Anesthesiology
V 75, No 3A, Sep 1991

A310

Title: The Pharmacokinetics of IV Dexmedetomidine in Adults

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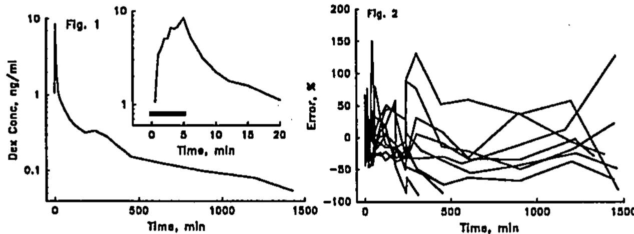
Introduction: Dexmedetomidine is a selective alpha-2 agonist with both anesthetic sparing and anxiolytic effects which may prove useful as an anesthetic premedication. We studied the pharmacokinetics of dexmedetomidine in healthy adult volunteers.

Methods: Informed consent was obtained from 10 healthy male volunteers. Dexmedetomidine in a dose of 2 ug/kg was administered IV as a zero order infusion over 5 min. After the start of the IV infusion arterial blood was sampled at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5, 6, 8, 10, 12, 15, 20, 30, 45, 60, 90, 120, 180, and 240 min, and venous blood at 180, 240, 300, 450, 600, 900, 1200, and 1440 min. The 5 ml K_2EDTA anticoagulated samples were centrifuged and the plasma frozen at -40C. The samples were assayed using gas chromatography/mass spectrometry with a quantitation limit of 0.1 ng/ml. The extended least squares nonlinear regression package, MKMODEL, was used to fit the observations for all 10 patients to a single best estimate of the three compartment pharmacokinetic parameters for the entire population. In our initial approach the individual parameters are averaged between subjects. In our subsequent pooled approach all the data points were fit simultaneously to give a single 6 parameter pharmacokinetic data set. Weight and age were examined as covariates of each volume and clearance parameter in the model to improve the goodness of fit. Log likelihood (LL) was the objective function used to evaluate the goodness of fit.



Results: Table 1 shows the results from each of the analyses. Figures 1 shows the plasma concentrations over time. Figure 2 shows the % residual error from the prediction of the pharmacokinetic model over time.

Table 1

	2 Stage	Pooled	Covariates
Volumes			
V1	7.72	8.73	8.66
V2	30.6	35.5	33.2
V3	191	221	213
Clearances			
CL_1	0.582	0.399	0.00388 *Wt+0.106
CL_2	2.82	2.55	2.49
CL_3	1.22	1.11	1.17

Discussion: The pooled approach is a simple technique which produced a pharmacokinetic model with less residual error than the two stage analysis. Dexmedetomidine appears to have systemic clearance of approximately half of hepatic blood flow. Overall, the volumes and clearances are fairly similar to those of fentanyl. Dexmedetomidine has extensive tissue distribution (large V_2 and V_3) and a moderately large hepatic clearance (large CL_1).

A311

TITLE: KETAMINE METABOLISM AS A PROBE FOR DEXMEDETOMIDINE EFFECTS ON HUMAN DRUG BIOTRANSFORMATION

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Medetomidine (MED) is a novel, selective α_2 adrenergic agonist pre-anesthetic agent with potent sedative, hypnotic and analgesic properties. The pharmacologic effects of MED are stereospecific, due entirely to the D-isomer (DMED). The L-isomer (LMED) is inactive. DMED, a 4(5)substituted imidazole, has been shown to inhibit human microsomal alfentanil metabolism and rat adrenal streroidogenesis *in vitro*.(1,2) Ketamine undergoes extensive hepatic biotransformation, and has been used previously to characterize imidazole anesthetic effects on human drug metabolism. The purpose of this investigation was to determine the mechanism of DMED effects on human microsomal metabolism, using ketamine as a probe. Furthermore, since ketamine is a racemic mixture of S(+) and R(-) isomers, the stereoselectivity of DMED (and LMED) effects could also be investigated.

Microsomes were prepared from livers of organ donors. Microsomal ketamine demethylation was determined from the formation of norketamine, measured by GC-mass spectrometry, or alternatively from the production of formaldehyde.

DMED (and LMED) were potent inhibitors of ketamine N-demethylation (Figure 1). At therapeutic ketamine concentrations (10 μM), the IC_{50} for DMED inhibition was 150 nM. DMED inhibition of ketamine demethylation was competitive, with a K_i of 100-300 nM for the low K_m ketamine demethylase. Preincubation of DMED with microsomes and an NADPH generating system prior to ketamine addition had no additional effect on the inhibition of ketamine demethylase activity. DMED inhibition of S(+) ketamine demethylation was greater than that of R(-) ketamine. Spectral studies showed that DMED interacted with cytochrome P-450 to elicit a Type II binding spectrum.

These results demonstrate that DMED is a potent inhibitor of cytochrome P-450 catalytic activity. DMED inhibits ketamine demethylation by ligand binding to P-450 heme iron and competitive inhibition at the substrate binding site.

(EDK is the recipient of a FAER Anesthesia Investigator Award.)

REFERENCES

1. Anesthesiology 73:A379, 1990.
2. Eur J Pharmac 183:2343, 1990.

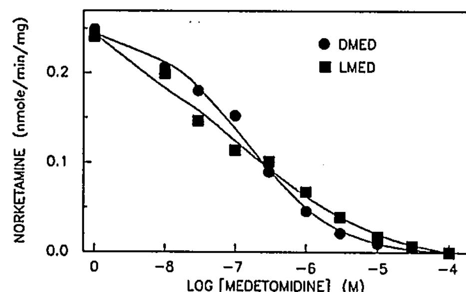

Figure 1: Inhibition of ketamine demethylation (10 μM) by DMED and LMED.

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