ABSorption and sedative effects of diazepam after oral administration and intramuscular administration into the vastus lateralis muscle and the deltoid muscle

K. KORTTILA and M. LINNOILA

SUMMARY

The absorption of diazepam 10 mg after oral administration and intramuscular administration into the vastus lateralis muscle or the deltoid muscle was compared in a double-blind cross-over study in eight healthy subjects. Serum diazepam concentrations were measured, and the presence of tiredness was noted 20, 40, 60, 90 and 150 min after the drug administration. Peak concentrations in serum were 209 ± 49, 152 ± 60 and 143 ± 62 ng/ml (means ± SD) at 90, 60 and 60 min after oral, shoulder and thigh administration respectively. Absorption was more rapid after intramuscular than after oral administration, serum mean diazepam concentrations at 20 min after oral administration being only 26% of those after shoulder administration. The rapid rate of absorption from the shoulder was associated with a more rapid feeling of tiredness and a greater sedative effect than after oral or thigh administration. There was no evidence that diazepam induced its own metabolism after one or two administrations. The results suggest that, if rapid pre-anaesthetic medication with diazepam is needed, shoulder administration might be superior to oral or thigh administration.

Diazepam has been used widely as a preanaesthetic i.m. medication (Haslett and Dundee, 1968; Kyles, 1968; Dundee, Loan and Morrison, 1970; Duncan and Marshall, 1973). However, McCaughey and Dundee (1972) reported that better sedative effects are achieved after oral than after i.m. administration. Further, Dundee, Gamble and Assaf (1974) reported plasma diazepam concentrations to be greater after oral than after i.m. administration, a result that suggests that oral administration of diazepam as preanaesthetic medication might be as effective or even more effective than i.m. administration.

Recently, Schwartz and colleagues (1974) reported that the absorption of lignocaine from the deltoid muscle of the shoulder is better and faster than that from the vastus lateralis muscle of the thigh. Since diazepam might also be absorbed more rapidly from the deltoid muscle, we conducted the present investigation in order to measure the sedative effects of diazepam and serum diazepam concentrations after i.m. injection into the deltoid muscle, and to compare them with those after the administration of diazepam i.m. into the vastus lateralis muscle, or orally.

SUBJECTS AND METHODS

Eight healthy students, four males and four females were studied. Their characteristics were as follows (mean and range):

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>22 (20-24)</td>
<td>72 (68-78)</td>
<td>180 (172-188)</td>
</tr>
<tr>
<td>Females</td>
<td>24 (21-27)</td>
<td>52 (48-56)</td>
<td>161 (160-163)</td>
</tr>
</tbody>
</table>

Two males and two females smoked 10-15 cigarettes per day and the rest did not smoke. They were all in good health, and measurements of plasma creatinine, alkaline phosphatase and serum transaminases were normal. None of the subjects had any previous experience with diazepam. Informed consent was obtained for the procedure.

Experimental design. Three times at 2-week intervals, each subject received an injection into the thigh and shoulder, and two capsules orally. We changed the method of administering diazepam 10 mg (Diapam, Orion, Helsinki) each time in a double-blind cross-over randomized (Latin square) fashion (table I). Oral diazepam was given in two gelatine capsules, the absorption of which had been shown to
TABLE I. Three different treatments for eight subjects receiving diazepam 10 mg in a cross-over randomized fashion.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oral</th>
<th>i.m. thigh</th>
<th>i.m. shoulder</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>diazepam 2 x 5 mg</td>
<td>saline</td>
<td>saline</td>
</tr>
<tr>
<td>II</td>
<td>placebo</td>
<td>diazepam 10 mg</td>
<td>saline</td>
</tr>
<tr>
<td>III</td>
<td>placebo</td>
<td>saline</td>
<td>diazepam 10 mg</td>
</tr>
</tbody>
</table>

occur rapidly (Linnoila, Otterström and Anttila, 1974). Diazepam was injected in a volume of 2 ml into the vastus lateralis muscle at the lateral aspect of the thigh or into the deltoid muscle at the lateral aspect of the shoulder. Aspiration was attempted, to avoid intravascular injection, and the needle was withdrawn 2 cm during the injection. Neither food nor drink was allowed during the experiment or for 4 hr before the experiment. The subjects rested in a horizontal or slightly recumbent position on their backs throughout the experiment.

