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Midazolam: kinetics and effects on memory, sensorium, and haemodynamics

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1 This study aimed not only to compare the pharmacokinetics of oral and intravenous doses of the new water-soluble benzodiazepine, midazolam, but also to study the effects on haemodynamics, sensorium, and memory performance.

2 Eight normal human volunteers each received a single 15 mg dose of midazolam base orally and intravenously in randomized sequence 2 weeks apart. Serial venous samples were obtained for 12 h after dosing. Vital signs, sensorium testing and memory testing using word lists were also performed. Computerized non-linear least squares curve-fitting of the two-compartment open model to the oral and intravenous data simultaneously yielded the following estimates: V_1, 0.33 l kg^{-1}, $V_{d_{ss}}$, 1.08 l kg^{-1}, $t_{½,\lambda}$, 0.10 h, $t_{½,z}$, 1.89 h, k_a 1.17 h^{-1} and bioavailability, 49%. The intravenous dose decreased the systolic pressure 22 mm Hg during the first half-hour and the oral dose had 50% less effect. Most subjects became drowsy halfway through the infusion and were only rousable to voice by its end. The sensorium was clear by 2–3 h. After oral dosing the peak sensorium effects of ataxia-dysarthria were seen at 30 min and had cleared by 2 h. Memory testing showed that memory acquisition was markedly impaired for at least 90 min after the intravenous dose and slight recovery was apparent at this time after the oral dose. Memory performance was proportionately more impaired than the sensorium score.

3 We conclude that: (a) midazolam kinetics are characterized by rapid absorption, but incomplete bioavailability and rapid elimination, (b) midazolam intravenously may lower blood pressure significantly, and (c) the level of consciousness correlates poorly with the degree of memory impairment.

Keywords midazolam pharmacokinetics haemodynamics sensorium memory

Introduction

Midazolam is a water-soluble 1,4-benzodiazepine with a brief plasma half-life just under 2 h. It is available both for intravenous administration as the hydrochloride salt and for oral dosing as a maleate salt. Its sedative properties are exploited in the treatment of insomnia, and, in anaesthesia it may be given as a premedication orally or parenterally for sedation and amnesic effects. Conner *et al.* (1978) and Dundee & Wilson (1980) have found that the amnesic effects lasted

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about 25 min. Moreover, this effect did not correlate with the soporific effects. This study aimed to compare 15 mg of oral midazolam with the same intravenous dose to assess the effects of level of consciousness, haemodynamics, and memory and to relate these effects to the pharmacokinetic disposition of the drug.

Methods

After giving written informed consent eight male volunteers with an average age of 24 years and a weight of 75.8 kg were confirmed acceptable for the study based on a normal medical history and physical exam (weight within 10% of height/physique norm), and normal laboratory investigations including a urinalysis, CBC, SMA[12], and creatinine clearance. All subjects were instructed to avoid all drugs including ethanol for 7 days prior to each study day. Three additional volunteers gave informed consent to participate in an oral placebo study with memory testing.

Each subject received single 15 mg doses of midazolam base orally and intravenously. The doses were given at least 14 days apart and in random sequence. Each subject fasted for 10 h before dosing. The oral dose of 15 mg of midazolam base was given with 250 ml of water, as a tablet containing 20.3 mg of midazolam maleate. The intravenous dose was given as 16.7 mg of midazolam hydrochloride diluted in 30 ml of 0.9% saline and this volume was infused over 20 min by a Harvard infusion pump.

Blood samples (10 ml) were drawn through an indwelling venous cannula (kept patent with heparinised saline) into oxalated Vacutainers. Samples were drawn pre-dosing, 10 and 20 min during the infusion and 5, 10, 20, 30, 45 min, 1, 1.25, 1.5, 2, 3, 4, 6, 8, and 12 h after the end of the respective dose.

Subjects underwent continuous ECG monitoring for 3 h after the intravenous dose. With both doses, heart rate and blood pressure were obtained every 10 min for the first hour and every 30 min until 3 h. Thereafter, vital signs were obtained hourly.

