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Dose Dependent Pharmacokinetics of Midazolam

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Summary. The pharmacokinetics of midazolam and 1-hydroxymethylmidazolam were investigated following oral administration of 7.5, 15 and 30 mg doses of midazolam in solution to 12 healthy subjects. Compared to the 7.5 mg dose, the C_{max} and AUC parameters of both midazolam and 1-hydroxymethylmidazolam increased proportionally after the 15 mg dose and more than proportionally after the 30 mg dose. The $t_{½}$ for midazolam remained relatively constant between the 7.5 and 15 mg doses whereas it increased slightly but significantly after the 30 mg dose. These data indicated that the pharmacokinetics of midazolam and 1-hydroxymethylmidazolam were linear between the 7.5 and 15 mg oral dose range. However, after the 30 mg dose, the systemic availability of midazolam and the AUC for 1-hydroxymethylmidazolam appeared to be greater than that anticipated from the lower doses, possibly due to saturation of midazolam first-pass metabolism. This ist not expected to have any clinical significance under the conditions of therapeutic use.

Key words: midazolam; 1-hydroxymethylmidazolam, pharmacokinetics, dose proportionality, benzodiazepine, healthy volunteers, side-effects

Midazolam is a short-acting, water-soluble benzodiazepine derivative with an elimination half-life ranging from 1.4 to 2.2 h [1-5]. Midazolam is administered as the hydrochloride salt by intravenous or intramuscular injection for the induction and maintenance of anesthesia and as the maleate salt orally for use as a sedative-hypnotic. Following oral administration to humans, midazolam is rapidly absorbed and undergoes first-pass metabolism resulting in a bioavailability of approximately 40% [4, 5]. The hepatic metabolism of midazolam is via hydroxylation; 1-hydroxymethylmidazolam is a pharmacologically active metabolite of midazolam [4, 5]. This metabolite is present in the conjugated and unconjugated forms in both plasma and urine [4]. In humans, 60 to 70% of an orally administered dose of ^{14}C-midazolam was recovered in the urine as conjugated 1-hydroxymethylmidazolam [4]. In a preliminary study, Heizmann and Ziegler [5] found that the apparent bioavailability of midazolam was higher after a 40 mg oral dose than that after a 10 or 20 mg oral dose; however, the pharmacokinetics were not adequately defined over this dosage range. The present study was, therefore, designed to evaluate the linearity in the pharmacokinetics of midazolam and 1-hydroxymethylmidazolam over a 7.5 mg to 30 mg oral dose range.

Materials and Methods

Study Design

Twelve healthy volunteers (8 males and 4 females) ranging in age from 24 to 52 years (mean age, 38 years) and in body weight from 54.9 to 92.5 kg (mean weight, 73.0 kg) were impaneled. The volunteers were in good general health as determined by baseline medical history, physical examination and laboratory tests consisting of hemoglobin, hematocrit, WBC (total and differential), platelet count, SMAC 20 and urinalysis. All volunteers gave written informed consent following study approval by the Research Committee of the Newark Beth Israel Medical Center, Newark, N.J.

Volunteers received a 7.5, 15 or 30 mg dose of midazolam in solution followed by 120 ml of water in a

