Title: ALFENTANIL CLEARANCE IS INDEPENDENT OF THE POLYMORPHIC DEBRISOQUIN HYDROXYLASE

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Introduction. Wide intersubject variability in the ability to oxidatively metabolize drugs and its capacity to affect response to drug therapy are now well recognized. A defect in the hydroxylation of debrisoquin is present in 5 to 10% of Caucasians and is thought to be inherited as an autosomal recessive trait. Poor metabolizers of debrisoquin have been shown to be poor oxidizers of other drugs as well, often with important therapeutic consequences.[1] The fact that the P-450 enzyme referred to as debrisoquin hydroxylase is also responsible for the oxidative metabolism of other drugs has provided the basis for using some of these other drugs (i.e., sparteine, desmethylimipramine, and dextromethorphan) as probes to classify the desbrisoquin hydroxylator phenotypes of individuals as either extensive metabolizer (EM) or poor metabolizer (PM).

Alfentanil is metabolized by the oxidative reactions of N-dealkylation and O-demethylation (Jos Heykants, Janssen Pharmaceutica; personal communication), reactions demonstrated to be mediated by debrisoquin hydroxylase.[1] McDonnell et al.[2] identified an apparently normal patient with plasma clearance of alfentanil that was more than 2 SDs from the mean of the other patients in their study; they later demonstrated[3] that this patient also had a lower clearance of phenacetin, a drug known to be metabolized by debrisoquin hydroxylase, than three of the other "normal" patients. Henthorn et al.[4] showed that alfentanil competitively inhibits this isozyme in vitro. These studies only suggest that alfentanil pharmacokinetics may be determined by the genetic polymorphism of debrisoquin hydroxylase. The patient in the studies of McDonnell et al.[2,3] has never had her debrisoquin oxidative phenotype determined and in vitro competitive inhibition only indicates an interaction with this isozyme, not its importance in the metabolism of a drug. Nevertheless, this pharmacogenetic explanation has been invoked as a possible explanation for observations of prolonged respiratory depression following infusions of alfentanil[5], abnormal alfentanil kinetics[6], and even reduced clearance of sufentanil in patients[7,8].

The purpose of this study was to determine the disposition of alfentanil in healthy volunteers of known debrisoquin oxidation phenotype in order to evaluate the effect of this genetic polymorphism on the pharmacokinetics of alfentanil.

Methods. Six healthy subjects, aged 23 to 44 years, who had been debrisoquin hydroxylator phenotyped according to their ability to metabolize dextromethorphan (4 EMs and 2 PMs) gave institutionally approved, written informed consent to participate in this study. The subjects were given 10 ug/kg alfentanil HCl by rapid intravenous infusion and 39 radial arterial blood samples were obtained at specified intervals over the subsequent 6 hours. Plasma alfentanil concentrations were measured by a direct, specific radioimmunoassay.[9] The data were fit to a three-compartment open mammillary model using the CONSAM digital computer program.

Results. The steady-state volume of distribution ranged from 16.44 - 23.63 liters, beta phase half-life ranged from 72.5 - 110.8 mins, and the elimination clearance ranged from 0.117 - 0.282 l/min in the six subjects. Figure 1 illustrates the relationship between the metabolic ratio of the dextromethorphan phenotyping test (abscissa) and alfentanil clearance (ordinate); it is clear that there is no relation between these variables (Spearman's rho = 0.66).

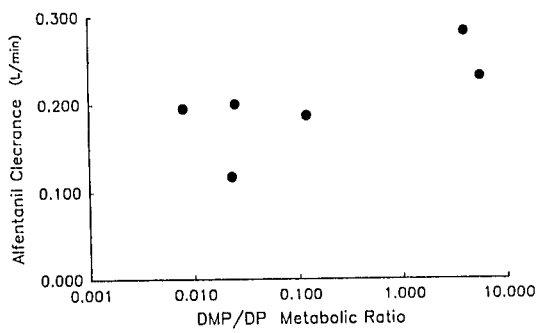

Figure 1

Discussion. Our results directly demonstrate that there is no important relationship between the debrisoquin oxidation phenotype (determined by the dextromethorphan urinary metabolic ratio) and the plasma clearance of alfentanil. Although alfentanil showed a weak competitive inhibition of desmethylimipramine 2-hydroxylation[4], the present results indicate that other, untested P-450 isozymes are most important for the metabolic clearance of alfentanil. Previous observations of reduced alfentanil clearance might be explained as variation within an unimodal Gaussian distribution, drug interaction, pathophysiology involving the liver, or another genetic polymorphism (e.g., of mephenytoin hydroxylase).

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