The level of consciousness was checked predosing and at times 0, 15, 30, 60 min, 2 and 3 h. We used the simple scale: 4 = alert, 3 = drowsy, 2 = ataxic + dysarthric, 1 = asleep (rousable by voice), and 0 = asleep (not rousable by voice).

In addition, memory was tested using four different 20-word lists which were read to the subjects. Subjects heard list 1 pre-dose and lists 2, 3 and 4 at 45 min, 90 min and 12 h post-dose respectively. Hereafter, these will be called L-Pre, L-45, L-90, and L-720. Recall of these lists was tested in three different ways: (1) *immediate* testing involved writing down as many words recalled from a list immediately after hearing it, (2) recent testing was performed similarly 45 min after hearing the list and (3) recognition testing required the subject to select from each of 20 word pairs, the word that was on the corresponding test list presented earlier. Recognition testing of L-Pre was performed at 90 min and 12.75 h, L-45 at 90 min and 135 min, L-720 at 12 h. If subjects were too drowsy to read or write, the tests were conducted orally. Those not rousable to voice at the time of any test, scored 0 on that test. The subjects were memory tested after both the intravenous and oral doses.

The three subjects on oral placebo had blood pressure and ECG monitoring as well as memory testing, but blood sampling was not performed.

The kinetic parameters were estimated from the time-concentration data using a computerized iterative non-linear least squares (Marquardt's modification of the Gauss-Newton procedure) curve-fitting program. Fitting was performed simultaneously on the oral and the intravenous data using a two-compartment open model with first order transfer processes and elimination from the central compartment. Simultaneous curve-fitting to the intravenous and oral data has several advantages over fitting each separately. The intravenous data points provide distribution phase information to the curve-fitting of the oral data points. Like the other kinetic parameters absolute bioavailability and lag time were estimated by the least-squares method. Simultaneous curve-fitting also permitted estimation of relative bioavailavility and the lag time after oral absorption.

Assay methods

To 1.0 ml of plasma was added 10 μl of 5N NaOH, 10 μl of internal standard solution (RO 21-4587, 100 μg ml^{-1}), and 4.0 ml of ethyl acetate. After vortexing and centrifugation, the organic layer was removed, and dried under nitrogen. The residue was then taking up in 50 μl of mobile phase solution and injected.

The assay was performed by high pressure liquid chromatography using a Brownlee MPLC micro column (10 cm × 4.6 mm) packed with LiChrosorb RP-18, 10 microns. The flow rate was 0.7 ml min^{-1} and absorbance detection set at 236 nm. The mobile phase was methanol/0.1 M sodium phosphate (monobasic) in a 70:30 ratio.

For all within-dose comparisons statistical analysis was performed with the Friedman test with multiple comparisons, a non-parametric

procedure for two or more samples with related data. The same test was employed for between dose comparisons and the Kruskal-Wallis for comparisons with placebo.

Results

Eight normal male subjects were studied in groups of four on 4 study days. Two subjects were cigarette smokers. All weighed within 10% of the normal for their height and build. The three additional normal male subjects who were given oral placebo only met similar weight criteria.

After intravenous dosing the mean plasma concentration profiles (Figure 1) indicated a short distribution and a longer elimination phase. A third even slower elimination phase was not clearly evident in our data. Even after adjusting for weight, concentrations showed wide inter-subject variability.

After oral administration plasma concentrations peaked between 0.5 h and 1.5 h (Table 1) at an average of 0.05 mg l^{-1}. Absorption (Table 1) appeared rapid with half-lives ranging from 0.32 to 1.69 h. Lag time was negligible being less than 5 min in all cases. A distribution phase was not apparent. The slope of the elimination phase appeared similar to the slope seen after intravenous dosing. The mean central compartment volume was 0.33 l kg^{-1} and the total volume of distribution at steady-state, calculated from the relationship $Vd_{ss} = V_1 (1 + k_{12}/k_{21})$, was 1.08 l kg^{-1}. The distribution half-life was 6 min and elimination half-life was 1.9 h. The mean clearance was 0.52 l h^{-1} kg^{-1}.

