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Variability of Human Drug Response

FOR MANY YEARS, the practicing anesthesiologist has recognized that humans vary in their response to drugs and that both anesthetic and non-anesthetic drug administration must be titrated to clinical effect. This variability may be due to differences in both the concentration of drug available at the site of action (pharmacokinetics) and to differences in intrinsic sensitivity to a given drug concentration (pharmacodynamics). Recently a number of the determinants of these differences in pharmacokinetic responses have been identified.

Although the therapeutic plasma concentrations of alfentanil are known,[1] there is considerable interindividual variation in the plasma-concentration time profile between patients. In an attempt to increase the accuracy of prediction of interindividual variability in patient response, conventional pharmacokinetic analysis in a small number of subjects has been extended to population pharmacokinetics in a large number of patients.[2] After taking into account age, weight, and gender, 48% of the variability in alfentanil clearance and 33% of the variability in volume of distribution of the central compartment (Vc) remains unexplained. Thus, there is wide interindividual variability in alfentanil pharmacokinetics during the perioperative period resulting in marked difference between individuals in the rate of alfentanil infusion required.

The pharmacokinetics of drugs are usually defined initially in a small number of healthy subjects, rather than in patients with cardiac, renal, or hepatic disease, or those receiving multiple drug therapy, all of which may be responsible for altering drug disposition. Anesthesia and surgery itself have recently been identified as important factors in altering drug disposition.[3-5] Thus, pharmacokinetic factors that might be responsible for variability in human response to drugs (including alfentanil) during surgery include drug dose, concomitant drug therapy leading to drug interactions, age, gender, disease states (renal, hepatic, cardiac, and possibly pulmonary), genetic polymorphism, and, finally, anesthesia and surgery.

Changes in drug disposition in disease states are due to a variety of factors that include altered organ blood flow, decreased drug metabolizing enzyme capacity, and changes in drug protein binding, resulting in altered distribution and/or displacement interactions. Thus disease states, such as renal and hepatic disease, often cause changes in drug volume of distribution and plasma clearance; for example, alfentanil clearance is reduced in patients with cirrhosis accompanied by a prolonged elimination half-life.[6] The free fraction of alfentanil is increased in patients with renal failure[7] and cirrhosis,[6] leading to an increased volume of distribution at steady state in patients with renal failure.[7] In uremic patients there is also a reduction in the volume of distribution of the central compartment,[8] resulting in higher plasma alfentanil concentrations immediately after administration with possible increased pharmacologic effect. Aging is associated with physiological and pharmacological changes that affect drug disposition and the clearance of many anesthetic drugs, including alfentanil, is reduced in the elderly.[9]

It is only recently that attention has been devoted to the study of pharmacokinetics in the perioperative period; most of the research in this area has been performed in the laboratory and definitive studies in humans are limited. During the perioperative period, albumin concentrations decrease, while plasma levels of free fatty acids

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and $alpha_1$ acid glycoprotein (AAG) increase,[10,11] all of which might be expected to contribute to altered drug binding. Lidocaine, quinidine, and propranolol binding increase after surgery, due to postoperative elevation in AAG concentrations.[11-13] The increase in lidocaine binding after cardiac surgery (the free fraction decreasing from 30.2% prior to surgery to 16.4% 3 days after surgery) results in a marked decrease in volume of distribution.[12] Thus, changes in plasma binding of drugs in the perioperative period may lead to changes in drug distribution, and theoretically, changes in uptake and effect. Changes in drug metabolism also occur perioperatively; antipyrine clearance, which reflects drug metabolizing ability, is increased in patients whose surgery lasts 2 h or less, but decreased in those whose surgery lasted longer.[3] Thus, the effects of surgery and anesthesia on drug metabolism may be dependent on the duration and type of surgery and/or anesthesia undertaken. Volatile anesthetics and iv agents inhibit drug metabolism,[4,5,14] and changes in hepatic blood flow may contribute to altered organ blood flow during anesthesia.[15,16] In contrast, spinal anesthesia has no effect on hepatic drug metabolism in animals.[5,17]

The importance of genetic variability for metabolism of drugs by acetylation and hydrolysis has been recognized for some time. Thus, poor acetylators metabolize drugs such as isoniazid, hydralazine, and procainamide more slowly than do extensive metabolizers and are more likely to develop adverse effects from these drugs. Similarly, the importance of the impaired ability to hydrolyze succinylcholine is well known to anesthesiologists. However, the majority of drugs are metabolized by a family of cytochrome P-450 enzymes found in the liver and other tissues, and it is only recently that genetic impairment of drug metabolism by this system has been recognized. The first oxidation defects to be described were in the metabolism of debrisoquine and sparteine.[18] Subsequent work showed that about 8–10% of the U. S. and U. K. population have a greatly reduced ability to oxidize debrisoquine to 4-hydroxydebrisoquine and that this was due to the inherited marked reduction in the activity of a specific cytochrome $P\text{-}450_{DB_1}$. It also soon became clear that the deficient ability to metabolize sparteine was due to deficiency of the same isozyme. The 8–10% of the population who are of the poor metabolizer (PM) phenotype are classically identified by measuring the ratio of unchanged debrisoquine to 4-OH-debrisoquine in a urine sample; a ratio of >12 has been used as the cutoff to identify poor metabolizers. Extensive metabolizers (EM) have a ratio below this value. The importance of this isozyme lies not in its ability to metabolize debrisoquine (an adrenergic neuron blocking agent available for the treatment of hypertension in Europe) but because of the large number of other drugs that are also metabolized by this enzyme, and whose metabolism therefore cosegregates with debrisoquine. These drugs include propranolol, metoprolol, timolol, encainide, amitriptyline, desipramine, and phenformin.