**Subjective assessments.** After each administration, we asked the subjects if they felt pain in the thigh or shoulder, and after the third administration they were asked which of the treatments had the greatest and the least sedative effect. To determine how quickly sedation and a feeling of tiredness or drowsiness began, we asked each subject if he or she was tired or drowsy at the time of each blood sample: at 20, 40, 60, 90 and 150 min after the administration of diazepam. The subjects were asked to choose one of the following descriptions: not tired or drowsy; slightly tired or drowsy; tired or drowsy; extremely tired or drowsy.

**Drug concentrations in serum.** We sampled venous blood from a cubital vein at 20, 40, 60, 90 and 150 min after administering diazepam. Sera were stored for 1 month at -22°C, and the serum diazepam and N-desmethyldiazepam concentrations were assayed by electron-capture gas liquid chromatography according to the method of Zingales (1973). The recovery percentage for diazepam was 98% and that for N-desmethyldiazepam was 100%.

The data were analysed using Student's t test.

**RESULTS**

**Subjective assessments**

Seven subjects reported pain at the diazepam injection site, while a total of only three subjects reported pain at the sites of saline injection (table II). Slight tenderness in the thigh or shoulder lasted for several hours in some subjects, but had ceased by the next day.

Six subjects considered shoulder administration to cause the greatest sedative effect, while two believed oral diazepam to be the most effective. The smallest sedative effect was reported after thigh and oral administration by six and two subjects respectively (table III). The onset of action was more rapid after shoulder administration than after thigh or oral administration (fig. 1). At 20 min after injection into the shoulder, the rate of tiredness or drowsiness was approximately 70% of the maximum effect, while after thigh and oral administration the respective figures were 25 and 30%.

**TABLE II. The percentage of subjects reporting pain during and after the simultaneous administration of saline and diazepam 10 mg.**

<table>
<thead>
<tr>
<th>Administration of diazepam</th>
<th>Reported place of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thigh (%)</td>
</tr>
<tr>
<td>Oral</td>
<td>25</td>
</tr>
<tr>
<td>I.m. thigh</td>
<td>87</td>
</tr>
<tr>
<td>I.m. shoulder</td>
<td>13</td>
</tr>
</tbody>
</table>

**TABLE III. Subjects' conception of the greatest and least sedative effect of diazepam 10 mg after i.m. or oral administration.**

<table>
<thead>
<tr>
<th>Subjective estimation</th>
<th>Oral (%)</th>
<th>I.m. thigh (%)</th>
<th>I.m. shoulder (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greatest sedation</td>
<td>25</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Least sedation</td>
<td>25</td>
<td>75</td>
<td>-</td>
</tr>
</tbody>
</table>

**Fig. 1. Subjective impression of tiredness or drowsiness as a function of time after the administration of diazepam 10 mg orally (O-O), i.m. into the thigh (●-●) and i.m. into the shoulder (■-■). Means ± SEM: 0 = not tired or drowsy, 1 = slightly tired or drowsy, 2 = tired or drowsy.
After shoulder and oral administration, the maximum effect occurred between 60 and 90 min, while after thigh administration the peak effect was not reached until 90 min. After each administration, irrespective of the route, most subjects felt slightly tired or drowsy at 150 min.

**Serum concentrations of diazepam**

The absorption of diazepam was more rapid after both i.m. methods of injection than after oral administration (fig. 2). Serum diazepam concentrations at 20 min were significantly greater after thigh (P<0.01) and shoulder (P<0.001) administration than after oral administration. The absorption from the shoulder was more rapid than from the thigh, but the difference was not statistically significant. However, oral treatment produced significantly (P<0.05) greater peak serum concentrations of diazepam than either of the i.m. routes. After oral treatment the highest serum diazepam concentration (209±49 ng/ml) was measured at 90 min, while the highest concentration after shoulder (152±60 ng/ml) and thigh (143±62 ng/ml) administration occurred at 60 min. At 150 min, the serum concentrations of diazepam were more than 85% of the maximum values with each treatment.

