Title: PHARMACOKINETICS OF MIDAZOLAM IN RENAL FAILURE PATIENTS

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INTRODUCTION: Midazolam is a water soluble (at pH<4) benzodiazepine used for anesthesia premedication and induction. The pharmacokinetics of midazolam in patients with chronic renal failure (CRF) have not been reported before, but are of clinical importance since this short acting benzodiazepine is efficacious as a hypnotic/sedative in patients with CRF.[1]

METHODS: Fourteen consenting patients (Table I) with end stage renal disease volunteered to participate in the investigation approved by the Institutional Review Board. The mean creatinine was 12.8 ± 4.36 mg/dl. The subjects were in a dialysis free interval, not taking any benzodiazepines, and scheduled for elective vascular access procedures under local anesthesia. Each patient received 0.2 mg/kg of midazolam over 15 seconds in a peripheral vein. Multiple (17) blood samples were obtained over the next 24 hours. Midazolam plasma levels were determined by gas chromatograph - electron capture, with a sensitivity of 2-3 ng/ml. Midazolam levels were analyzed by least squares regression technique. Coefficients and exponents from the fitted function were used to calculate midazolam volume of distribution (Vd), elimination half-life ($t_{1/2\beta}$) and total clearance. For comparison, kinetic data obtained by identical methods from 6 healthy volunteers are presented in Table I. Plasma protein binding was determined by equilibrium dialysis. Values of Vd and clearance were corrected for the individual differences in binding, yielding corresponding values of unbound Vd and unbound clearance in the CRF patients and in 8 normal controls.

RESULTS: All but one patient fell asleep. The mean duration of sleep was 53 ± 30.9 minutes and the threshold blood level for awakening was 81 ± 47.2 ng/ml. The plasma protein binding was 88.5% in CRF patients and 96.4% in normal patients ($p < .001$). The drug serum blood disappearance data fit a 3 compartment model and kinetic parameters appear in Table II. Vd, clearance and $t_{1/2\beta}$ are significantly greater for total drug in CRF patients compared to normals. However, clearance (99 ml/min/kg) and Vd (33 l/kg) of unbound midazolam in CRF patients are less than clearance (211 ml/min/kg) and Vd (37 l/kg) in normal patients.

DISCUSSION: Midazolam is biotransformed in man by the liver; therefore, CRF should not alter the ability of the liver to biotransform the free drug. However, protein binding is different in CRF (this has been confirmed for many drugs including diazepam[2]) resulting in important differences in the kinetics of free midazolam. The three-fold increase in free fraction leads to an artefactual difference in Vd of total drug. The kinetics of total (free plus bound) midazolam indicated higher clearance in patients as opposed to controls, incorrectly suggesting that larger doses may be required by renal insufficiency patients to produce equivalent plasma concentrations over time. However, proper comparison of midazolam kinetics requires correction for individual differences in plasma binding. Indeed, the comparison of free drug clearance between CRF and normal patients shows a two-fold decreased free drug clearance in renal failure patients. It is important to recognize that this group of patients were taking multiple other medications including antihypertensives, antacids (not cimetidine) which may have affected the hepatic clearance of midazolam.

The sleep time of 53 minutes is almost 3 times longer than the hypnotic effect found in healthy volunteers who were given 0.13 mg/kg IV (19 min).[3] The explanation for the moderately prolonged effect of midazolam in CRF patients may be due to the reduced clearance of free drug (active compound) or to some inherent sensitivity of CRF patients to midazolam. Induction doses of midazolam were shown to be safe when used in CRF patients;[1] however, our data (decreased free drug clearance and prolonged sleep time) suggest that the dosage of midazolam may need to be reduced in patients with chronic renal failure.

REFERENCES:

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Table I: CHARACTERISTICS OF CRF PATIENTS GIVEN MIDAZOLAM (.2 mg/kg)

		Range
Age (yrs)	50 ± 14.5	25-67
Weight (kg)	75 ± 12.51	58-92
BUN (mg/dl)	69 ± 22.3	38-108
Creatinine (mg/dl)	12.8 ± 4.36	5-20

Sex - males = 6, females = 8

Table II: COMPARISON OF PHARMACOKINETICS OF CRF PATIENTS WITH NORMAL CONTROLS

	CRF (n=14)	NORMAL (n=6)	P
$t_{1/2\alpha}$ (min)	3.4 ± .49	7.2 ± 1.6	.04
$t_{1/2\beta}$ (hrs)	4.73 ± .70	2.5 ± 0.2	.01
Vd total drug (l/kg)	3.78 ± .30	1.72 ± 0.05	.003
Clearance total (ml/min/kg)	11.41 ± 1.54	8.1 ± 0.52	.03