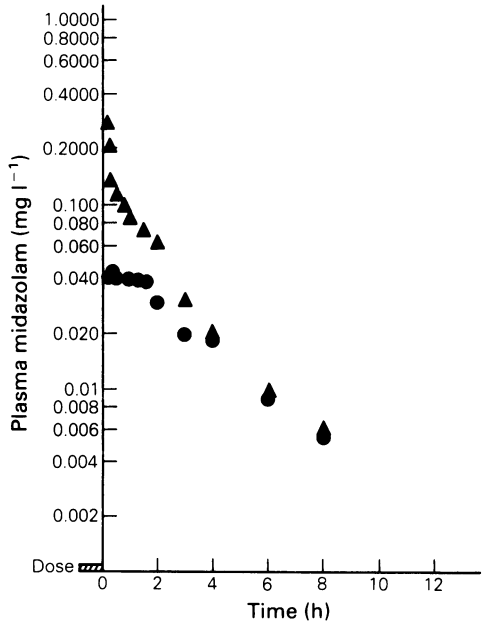

Figure 1 Average plasma midazolam concentrations after intravenous (▲) and oral (●) dosing with 15 mg of midazolam base.

Table 1 Midazolam kinetic parameters estimated by computer-fitting of oral and intravenous data simultaneously

Parameter	*Mean*	*s.d.*	*Range*
V_c (l kg^{-1})	0.33	0.10	(0.18–0.46)
Vd_{ss} (l kg^{-1})	1.08	0.40	(0.59–1.87)
$t_{½,\lambda_1}$ (h)	0.10	0.06	(0.04–0.21)
$t_{½,z}$ (h)	1.89	0.56	(1.07–2.89)
Clearance (l h^{-1} kg^{-1})	0.52	0.09	(0.40–0.65)
k_a (h^{-1})	1.17	0.63	(0.41–2.15)
Lag time (h)	0.08	0.13	(0.00–0.39)
Bioavailability (%)	49.00	7.00	(39–55)
t_{max} (h)	0.64	0.45	(0.33–1.5)
C_{max} (mg l^{-1})	0.05	0.01	(0.04–0.07)

During the first half hour after the end of the intravenous infusion, the systolic pressure (Table 2) fell an average of 22 mm Hg (range, 5 to 45) to a mean minimum systolic pressure of 102 mm Hg (range, 86 to 112). Concomitantly, the average heart rate increased 8 beats min^{-1}. Similar, but 50% less marked cardiovascular effects were seen after about 1 h (range 10 min to 2 h) after oral dosing in six subjects.

During the intravenous dose (Figure 2) most subjects developed drowsiness halfway through the 20 min infusion and by its end the average subject was rousable only to voice. Thirty minutes after the end of the infusion, the mean effect had lessened to drowsiness with dysarthria and by 2 to 3 h the subjects were awake. Four of the eight subjects also manifested myoclonic jerks of the extremities during the infusion.

After the oral dose, the mean peak effect of ataxia plus dysarthria occurred at 30 min and by 2 h the average subject was awake. In one subject these effects were delayed for 2 h, but his plasma concentrations did not correlate with these delayed effects.