One volunteer who received an injection of diazepam into the thigh showed markedly lower serum concentrations than the others (about 80% less than the others). One subject who received diazepam into the shoulder had serum concentrations of diazepam which were about one-third of those in the other subjects. These subjects were not excluded from the study. These exceptional results might be the result of accidental subcutaneous injection of the drug.

The mean serum concentrations of diazepam were similar on each of the three experimental days.

**Serum concentrations of N-desmethyldiazepam**

After the first administration N-desmethyldiazepam could be measured in only one subject at 150 min after the administration (18 ng/ml). After the second and third administration, most of the subjects had detectable concentrations of N-desmethyldiazepam in the serum at 20 min, and at 150 min it was present in all subjects. The mean values for N-desmethyldiazepam at 150 min after the second and third administration were 25±5 ng/ml and 34±7 ng/ml respectively.

These high values for the main metabolite of diazepam after the second and third administration could be explained by diazepam having induced its own metabolism after the first injection or by a "subthreshold" saturation of tissues with the metabolite, the next administration resulting in increased serum concentrations. Therefore, another five subjects were given N-desmethyldiazepam twice orally, at an interval of 2 weeks. Serum concentrations of N-desmethyldiazepam were measured at 4, 5, 6 and 7 hr after each administration and immediately before the second administration. None of the subjects had demonstrable concentrations of N-desmethyldiazepam in the serum at 2 weeks after the first administration. N-desmethyldiazepam values after the two administrations are shown in table IV. After the second administration the values were about twice as great as those after the first administration.

<table>
<thead>
<tr>
<th>Time after administration</th>
<th>4 hr</th>
<th>5 hr</th>
<th>6 hr</th>
<th>7 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st administration</td>
<td>128±44</td>
<td>117±37</td>
<td>119±44</td>
<td>110±35</td>
</tr>
<tr>
<td>2nd administration</td>
<td>213±62*</td>
<td>215±76*</td>
<td>207±54*</td>
<td>215±49†</td>
</tr>
</tbody>
</table>

*P<0.05; †P<0.01 as compared with the first administration.

**DISCUSSION**

In this study we tried to simulate the clinical situation by asking the subjects to fast and lie in a horizontal position.
Oral administration

Baird and Hailey (1972) reported that plasma diazepam concentrations increase to 300 ng/ml after an oral dose of 10 mg, the concentration being 150 ng/ml at 15 min after the administration. In a recent study by Dundee, Gamble and Assaf (1974), the greatest plasma concentration after oral diazepam 10 mg was 176±11.4 ng/ml (mean±SD) and Kangas and colleagues (1974) found that with the same dose the mean plasma concentrations was 130±20 ng/ml (mean±SD) at 2 hr after administration. Gelatine capsules should ensure the best possible absorption from the gastrointestinal tract, and those which we used are known to be absorbed very rapidly (Linnoila, Otterström and Anttila, 1974). However, we could not demonstrate absorption as rapid as that found by Baird and Hailey (1972). Our results show a slow increase of serum diazepam concentration and a peak value of 209±49 ng/ml, and agree with the results of Dundee, Gamble and Assaf (1974) and Kangas and colleagues (1974) although our peak values are greater. It may be that the gelatine capsules used in this study yield higher diazepam concentrations than the tablets which were used in other studies. Most of the subjects in our study were of lean build and this may be an additional factor.

Intramuscular administration

Diazepam has been used with success for pre-anaesthetic medication, and Haslett and Dundee (1968) and Dundee, Loan and Morrison (1970) have reported that in this respect diazepam may be superior to any of the opiates. Further, Baird and Hailey (1973) have found that, in volunteers, i.m. injection into the vastus lateralis muscle provides a better sedative effect than oral administration. On the other hand, McCaughey and Dundee (1972) found sedation to be greater in patients after oral than after i.m. administration into the buttock. The discrepancy in these studies is probably a result of different injection sites and their differences in circulation and perhaps also a result of the different amounts of exercise by the subjects (Dundee, Gamble and Assaf, 1974; Korttila and Linnoila, 1975a). Similarly Idänpään-Heikkilä and colleagues (1971) found that after diazepam 5 mg the peak plasma concentration (38±3.3 ng/ml) occurred at 30 min after injection in pregnant women (12–16 weeks), while at full-term the highest plasma diazepam concentration was 151±90 ng/ml between 0 and 15 min after an injection of diazepam 10 mg (Erkkola, Kangas and Pekkarinen, 1973).

