

Title : STEADY-STATE PHARMACOKINETICS OF MIDAZOLAM MALEATE

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Introduction. Midazolam maleate (MM) is an investigational benzodiazepine, similar in clinical effect to diazepam, but water-soluble, and with an apparently shorter half-life. These properties make it a promising drug for use in anesthesia. A single dose pharmacokinetic study¹ found that MM has a much shorter elimination phase half-life ($T_{1/2\beta} \approx 2$ hrs) than diazepam ($T_{1/2\beta} = 15-31$ hrs). However, in the absence of an extremely sensitive assay method, such a study can be misleading, as a long terminal phase may be missed. We, therefore, studied the pharmacokinetics of MM in 5 volunteers who were rapidly brought to a MM plasma level steady-state and held there for several hours. In addition, we searched for metabolites of MM.

Methods. Five healthy, male volunteers (mean age, 30; mean BW, 75 kg) received a two-phase intravenous infusion of MM, the first phase consisting of 10.5 mg of MM infused over 15 mins, followed by an additional 15.5 mg infused over 3 hrs and 45 mins. These doses and infusion rates were calculated from the results of the prior study using the method of Wagner² and are designed to bring the subject quickly to a steady-state blood level. Blood was taken at appropriate intervals from the arm opposite the infusion site. Urine was also collected. Samples were immediately frozen and then analyzed by an electron-capture gas-liquid chromatographic technique, with a sensitivity to 2 µg/ml of blood. The data were analyzed using an iterative least squares program, NONLIN. All volunteers gave informed consent and the protocol was approved by the Committee for the Protection of Human Subjects in Research at the Stanford University Medical Center.

Results. The kinetic results are summarized in the following table.

Pharmacokinetic Parameters of Midazolam Maleate in 5 Volunteers

Subject Number	1	2	3	4	5
Total Dose (mg)	26	26	26	26	26
Weight (kg)	86	68	75	75	70
Dose (mg/kg)	.31	.39	.35	.35	.37
$T_{1/2\alpha}$ (min)	7	13	11	2	4
$T_{1/2\beta}$ (hrs)	1.7	2.0	2.2	1.6	1.8
β (hr ⁻¹)	.40	.34	.32	.42	.39
TBC (liter/hr)	61	46	61	63	48
AUC (µg/ml ^{-hr})	434	587	416	426	547

No parent compound was found in the urine. Results of the analysis for the predominant metabolite, the apparently inactive 1-hydroxymethyl analog, are shown below.

Urinary Excretion of Metabolite

Subject Number	1	2	3	4	5
Collection Period	Percent of Dose				
0 - 12 hrs	41	41	35	40	35
12 - 24 hrs	10	4	11	8	17
Total %	51	45	46	48	52

Discussion. The data closely approximated the estimates we made with the computer and steady-state was quickly reached and maintained for three hours. As in the previous study, the elimination phase half-life ($T_{1/2\beta}$) was short, approximately 2 hours. With this study we can be quite certain that we have not missed a prolonged terminal phase of the drug's kinetics. Thus, clinical usage of MM should not be limited by unexpected cumulative effects or long-acting metabolites as it is with diazepam. Further evidence of the brevity of action of MM comes from the rapid rate of clearance and the high recovery rate of the 1-hydroxymethyl metabolite in the urine over the first 12 hours. No other metabolites could be identified in more than trace amounts.

In conclusion, midazolam maleate does have a short (two-hour) half-life verified by this steady-state study. This short duration of action, coupled with its pharmacologic profile and water solubility make midazolam maleate a promising agent for anesthesia use.

References.

1. Brown CR, Sarnquist FH, Canup CA, et al: Clinical, electroencephalographic, and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate. ANESTHESIOLOGY 50:467-470, 1979.
2. Wagner JG: A safe method for rapidly achieving plasma concentration plateaus. Clin Pharmacol Ther 16:691-700, 1974.

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