Comparative absorption kinetics of intramuscular midazolam and diazepam

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Purpose: This study investigates the rate and extent of absorption following intramuscular injection of midazolam and diazepam.

Methods: Four healthy male volunteers were recruited in this randomized three-way cross-over study. On one occasion each subject received simultaneous im injections of 5 mg midazolam and 10 mg diazepam in separate deltoid muscles. On two other separate occasions each subject received an iv infusion of 7.5 mg midazolam and 30 mg diazepam over five minutes. Frequent arterial blood samples were collected for up to two hours and venous blood samples were collected for up to 24 hours for midazolam and ten days for diazepam. A gas chromatography assay was used to determine the plasma concentrations of midazolam and diazepam. The im absorption profiles were estimated using constrained least-squares deconvolution.

Results: There were substantial intersubject variabilities in the estimated pharmacokinetic parameters (volumes and clearances) of intravenous midazolam and diazepam. The mean ($\pm$ sd) time to peak plasma concentration (C_{max}) was shorter for im midazolam (17.5 ± 6.5 min) relative to dia-

zepam (33.8 ± 7.5 min). The mean ($\pm$ sd) time to peak absorption rate was also shorter for midazolam (9 ± 2 vs 13.8 ± 7.5 min). The peak rate of absorption was identical ($0.18 \text{ mg} \cdot \text{min}^{-1}$) and bioavailability was 1.0 for both drugs.

Conclusions: We conclude that midazolam has more rapid absorption than diazepam following im administration.

Objectif: Cette étude porte sur la vitesse et l'importance de l'absorption du midazolam et du diazépam par la voie intramusculaire

Méthodes: Quatre volontaires en bonne santé de sexe masculin ont pris part à cette étude aléatoire à trois voies. A une occasion, chacun des sujets a reçu simultanément des injections intramusculaires de midazolam 5 mg et de diazépam 10 mg. En deux occasions séparées chaque sujet a reçu une perfusion iv de midazolam 7,5 mg et de diazépam 30 mg en cinq minutes. De nombreux échantillons de sang artériel ont été prélevés pendant deux heures et de sang veineux pendant 24 heures pour le midazolam et dix jours pour le diazépam. La chromatographie en phase gazeuse a servi à déterminer la concentration plasmatique du diazépam et du midazolam. Les profils d'absorption ont été estimés avec le test de déconvolution forcée de la régression linéaire.

Résultats: Des variations substantielles ont été trouvées au regard de l'estimation des paramètres pharmacocinétiques (volumes et clairances) du midazolam et du diazépam intraveineux. Le temps (moyenne $\pm$ ET) requis pour l'atteinte de la concentration plasmatique maximale (C_{max}) a été plus court pour le midazolam ($17,5 \pm 6,5$ min) que pour diazépam ($33,8 \pm 7,5$ min). Le temps (moyenne $\pm$ ET) requis pour l'atteinte de la vitesse d'absorption maximale ($0,18 \text{ mg} \cdot \text{min}^{-1}$) et la biodisponibilité ont été identiques.

Conclusion: Après son administration intraveineuse, le midazolam est absorbé plus rapidement que le diazépam.

Key words

PHARMACOKINETICS: intramuscular administration, intravenous administration;
BENZODIAZEPINES: midazolam, diazepam.

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With its anxiolytic, amnesic and anticonvulsive properties, intramuscular administration of diazepam has been used clinically to provide preoperative sedation as well as to treat status epilepticus.¹ However, intramuscular administration of diazepam is uncomfortable due to its solvent propylene glycol and is associated with slow

and unpredictable absorption.²⁻⁴ The 1,4-benzodiazepine, midazolam is a water soluble compound with similar therapeutic effects as diazepam.⁵⁻⁶ It has been reported that the peak plasma midazolam concentration following intramuscular administration is achieved rapidly.³ However, the intramuscular absorption kinetics of midazolam relative to diazepam are unknown. This study investigated the comparative absorption profiles and the pharmacokinetic characteristics of intramuscular administration of both midazolam and diazepam in healthy volunteers.

Methods

Subject preparation

After obtaining institutional approval and informed consent, four healthy male volunteers participated in the study. Inclusion criteria were age 18–60 yr; non-smokers; no concurrent medications; no serious central nervous system, respiratory, cardiac, hepatic or renal dysfunction. Exclusion criteria included a history of allergy or adverse reactions to benzodiazepines; and a history of alcohol or substance abuse. After fasting for a minimum of six hours, the subjects were brought to the operating room or the postanesthetic care unit where an 18 gauge intravenous catheter was inserted for fluid and drug administration. A 20 gauge catheter was inserted into the radial artery for blood sampling and haemodynamic monitoring. During the study, the subjects were breathing 50% oxygen in air via a face mask.