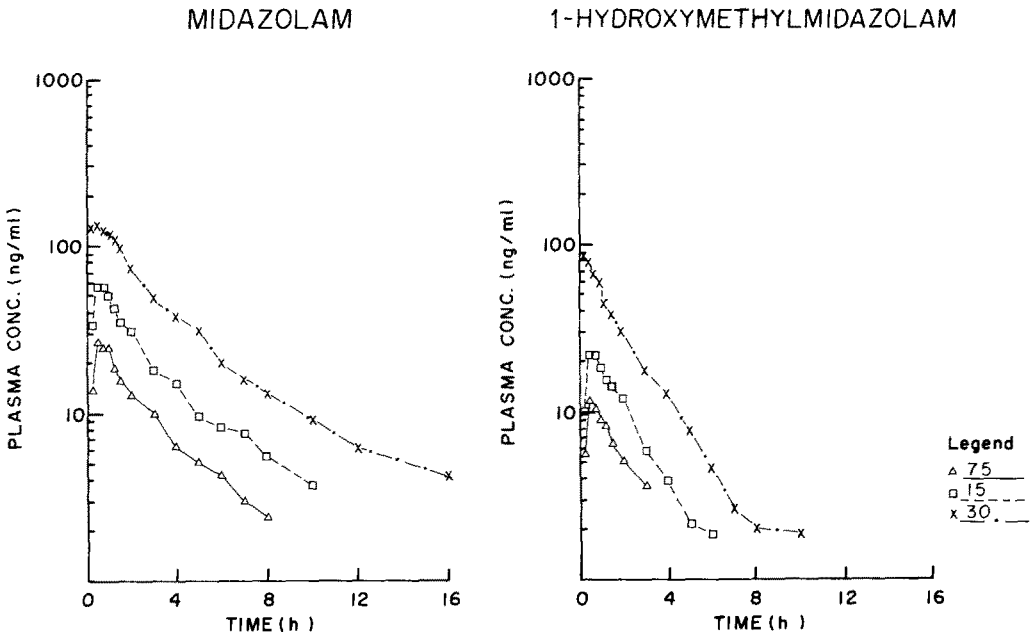

Fig. 1. Average concentrations of midazolam and 1-hydroxymethylmidazolam following 7.5 mg, 15 mg and 30 mg single oral doses of midazolam

three-way randomized crossover design with a one-week washout after each dose. The doses were administered at approximately 8 a.m. following an overnight fast which was continued for 4 additional h postdose. Water was permitted ad libitum. After each dose, the volunteers were confined to bed until the 8-h blood sample was obtained.

Blood samples were drawn into heparinized vacutainer tubes prior to drug administration and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 h post-dose. Blood samples were immediately centrifuged and the plasma was transferred to labelled scintillation vials and stored at or below −17 °C until analysis. The plasma samples were assayed for midazolam and unconjugated 1-hydroxymethylmidazolam using the GC-MS method of Rubio et al. [6]. Over a 2 to 60 ng/ml concentration range, the inter-and intra-assay precisions were 4% and 7%, respectively for midazolam and 10% and 12%, respectively for 1-hydroxymethylmidazolam.

Pharmacokinetic and Statistical Analysis

The maximum plasma concentration (C_{max}) as well as the time (t_{max}) of its occurrence following drug administration were read directly from the plasma concentration-time data for both midazolam and 1-hydroxymethylmidazolam. The area under the plasma concentration-time curve from time zero to infinity (AUC) was calculated using conventional trapezoidal summation and extrapolation methods. The elimination rate constant (β) was estimated from the terminal log-linear portion of the concentration-time profiles (from 2 h post-dose or thereafter) by linear regression analysis. The apparent oral clearance (CL) was calculated for midazolam from the dose/AUC ratio assuming complete absorption of the orally administered dose. In addition, the ratio of the AUC for the metabolite (AUC_M) to that for the parent drug (AUC_p) was calculated.

Statistical analysis was performed on several pharmacokinetic parameters of midazolam and 1-hydroxymethylmidazolam. C_{max} and AUC parameters were normalized for a 7.5 mg dose prior to statistical evaluation. Analysis of variance was performed for each parameter to account for the effects of sequences, subjects within sequences, treatments, time periods and possible carryover effects from the preceding treatment. Comparisons were made between the estimated treatment means using 2-tailed *t*-test.

Results

Midazolam

Midazolam was rapidly absorbed from the solution, as indicated by the t_{max} which ranged from 0.25 to 2 h, regardless of the dose administered (Fig. 1, Table 1). Compared to the 7.5 mg dose, the increase in both C_{max} and AUC was proportional to dose at

Table 1. Pharmacokinetic parameters (mean[a] ± SD and range) for midazolam

Dose [mg]	C_{max} [ng/ml]	Normalized[b] C_{max} [ng/ml]	t_{max} [h]	AUC [ng·h/ml]	Normalized[b] AUC [ng·h/ml]	β [h^{-1}]	$t_{½}$ [h]	CL [l/h]
7.5	34± 13 (20– 57)	34±13 (20–57)	0.71±0.26 (0.5 –1.25)	92± 47 (39–173)	92± 47 (39–173)	0.27±0.09 (0.08–0.41)	2.6 (1.7–8.7)	103 ± 48.7 (43.4–192)
15	67± 19 (41– 97)	34± 9.7 (21–49)	0.81±0.44 (0.5 –2)	188± 75 (108–351)	94± 37 (54–176)	0.27±0.12 (0.12–0.55)	2.6 (1.3–5.8)	90.5± 30.9 (42.7–139)
30	212± 90 (79–375)	53±23[c, e] (20–94)	0.63±0.58 (0.25–2)	503±211 (265–982)	126± 53[d, e] (66–246)	0.21±0.06[e] (0.11–0.30)	3.3 (2.3–6.3)	68.5± 25.0[d, e] (30.6–113)

