

Title: COMPARATIVE PHARMACODYNAMICS OF MIDAZOLAM AND DIAZEPAM

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**Introduction:** The CNS effect of a benzodiazepine given in hypnotic doses (unconsciousness) can be quantitated by electroencephalography (EEG)<sup>1</sup>. The goal of the present study was to demonstrate the relationship between CNS drug effect and plasma concentrations for the benzodiazepines midazolam (M) and diazepam (D).

**Methods:** Following institutional approval and informed consent 4 healthy volunteers (36 - 40 yr, 70 - 83 kg) were studied on 17 different occasions. M was administered in 3 subjects at 2 or 3 doses (7.5, 15 and 25 mg, infusion rate of 5 mg/min); D was administered in 3 subjects at 3 doses (15, 30 and 50 mg, infusion rate of 10 mg/min). In 2 subjects only M or D was investigated. Fronto-occipital EEG leads were used. After recording 5 min of baseline EEG, either drug was infused iv and EEG recorded for 2-3 hr. Ventilation was assisted with a face mask when needed. Aperiodic analysis<sup>2</sup> of EEG signals was performed with Lifescan EEG monitor (Neurometrics). EEG total voltage (frequency range: 0.5 - 30 Hz) was used as the descriptor of EEG drug effect. Arterial blood was sampled every min during the first 5 - 10 min and at increasing intervals during the following 2 - 3 hr. Plasma drug concentrations (Cp) were measured by gas chromatography with electron capture detection. A time lag between Cp and EEG effect was present in the data and could be quantitated by an effect compartment model. Equilibration half-life (Tl/2 keo) between Cp and apparent concentration at effect site (Ce) was determined by using a nonparametric method<sup>3</sup>. Ce is proportional to Cp at steady state. This method generates the Ce-effect relationship directly from Cp vs time and effect vs time curves. The generated Ce-effect data (figure) were fitted to the sigmoid Emax model

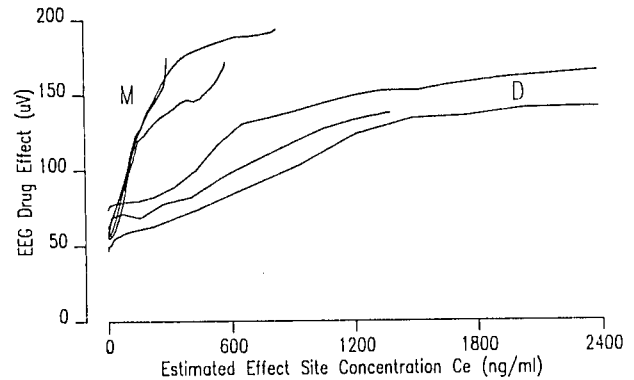
$$\text{effect} = \text{predrug effect} + (\text{Emax} * \text{Ce}^N / \text{EC50}^N + \text{Ce}^N)$$

where Emax = maximal effect, EC50 = Ce producing 50% of Emax, N = exponent (steepness of curve).

**Results:** The equilibration (Tl/2 keo) of drug concentrations in plasma and effect site for M is 3 times slower than for D (table). Predrug effect and maximal drug effect are the same in both drugs. The average EC50 (measure of drug potency at steady state Cp and of individual brain sensitivity) is 5 times higher for M vs D. The variability in brain sensitivity is greater between than within individuals. For each subject the EC50 are consistent with repeated doses (table, figure).

**Discussion:** Using EEG as a drug effect measure we found clinically important differences in pharmacodynamics of M and D. Because of the difference in Tl/2 keo, maximal drug effect occurs later with M relative to D. This suggests that the clinician should wait a longer period of time before redosing M compared to D. Furthermore, M appears to be at least 5 times more potent than D.

Figure : Effect-Ce relationship for three doses of midazolam and three doses of diazepam in subject C



Table

Sub-ject	Drug	Dose (mg)	Tl/2keo (min)	Eo (uV)	Emax (uV)	EC50 (ng/ml)	N
A	M	7.5	4.10	21	128*	94	1.80
A	M	15	5.53	28	138	109	2.20
A	M	25	4.90	21	128	125	2.14
B	M	7.5	-	49	138*	385	1.02
B	M	15	5.72	47	138	329	1.17
C	M	7.5	5.59	60	133*	151	2.00
C	M	15	6.78	55	122	165	1.57
C	M	25	5.29	64	133	164	1.74
Midazolam mean:			5.42	43	132	190	1.71
A	D	15	1.77	22	174*	1256	1.06
A	D	30	2.40	21	267	1090	1.30
A	D	50	1.79	19	174	907	1.87
C	D	15	1.20	56	115*	781	1.66
C	D	30	2.26	74	87	607	3.20
C	D	50	1.21	47	115	871	1.65
D	D	15	0.99	42	94*	1151	0.99
D	D	30	1.87	27	83	819	1.42
D	D	50	1.22	40	94	1138	1.43
Diazepam mean:			1.63	39	134	958	1.62

\* duration of peak effect too short to provide sufficient points for Emax estimation by nonlinear regression. Emax was constrained to the value estimated for the high dose experiment.

References:

1. Anesthesiology 67(suppl): A658, 1987
2. J Clin Monit 2: 190-197, 1986
3. Clin Pharmacol Ther 40:86-93, 1986