Drug administration and blood sampling

The study was conducted in a randomized three-way crossover design with a minimum of four week separation between each experiment. During one of these experimental sessions, each volunteer received simultaneous administrations of midazolam 5 mg *im* and diazepam 10 mg *im* over one minute in separate deltoid muscles. Following drug administration, arterial blood samples were collected at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120 min and venous blood samples were collected at 4, 6, 8, 12, 16, 20, 24, 36, 48 hr, and 4, 6, 8, 10 days. On two other separate occasions and under the same conditions, the same volunteer received an *iv* infusion of 7.5 mg of midazolam or 30 mg of diazepam over five minutes. During and following the *iv* drug administration, arterial blood samples were drawn at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 10, 15, 20, 25, 30, 60, 90, 120 min and venous blood samples were collected at similar times as the *im* study up to 24 hr for midazolam and for up to ten days for diazepam. The plasma was separated within 30 min following the blood collection and stored at -20°C until analyzed. The plasma concentrations of midazolam

and diazepam were determined using a modified gas chromatography technique as described by Arendt and Greenblatt.^{7,8} The detection limits of midazolam and diazepam were 0.1 and 0.5 $\text{ng} \cdot \text{ml}^{-1}$ respectively with a coefficient of variation of approximately 5%.

Pharmacokinetic analysis

The peak plasma benzodiazepine concentration (C_{max}) and the time to reach this peak concentration (T_{max}) were determined from the concentration versus time profiles. For the intravenous study, plasma benzodiazepine concentration versus time profiles were fitted to a three-compartment mamillary model using the extended least squares nonlinear regression method.⁹ The pharmacokinetic parameters (V_1 , V_2 , V_3 , CL_1 , CL_2 , and CL_3) were estimated, where V_1 represents the initial volume of distribution and CL_1 is the clearance (elimination) from this compartment. The remaining volumes of distribution (V_2 and V_3) represent the rapid and slow redistribution respectively. The CL_2 and CL_3 are the respective intercompartmental clearances.

The areas under the benzodiazepine concentration versus time profile (AUC) following the *iv* and *im* administrations were calculated using the linear trapezoidal method.⁹ The extrapolation to infinity was calculated by dividing the last measurable plasma concentration by the first-order rate constant of the terminal phase. The sum of these two components was the estimate of the total AUC. The clearances of the benzodiazepines were calculated as $\text{DOSE}_{\text{iv}}/\text{AUC}_{\text{iv}}$. The amount of benzodiazepines absorbed from the *im* injections was calculated as the product of clearance and AUC_{im} . The bioavailabilities of *im* benzodiazepines were calculated as the ratio of the total amount of benzodiazepine absorbed and the *im* benzodiazepine dose.

Following *im* administration of a benzodiazepine, three independent processes (absorption, distribution and elimination) occur simultaneously. It is difficult to determine each of these unknown processes by examining the plasma benzodiazepine concentration vs time profile. With *iv* administration, the total dose of the drug can be assumed to reach the plasma compartment almost instantaneously. So the contribution of drug absorption to the plasma concentration vs time profile can be removed. The rate and extent of the drug distribution and elimination can then be estimated from the concentration vs time profile from the *iv* administration. By studying the pharmacokinetics of *iv* administration and *im* administration from the same individual on two separate occasions, it is possible to use a mathematical approach (deconvolution) to extract the absorption profile of *im* administration from that of distribution and elimination (*iv* administration). The constrained numeri-

FIGURE 1 Plasma concentration versus time profiles following *iv* and *im* administration of midazolam and diazepam.

cal deconvolution method described by Verotta¹⁰ was used to estimate the *im* absorption profiles in this study. This is a model-independent deconvolution technique which uses the plasma concentrations from the *iv* portion of the study to extract absorption information from the plasma concentrations following the *im* administration of benzodiazepines.¹¹ The deconvolution was performed with the constraint that the absorption profile be a positive function. The data were analyzed using paired *t* test and ANOVA with repeated measures where appropriate.

Results

The mean ($\pm$ sd) age, weight and height of the subjects were 33.5 ($\pm$ 9.0) yr, 80.5 ($\pm$ 9.7) kg, and 171.3 ($\pm$ 4.8) cm respectively. All the laboratory investigations before the studies were within normal limits. None of the subjects had any complications during the studies.