[a] Arithmetic treatment means are reported for all parameters except the $t_{½}$ for which the harmonic means are reported. [b] Normalized for a 7.5 mg dose. [c] $p < 0.05$ when compared to the 7.5 mg dose; [d] $p < 0.01$ when compared to the 7.5 mg dose; [e] $p < 0.05$ when compared to the 15 mg dose

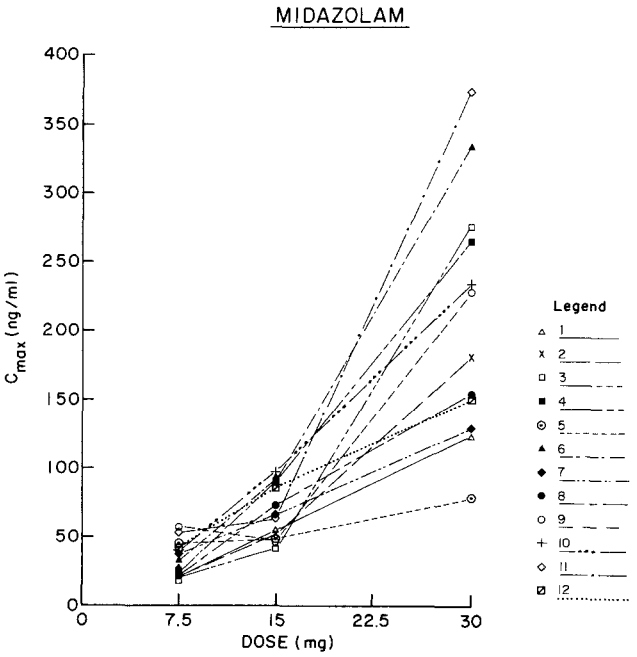

Fig. 2. C_{max} of midazolam vs. midazolam dose in individual subjects

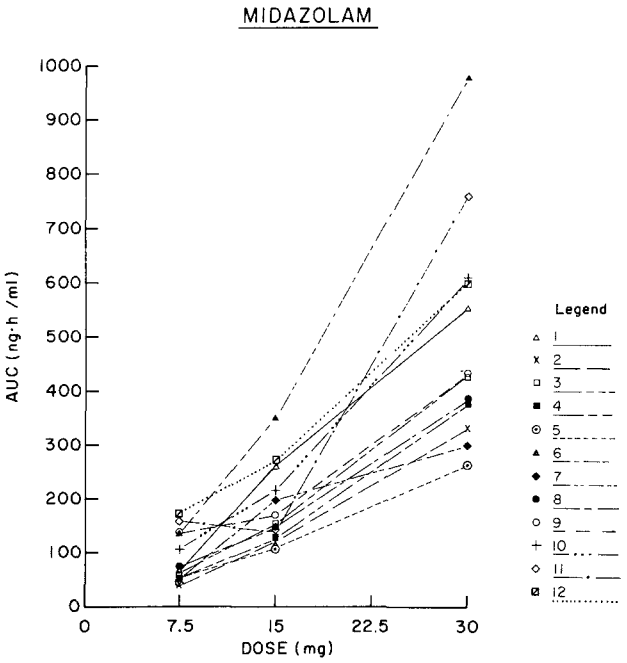

Fig. 3. AUC of midazolam vs. midazolam dose in individual subjects

15 mg but more than proportional at 30 mg (Figs. 2 and 3). It was of interest to note that 5 subjects seemed to demonstrate a dose proportional increase in C_{max} (Fig. 2) and AUC (Fig. 3) but such was not the case in the remaining 7 subjects. Following the 30 mg dose, the increase was 56% more for the mean C_{max} and 36% more for the mean AUC than that predicted from the 7.5 and 15 mg dose data. Statistical analysis of the dose normalized values of C_{max} and AUC indicated that statistically significant differences were not observed between the 7.5 and 15 mg treatments (Table 1). However, statistically significant increases in both parameters occurred at the 30 mg dose when compared to both 7.5 and 15 mg dose date (Table 1).

As expected from the AUC data, dose-related variations were noticed in the CL (Fig. 4). The mean values of CL estimated for the 7.5 and 15 mg doses were similar. In contrast, the estimated CL value was consistently reduced in a majority of subjects after the 30 mg dose (Fig. 4). The mean value of CL at the 30 mg dose was 34% and 24% lower than that estimated from the 7.5 and 15 mg doses, respectively, and these differences were statistically significant (Table 1).