Schwartz and colleagues (1974) reported that the absorption of lignocaine is more rapid from the deltoid muscle than from the vastus lateralis muscle, a twofold increase in plasma concentrations being achieved after injection into the deltoid muscle. There are no previous reports about the absorption of diazepam from the deltoid muscle, but in this study injection of diazepam into the deltoid muscle did not cause greater serum concentrations than after injection into the vastus lateralis muscle, and the peak value was significantly less than after oral administration. The discrepancy between the absorption of lignocaine hydrochloride and diazepam from the deltoid muscle is probably related to the insolubility of diazepam in water. However, the speed of absorption of diazepam from the deltoid muscle was slightly greater than after a thigh injection and significantly greater than after oral administration.

Serum concentration of N-desmethyldiazepam

Serum concentrations of N-desmethyldiazepam increased significantly after the second and third administration as compared with the first administration. We have demonstrated this more clearly in a study with i.v. diazepam (Linnoila, Korttila and Mattila, 1974). The possibility of "subthreshold" saturation of N-desmethyldiazepam in tissues seems to be a better explanation for this occurrence than the suggestion that diazepam is capable of inducing its own metabolism after a single administration, in view of the results of repeated administration of N-desmethyldiazepam (table IV).

Correlation of serum concentration of diazepam with clinical effects

Baird and Hailey (1972) found that amnesia after oral diazepam occurred for the period when the plasma concentrations were increasing. Further, Linnoila and Mattila (1972) and Linnoila, Otterström and Anttila (1974), and Bliding (1974) have demonstrated that, for the impairment of psychomotor performance, the rapidity of increase in diazepam concentration is more important than the absolute concentration. It seems that a rapid increase in plasma diazepam, such as occurs soon after administration via the shoulder, affects the central nervous system more than when the increase occurs after a latent period (oral administration) (Linnoila and Mattila, 1973; Korttila and Linnoila, 1975b; Linnoila, Korttila and Mattila, 1974).

In this study a feeling of fatigue was related to the serum diazepam concentration (figs. 1 and 2). The more rapid increase in serum diazepam concentration after shoulder than after thigh injection seems to be sufficient to cause greater clinical sedation and a
more rapid onset of tiredness. The rapid increase in serum diazepam concentration from 40 to 60 min after oral administration probably does not produce so great an effect as the rapid initial increase after shoulder administration.

CONCLUSIONS

Intramuscular injection of diazepam into the deltoid muscle of the shoulder resulted in a more rapid onset of tiredness and greater sedation than after oral administration or after injection into the vastus lateralis muscle of the thigh. The deltoid route was associated with a rapid increase in serum diazepam concentration. There was no evidence that diazepam induces its own metabolism after one or two administrations. The results suggest that if a rapid preanaesthetic effect with diazepam is required, i.m. administration into the deltoid muscle might be superior to i.m. administration into buttock or thigh or to oral administration.

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REFERENCES


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SUMARIO
La absorción de 10 mg de diazepam después de su administración oral e intramuscular en los músculos vastus lateralis y deltóide se comparó en un estudio cruzado a doble puerta con ocho personas sanas. Se midieron las concentraciones del diazepam en el suero y se tomó nota de la aparición de cansancio a los 20, 40, 60, 90 y 150 minutos después de la administración de la droga. Las concentraciones máximas en suero fueron de 209 ± 49, 152 ± 60 y 143 ± 62 ng/ml (promedio ± SD) a los 90, 60 y 60 min después de la administración oral, en la hombro y en el muslo, respectivamente. La absorción fue más rápida después de la administración intramuscular que la oral; siendo la concentración media de diazepam en el suero a los 20 min después de la administración oral de sólo el 26 % de la registrada después de la administración en el hombro. La rapidez de absorción después de la administración en el hombro estaba asociada con una sensación más rápida de cansancio y un efecto sedativo mayor que después de la administración oral o en el muslo. No hay motivos para pensar que el diazepam induce su propio metabolismo después de una o dos administraciones. Los resultados sugieren que si se necesita una administración rápida preanestésica con diazepam, la administración en el hombro puede ser superior a la oral o a la intramuscular en el muslo.