Immediate recall scores (Figure 3) at 0.75 h and 1.5 h were depressed from baseline. By 12 h these recall scores had returned to baseline. Oral dosing did not differ from intravenous dosing in the effects of immediate recall. Recent (45 min after presentation) recall scores (Figure 4) on the L-Pre list were lower than the immediate scores on this test. This was also seen with L-720 at 12 h. Recent recall scores were greatly depressed on both tests L-45 and L-90. Again, the

Table 2 Individual extremes of blood pressure compared to baseline

Subject	*Baseline*	*BP (mm Hg) Extreme*	*Maximum change*	*Time of change (min)*
*Intravenous**				
1	122/82	112/74	−10/−8	15
2	110/80	105/75	−5/−5	20
3	130/70	90/70	−40/0	15
4	150/100	105/70	−45/−30	25
5	120/85	100/75	−20/−10	0
6	120/58	110/78	−10/+20	-5
7	120/60	96/58	−34/−2	30
8	125/80	106/72	−19/−8	0
Mean	125/77	103/72	−22/−5	13
s.d.	11.7/13.8		15/14	13
Oral				
1	130/88	110/80	−20/−8	90
2	120/75	118/80	−2/+5	30
3	100/60	98/60	−2/0	10
4	130/90	130/90	0/0	—
5	120/80	120/50	0/0	—
6	120/80	110/84	−10/+4	120
7	128/60	110/60	−18/0	60
8	130/70	98/78	−32/8	60
Mean	122/75	111/76	−11/1	62
s.d.	10.2/11.5		12/5	340

*Infusion given from −20–0 min, oral dose given at 0 min.

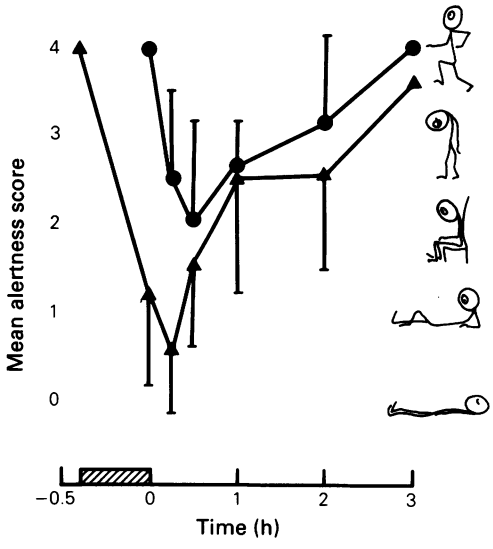

Figure 2 Average alertness scores after midazolam administration. 0 = unrousable to voice, 1 = rousable to voice, 2 = ataxic + dysarthria, 3 = drowsy, 4 = alert. Hatched area indicates intravenous infusion. • oral, ▲ i.v. administration.

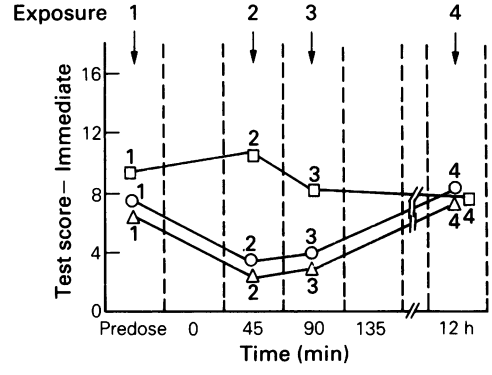

Figure 3 Average immediate recall scores after oral (○) and intravenous (△) midazolam and placebo (□).

effects on recent recall with intravenous dosing were not distinguishable from those after oral dosing. Recognition scores on test L-45 and L-90 (Figure 4) were better than recent recall scores performed at the same time on the same lists. In the case of L-45, only the recognition scores after oral administration were better than those after the i.v. dose (Figure 5). As might be expected on L-720 recognition scores were better

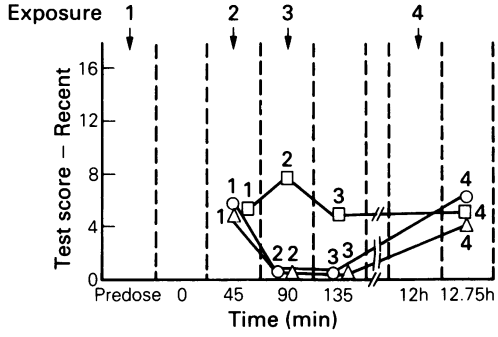

Figure 4 Average recent recall scores after oral (○) and intravenous (△) midazolam and placebo (□).