The plasma midazolam and diazepam concentration vs time profiles following the *im* and *iv* administrations are shown in Figure 1. The insets show the initial 90 min of concentration – time profiles of the two benzodi-

azepines following their administration. The estimated pharmacokinetic parameters of intravenous midazolam and diazepam are summarized in Table I. There are substantial intersubject variabilities in both volumes and clearances of these two benzodiazepines.

The mean ($\pm$ sd) maximum plasma benzodiazepine concentrations (C_{max}) were 100.5 ($\pm$ 21.0) ng·ml⁻¹ for midazolam and 199.3 ($\pm$ 89.3) ng·ml⁻¹ for diazepam following the *im* injections. The time to C_{max} was shorter for midazolam (17.5 $\pm$ 6.5 min) than for diazepam (33.8 $\pm$ 7.5 min). ($P < 0.05$, Table II) The *im* absorption profiles for midazolam and diazepam demonstrate that there is more variability in the absorption rates of *im* diazepam than those of *im* midazolam (Figure 2). The mean ($\pm$ sd) time to peak absorption rate (ABS_{peak}) was shorter for midazolam (9 $\pm$ 2 min) than for diazepam (13.8 $\pm$ 7.5 min). The absorption of midazolam was almost complete within one hour following the *im* administration. However, for diazepam, considerable drug absorption continued, with larger variability, beyond one hour after the *im* injection. Table II summarizes the absorption peak (ABS_{peak}), the time to ABS_{peak} ,

TABLE I Estimated pharmacokinetic parameters of intravenous midazolam and diazepam for all the subjects

Sub- ject	V_1 (L)		V_2 (L)		V_3 (L)		Cl_1 (L·min ⁻¹)		Cl_2 (L·min ⁻¹)		Cl_3 (L·min ⁻¹)	
	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam
1	3.78	3.55	27.34	9.33	84.36	90.6	0.377	0.020	2.078	1.20	0.293	0.272
2	4.54	3.11	16.23	9.05	47.64	62.52	0.362	0.031	1.738	1.694	0.482	0.267
3	2.79	4.18	7.66	5.45	46.88	75.29	0.338	0.023	0.978	0.517	0.643	0.505
4	2.95	2.87	18.15	10.06	102.64	121.63	0.346	0.034	1.318	1.002	0.494	0.295
Mean	3.52	3.43	17.34	8.47	70.38	87.51	0.356	0.027	1.528	1.103	0.478	0.335
SD	0.70	0.50	6.99	1.78	24.01	22.06	0.015	0.006	0.416	0.422	0.124	0.099

FIGURE 2 Comparative time course of absorption rate and percent of maximum absorption of *im* midazolam and diazepam.

the amount of drug absorbed, the AUCs, and the bioavailability (obtained from dose normalized AUC's and numerical deconvolution) of the *im* midazolam and diazepam.

Discussion

Our data demonstrate that *im* administration of midazolam provides rapid absorption with a peak plasma drug concentration within 25 min of drug administration compared with 40 min for diazepam. Following *im*

administration of 12.5 mg midazolam, Crevoisier *et al.* showed a similar time to C_{max} (30 min) in human volunteers.¹² These findings suggest that *im* administration of midazolam has an advantage over diazepam in providing a faster onset of drug effect.

In order to compare the absorption profiles of these two benzodiazepines directly, fractional absorption rates (i.e., the rate as a fraction of the peak absorption rate for that drug and subject) were used (Figure 2). Following the peak, the absorption rate for midazolam decreases

TABLE II Comparative absorption kinetics of intramuscular midazolam and diazepam

Sub- ject	C_{max} (ng · ml ⁻¹)		Time to C_{max} (min)		Peak absorption rate (mg · min ⁻¹)		Time to peak absorption (min)		Bioavailability from numerical deconvolution		Bioavailability from dose normalized AUCs	
	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam
1	109	107	25	40	0.27	0.08	6	10	1.26	1.09	1.62	1.01
2	94	317	20	40	0.19	0.36	10	10	0.97	1.31	0.90	1.25
3	24	211	10	30	0.17	0.18	10	10	0.96	1.06	0.96	0.91
4	75	162	15	25	0.11	0.12	10	25	0.85	0.99	0.76	0.97
Mean	100.5	199.3*	17.5	33.8†	0.18	0.18*	9.0	13.8*	1.01	1.11	1.06	1.03
SD	21.0	89.3	6.5	7.5	0.06	0.12	2.0	7.5	0.18	0.14	0.38	0.15

*No statistically significant difference.

