oxygen saturation, many seem to view the device as a means of detecting the often less subtle hypoxemia accompanying accidents as a final common pathway. I suspect that further advances in anesthesia safety await our getting beyond narrow monitoring issues and developing a better understanding of accident evolution, especially the role of human factors.

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REFERENCES


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Narcotic Analgesics and Debrisoquine Polymorphism

To the Editor—In a recent publication, Henthorn et al. suggested that “a genetic defect may be important for elimination clearance by metabolism for dextropropoxyphene, alfentanil, and fentanyl.” This could contribute to interindividual differences in elimination clearance for these analgesics and therefore complicate their clinical use. The conclusions of Henthorn et al. were based on the interaction of the analgesics with the 2-hydroxylation of desmethyliimipramine, a prototypical reaction for the debrisoquine polymorphism, in a human liver microsomal preparation. The competitive character of the analgesics was regarded to be decisive to reach their conclusions. We, however, believe that the investigators ignored a second factor that is equally important for the interpretation of kinetic data obtained in competitive inhibition experiments, i.e., the relative values of the inhibition constant Ki versus the Km.

As pointed out by Boobis et al., two conditions have to be met in order to conclude that the same form of cytochrome P-450 is involved in the metabolism of two substrates: first, the two substrates should be competitive inhibitors of the metabolism of each other, and secondly, the Ki for inhibition should be the same as the Km for metabolism. In their study, Henthorn et al. found a Km for alfentanil of 176 μM. This Km however, exceeds by far the recently published Km for alfentanil, 22.8 μM. So, the inhibition by alfentanil of the 2-hydroxylation of desmethyliimipramine observed by Henthorn et al. occurs at a high concentration relative to its Km, which indicates that the cytochrome P-450 form involved in the debrisoquine polymorphism contributes at most to only a small part of the total metabolism of the drug. Although Henthorn et al. also suggest this may be the case, the authors overemphasize the competitive character of the analgesics as inhibitors and therefore reach faulty conclusions. Recently, we demonstrated that debrisoquine itself is a noncompetitive inhibitor of any of the in vitro metabolic pathways of alfentanil in human liver microsomes, and that the Ki for debrisoquine (2.0–3.2 mM) was much greater than its Km (0.086–0.090 mM). From the data summarized above, we may conclude that a genetic
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, 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 make a valid analysis as to an extended interpretation of our data. They point out that the Kᵢ of alfentanil being nearly eightfold higher than the Kᵢ of Kᵢ 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 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 dextromorphphene deserves investigation.” These conclusions are conservative and completely consistent with the use for which this test was originally designed.

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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