The mean β value for the 30 mg dose was slightly lower (0.21 h^{-1}) than that observed following the 7.5 or 15 mg doses (0.27 h^{-1}). A statistically significant difference was observed in β between the 15 and 30 mg doses (Table 1). The harmonic mean half-lives were 2.6 h, 2.6 h and 3.3 h for the 7.5, 15 and 30 mg doses, respectively.

Table 2. Pharmacokinetic parameters (mean[a] ± SD and range) for 1-hydroxymethylmidazolam

Dose [mg]	C_{max} [ng/ml]	Normalized[b] C_{max} [ng/ml]	t_{max} [h]	AUC [ng·h/ml]	Normalized[b] AUC [ng·h/ml]	β [h^{-1}]	$t_{½}$ [h]	AUC_M AUC_P
7.5	20 ± 8.6 (5.6 – 34)	20 ± 8.6 (5.6 – 34)	0.69 ± 0.24 (0.5 – 1.25)	48 ± 21 (18 – 92)	48 ± 21 (18 – 92)	0.44 ± 0.17 (0.24 – 0.76)	1.6 (0.9 – 2.9)	0.50 ± 0.36 (0.17 – 1.26)
15	36 ± 10 (20 – 53)	18 ± 5.2 (10 – 27)	0.85 ± 0.47 (0.25 – 1.5)	92 ± 43 (45 – 189)	46 ± 22 (23 – 95)	0.43 ± 0.17 (0.08 – 0.69)	1.6 (1.0 – 8.7)	0.55 ± 0.32 (0.21 – 1.25)
30	156 ± 102 (51 – 378)	39 ± 26[c, d] (13 – 95)	0.54 ± 0.23 (0.25 – 1)	258 ± 95 (104 – 426)	65 ± 24[e] (26 – 107)	0.33 ± 0.18 (0.12 – 0.67)	2.1 (1.0 – 5.8)	0.56 ± 0.25 (0.30 – 0.99)

[a] Arithmetic treatment means are reported for all parameters except the $t_{½}$ for which the harmonic means are reported; [b] Normalized for a 7.5 mg dose; [c] $p < 0.05$ when compared to the 7.5 mg dose; [d] $p < 0.01$ when compared to the 15 mg dose; [e] $p < 0.05$ when compared to the 7.5 mg dose

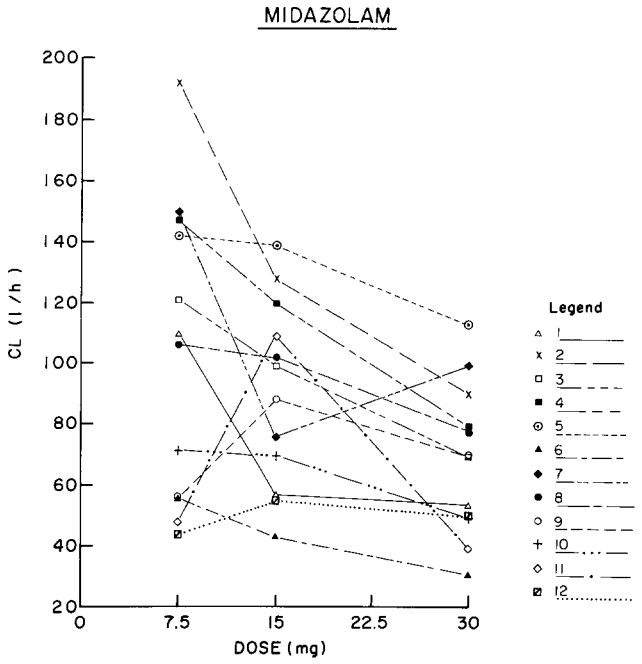

Fig. 4. CL of midazolam vs. midazolam dose in individual subjects

1-Hydroxymethylmidazolam

The t_{max} for 1-hydroxymethylmidazolam ranged from 0.25 h to 1.5 h regardless of the dose administered (Table 2, Fig. 1). Both C_{max} and AUC for 1-hydroxymethylmidazolam increased proportionally with dose between the 7.5 and 15 mg dose range and more than proportionally at the 30 mg dose, as was the case with midazolam. At the 30 mg dose, the increase was 49% more for the mean C_{max} and 73% more for the mean AUC than that predicted from the 7.5 and 15 mg dose data. Statistical analysis of these parameters showed a statistically significant difference between the 7.5 and 30 mg doses for the C_{max} and AUC parameters and between the 15 and 30 mg doses for the C_{max} parameter. The mean ± SD values for β were $0.44 \pm 0.17\ h^{-1}$, $0.43 \pm 0.17\ h^{-1}$, and $0.33 \pm 0.18\ h^{-1}$ following the 7.5, 15 and 30 mg doses, respectively and the corresponding harmonic mean values for the $t_{½}$ were 1.6 h, 1.6 h and 2.1 h. These differences were not statistically significant (Table 2).