† $P < 0.05$.

more rapidly than for diazepam. By one hour, the absorption of midazolam is almost complete with the fractional absorption rate approaching zero. However, the fractional absorption rate was between 20–50% at one hour for diazepam. The decrease from peak plasma concentration is much quicker following *im* midazolam administration than following *im* diazepam (Figure 1). This decrease is partially due to the rapid clearance of midazolam from the body and partially due to the more rapid absorption of midazolam than of diazepam. In other words, following a single *im* injection of midazolam, there is a rapid onset of drug effect due to rapid increase of plasma drug concentration, however, the CNS drug effect is brief due to both rapid completion of absorption and rapid clearance from the body. This would be appropriate for clinical situation that requires prompt onset but brief duration of drug effect such as preoperative sedation. Pharmacokinetically, *im* diazepam is less desirable for preoperative sedation as it has a slower onset of drug effect due to slower absorption and a potentially prolonged CNS effect due to residual absorption and sustained plasma concentration (Figures 1 and 2).

The constrained-numerical deconvolution method is a model-independent analytical deconvolution technique which uses the plasma concentrations from the *iv* portion of the study to extract absorption information from the plasma concentrations following the *im* injection. In doing so, we have assumed that the disposition characteristics (i.e., distribution and elimination) of the studied benzodiazepines were constant for each individual throughout the series of studies. If this assumption is false, it could introduce a substantial error into the estimates of the absorption parameters. Special efforts were made to complete the series of studies for the same subject within six months to minimize this variability. For confirmation of the absorption profile obtained by deconvolution, bioavailability calculated from this deconvolution was compared with bioavailability from

dose normalized AUC's. Deconvolution analysis yielded the expected bioavailability of close to 1 for each benzodiazepine, lending support to the validity of our assumption of time invariance in individual *iv* benzodiazepine disposition.

There was a larger intersubject variability in the absorption rate of diazepam than that of midazolam (Figure 2 and Table 2). Although the small number of subjects in this study does not permit us to address the problem of variability properly, many factors such as the site of injection,¹³ depth of injection,¹⁴ gender,² and body habitus¹⁵ have been suggested to influence the absorption of diazepam. In this study, healthy young male volunteers were involved with a standardized injection site (deltoid muscles) to minimize the influence of these factors on the absorption. Absorption at the *im* sites is also susceptible to changes in blood flow and body movement.¹⁶ However, it is unlikely that body movement contributed to the larger variability of diazepam absorption since midazolam and diazepam were administered simultaneously to each subject during the study. Tissue sites at which the drug was deposited could be a major source of variability since different absorption rates have been reported between *intramuscular* and *intermuscular* injections.^{11,17} The discrepancy between the absorption variability of diazepam and midazolam may also be related to the insolubility of diazepam in aqueous medium. Following *im* injection, most of the diazepam precipitates at the site of injection and is slowly absorbed. In contrast, owing to its greater solubility in aqueous medium, midazolam is rapidly mobilized and absorbed into the circulation following *im* administration.¹⁸

To simplify the study and to permit more efficient drug assay, midazolam and diazepam were administered simultaneously to the subjects in this study. It is unlikely that simultaneous injections of midazolam and diazepam influence the absorption profiles and the pharmacokinetics of the studied drugs. It is reasonable to

assume that the cardiac output and organ perfusion were unchanged following the *im* administration of the two benzodiazepines since there were no hemodynamic changes (arterial blood pressure and heart rate) observed. Furthermore, ventilation and oxygenation were maintained following the simultaneous *im* benzodiazepine administrations.

The bioavailability of *im* midazolam and diazepam are similar and complete. (i.e., $F = 1.0$) The bioavailability results obtained from constrained numerical deconvolution is in agreement with those obtained from the dose normalized AUCs method (Table I). Similar bioavailability for midazolam has been reported by Bell³ (87%F) Avram,¹⁸ and Crevoisier^{12,19} (91%F). However, the bioavailability of diazepam appeared higher than previously reported.² The difference may be partially explained by the smaller number of subjects in our study involving only males.

Although the number of subjects in this study is small, each subject was studied on three different occasions with a collection of over 100 samples of blood. The repeated catheterization of radial artery of the same subject, the assay work and the study cost make it difficult to recruit large number of subjects for such a study. Although the number of subjects is small, differences in the absorption kinetics were found between the two benzodiazepines, hence, a statistical power (sample size) is not such an important issue.

We conclude that *im* injection of midazolam provides a rapid onset and short duration of effect due to rapid absorption and clearance relative to diazepam. Clinically, *im* midazolam would be a better choice as pre-operative medication than *im* diazepam because of prompt onset but brief duration of drug effect.

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