For drugs whose metabolism cosegregates with debrisoquine, it is therefore also possible to identify a subset of the population who are poor metabolizers of these drugs. The clinical consequences of this polymorphism depend on the contribution made to each drug's total clearance by the specific metabolic pathway that is dependent on $P\text{-}450_{DB_1}$. Thus, if most of a drug's elimination is by this pathway, then the absence of this pathway will result in reduced total drug clearance and increased parent drug concentrations with the potential for concentration related toxicity in the poor metabolizer phenotype. On the other hand, if only a small proportion of the drug's total clearance uses $P\text{-}450_{DB_1}$, such as is seen with propranolol, there may be almost total loss of the ability to form one metabolite (4-hydroxypropranolol) with little overall effect on the drug's total clearance and hence plasma concentrations and pharmacologic effects.[19] For some drugs, their therapeutic effect is normally produced by a pharmacologically active metabolite. When the ability to produce that metabolite is dependent on $P\text{-}450_{DB_1}$, as in the case of the recently introduced antiarrhythmic encainide, the concentration of parent drug required to produce antiarrhythmic effects is substantially altered in the poor metabolizer phenotype. Other oxidative polymorphisms have also been identified, *e.g.*, mephenytoin and tolbutamide.

Because of the large number of drugs whose metabolism is dependent on the debrisoquine isozyme, it is therefore important to develop techniques that will allow such drugs to be easily identified. How can this be done? A number of approaches can be used. The first is the use of the so-called phenotypic panel approach that uses two groups of subjects: one group known to be poor metabolizers of debrisoquine and another group known to be extensive metabolizers. The drug of interest is then administered to each group, and its clearance and metabolic disposition determined in the two groups. It is important not only to examine the clearance of the parent drug, as was described for alfentanil by Henthorn *et al.*[20] in this issue, but also to examine the production of metabolites. If metabolite production is not examined, the pathway of metabolism dependent on the debrisoquine isozyme may be missed. In addition, it is important to ensure that an adequate number of subjects of both phenotypes are included as considerable interindividual variability still occurs within each phenotype. A minimum of five to six individuals of the poor metabolizer phenotype are required for comparison with extensive metabolizers.

A second approach that has been advocated is to make

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use of the fact that if two drugs are metabolized by the same isozyme, they must both bind to that isozyme, and hence, the binding of one drug limits the binding of the other. This means that *in vitro* a drug metabolized by the debrisoquine isozyme will inhibit the oxidation of debrisoquine and vice versa. The same interaction will also occur *in vivo* if the drugs' relative affinities for the debrisoquine isozyme allows the achievement of appropriate concentrations of each drug after coadministration. Although this technique has been advocated as an easy way to screen compounds (and was used with alfentanil)[21,22] it has a major drawback; some compounds, for example, quinidine, bind to the isozyme but are not themselves metabolized by it. Thus, quinidine is a potent inhibitor of the clearance of other drugs such as propranolol metabolized by P-450_{DB_1}, but the metabolism of quinidine itself does not cosegregate with debrisoquine *in vivo* because it is not metabolized by the isozyme.[23] There is therefore no difference in quinidine metabolism in poor or extensive metabolizers. Because of *in vitro* evidence that alfentanil competitively inhibits debrisoquine hydroxylase,[21] it has been suggested that the considerable variability in the pharmacokinetics of alfentanil might be due in part to alfentanil metabolism exhibiting genetic polymorphism. Other *in vitro* studies have shown that debrisoquine is only a weak noncompetitive inhibitor of alfentanil metabolism and of the formation of its major metabolites,[22] while a limited *in vivo* study demonstrated that a single poor metabolizer of debrisoquine did not differ significantly in either alfentanil disposition or in the urinary excretion of metabolites from two other individuals who were extensive metabolizers of debrisoquine.[24] Clearly, there was a need for a larger study to evaluate the effect of debrisoquine polymorphism in the disposition of alfentanil, and the work by Henthorn *et al.* in this issue addresses this point.[20] The debrisoquine phenotype was assessed using the urinary dextromethorphan/dextrorphan metabolic ratio in seven subjects (three poor metabolizers), and clearly demonstrated that there was no relationship between alfentanil clearance and dextromethorphan metabolic ratio, indicating that polymorphism of the debrisoquine hydroxylase enzyme does not influence the clearance of alfentanil,[20] although the metabolites of alfentanil were not measured in this study. Thus, genetic polymorphism does not appear to be a major contributing factor to variability in alfentanil response. How do we resolve the apparent conflict between the *in vivo* and *in vitro* data? This may well be due to a mechanism similar to that seen with quinidine. Thus, alfentanil may bind to the debrisoquine isozyme and hence inhibit the metabolism of debrisoquine as seen by Henthorn *et al.*,[21] but as it is itself not metabolized by the isozyme, debrisoquine will not competitively inhibit alfentanil metabolism *in vitro,* as demonstrated by Lavrijsen.[22] In addition, alfentanil clearance will not be altered in the poor metabolizer phenotype as shown by Henthorn *et al.*[20] in this issue.

Thus, although some of the mechanisms of interindividual variability in drug response in surgical patients have now been defined, much of the variability, including that seen with alfentanil, is still unexplained, and the ability to predict response in any particular patient remains poor. These studies serve to re-emphasize the importance of titrating drug dose with the careful monitoring of effect.

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