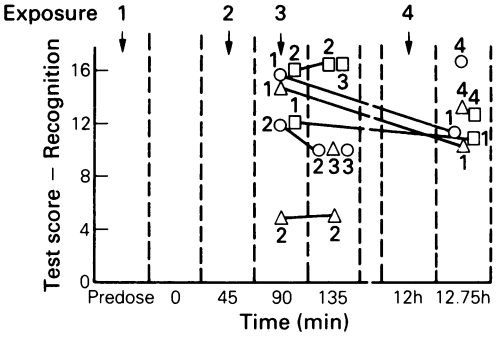

Figure 5 Average recognition scores after oral (○) and intravenous (△) midazolam and placebo (□).

than immediate scores which were better than recent scores. Finally the recognition score on L-Pre was lower at 12 h than at 1.5 h.

Discussion

The pharmacokinetic parameters obtained in this study are in close agreement with the results of others (Smith *et al.*, 1981; Allonen *et al.*, 1981). It is noteworthy that despite rapid absorption, the bioavailability of midazolam is only 50%, secondary to a marked first-pass effect which has been further delineated by Smith *et al.* (1981) and Allonen *et al.* (1981). Bornemann *et al.* (1985) have shown a characteristic dose-dependency of the first pass effect for oral doses over 15 mg.

Although the initial animal studies showed minimal cardiovascular effects in the anaesthetized dog (Pieri, 1983; Hilfiker & Ketler, 1981) more pronounced cardiovascular effects have been reported in man (Hilfiker & Ketler, 1981; Forster, 1981; Muller *et al.*, 1981). These early human studies involved mostly anaesthetic induction with midazolam on a background of other medications. Our normal subjects on no other medications all had transient, but significant decreases in systolic pressure which were larger than those reported in the studies cited above which utilized similar doses. Therefore, we advise caution particularly during intravenous administration of midazolam.

Benzodiazepines are well-known to have amnesic effects and midazolam is no exception. In our study it was clear with both oral and intravenous midazolam that the sensorium score was not indicative of memory acquisition ability. For example, at 90 min after intravenous dosing the mean sensorium rating was close to 3 (drowsy), but the L-90 immediate test score was only 3. This score did not differ from the L-45 immediate score 45 min earlier when the average subject had a sensorium rating of 2 (ataxic/dysarthric). Furthermore, recent (45 min after) recall of the list presented before drug exposure was as good as its immediate recall, but with both dosing routes, recent recall of both L-45 and L-90 was even worse than their immediate recall. Even though they appeared to be memorizing the lists properly and were confident that they indeed had learned L-45 and L-90, the subjects were often surprised to find how poorly they performed on both immediate and recent recall of these lists. This suggests that midazolam impairs the ability to acquire new memory more deeply than it impairs the sensorium or the ability to recall lists memorized before drug administration. This specific effect on memory acquisition has been termed anterograde amnesia. Our findings corroborate and extend those of other investigators who found the duration of anterograde amnesia to be 20–30 min after midazolam, 5 mg intravenously (Conner *et al.*, 1980; Dundee & Wilson, 1980) and at least 1 h after 15 mg orally (Subhan & Hindmarch, 1983). In our more extensive memory testing we found that the anterograde amnesic effect of 15 mg of midazolam, by either route of administration, lasts at least 90 min. Unfortunately, we did not test between 90 min and 12 h and therefore cannot say when thereafter the effect disappeared. However, the recognition scores after oral dosing were better on L-90 than L-45 which suggests that the memory effect is lessening by 90 min and after a 15 mg oral dose. Because of the dose-dependent kinetics of midazolam (Bornemann *et al.*, 1985) one could predict that, near saturation (circa 15 mg) small changes in midazolam dose or elimination rates might result in large changes in duration of effect on memory. This is potentially a major concern in the elderly who may already have both mildly impaired memory acquisition and metabolic capacity.

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