The mean ± SD ratios of AUC for 1-hydroxymethylmidazolam (AUC_M) to the AUC for midazolam (AUC_P) for the 7.5, 15 and 30 mg doses were 0.50 ± 0.36, 0.55 ± 0.32 and 0.56 ± 0.25, respectively. No statistical differences were noted between the three doses in the AUC_M/AUC_P ratio.

Clinical

Five subjects complained of a headache and one subject complained of abdominal discomfort after administration of midazolam. These incidents were considered possibly related to midazolam. Sedation (the desired pharmacologic effect) was generally not observed at lower doses; however severe sedation occurred in all twelve subjects at the 30 mg dose. Stridor occurred in one subject after the 30 mg dose. These incidents were considered probably related to midazolam.

Discussion

The pharmacokinetics of midazolam and 1-hydroxymethylmidazolam were found to be linear (first order kinetics) between the 7.5 and 15 mg dose range. However, after a 30 mg oral dose, the systemic availability (e.g., C_{max} and AUC) of midazolam and 1-hydroxymethylmidazolam was greater than that anticipated from the lower doses and this increase was found to be statistically significant.

The higher systemic availability of midazolam at the 30 mg dose is unlikely to be due to the higher extent of absorption of midazolam from the gastrointestinal tract because previous studies have shown that midazolam is completely absorbed from the gastrointestinal tract and the systemic availability of in-

tact midazolam is only about 40% due to first-pass hepatic metabolism [4, 5].

A transient saturation of the first-pass metabolism of midazolam to 1-hydroxymethylmidazolam may be the most likely explanation for the observed data. Saturation of the hepatic first pass metabolism has been shown to occur for propranolol [7], phenacetin [8], lorcainide [9] and fluorouracil [10]; drugs with significant first-pass metabolism. Thus, it would not be surprising if saturation of metabolism also occurred for midazolam at the 30 mg dose. As observed in the present study, the saturation effect would be more pronounced on the C_{max} than AUC because saturation of metabolism is a transient and concentration[1] dependent effect. Saturation of hepatic metabolism would be expected to occur before t_{max} when absorption rates are relatively higher, especially after the 30 mg dose, resulting in portal blood concentrations that exceed the threshold value for saturation of midazolam metabolism.

It is not readily apparent why the AUC_M/AUC_P ratio remained essentially unchanged at the three midazolam doses in this study in light of the probable saturation of midazolam first-pass metabolism. One would expect this ratio to decrease to some extent as metabolism of midazolam to 1-hydroxymethylmidazolam was saturated.

The observed nonlinearity in the midazolam pharmacokinetics at the 30 mg oral dose is not expected to have any clinical significance since the clinical dosages are anticipated to be 15 mg or lower for patients with sleep disorders. In addition, it has been observed that midazolam and 1-hydroxymethylmidazolam do not accumulate in plasma during administration of 10 or 20 mg doses of midazolam at daily intervals (unpublished data), thereby avoiding the potential of saturation of metabolism on multiple dosing. This problem has been found to occur with propranolol [11]. Even at the 30 mg oral solution dose, the 24-h post-dose plasma concentrations of midazolam and 1-hydroxymethylmidazolam were nonmeasurable (< 2 ng/ml) suggesting that midazolam and/or the metabolite would not accumulate in plasma even after ingestion of 30 mg doses of midazolam at daily intervals.

The reported values of elimination half-life for 1-hydroxymethylmidazolam in Table 2 are apparent values because its decay in plasma is influenced by its formation from midazolam. Following intravenous administration of 1-hydroxymethylmidazolam to 6 healthy subjects (unpublished data), the true mean elimination half-life was found to be 0.8 h, much shorter than that for midazolam.

[1] drug concentration entering the liver, i.e., in the hepato-portal blood

The pharmacokinetics of midazolam and 1-hydroxymethylmidazolam were found to be linear between the 7.5 and 15 mg oral dose range. After the 30 mg dose, systemic availability of first-pass midazolam and 1-hydroxymethylmidazolam was greater than that anticipated from the lower doses possibly due to saturation of metabolism of midazolam. This is not expected to have any clinical significance under the conditions of therapeutic use.

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