COMPARISON OF THE RECOVERY CHARACTERISTICS OF DIAZEPAM AND MIDAZOLAM

Midazolam has a useful role as a premedicant, a sedative for minor surgical procedures and an induction agent. In comparison with diazepam in propylene glycol, the water-soluble midazolam produces a lower incidence of pain on injection and of thrombophlebitis [1], and has advantageous physicochemical and pharmacokinetic properties [2]. Although it has the shortest elimination half-life of all the commercially available benzodiazepines, clinical studies suggest that the recovery from equipotent doses of midazolam and diazepam is comparable [3–6]. The purpose of this study was to compare the efficacy and recovery characteristics of midazolam and diazepam following the administration of equipotent doses of each drug.

SUBJECTS, MATERIALS AND METHODS

Eight male volunteers in the age range 22–28 yr (mean 25 ± SD 3 yr; weight 75 ± 11 kg; height 182 ± 9 cm) were selected. All were healthy, were not receiving any psychotropic drugs and had been asked to refrain from ingesting alcohol for 24 h, or coffee for 6 h, before the study period.

On each of two study days an 18-gauge cannula was inserted to a vein in the right antecubital fossa and physiological saline was infused at a constant rate. The volunteers then received diazepam in propylene glycol (Valium, Roche) 10 mg i.v., or midazolam (Hypnovel, Roche) 5 mg i.v. according to a random order crossover design. The midazolam was diluted in physiological saline to the same volume (2 ml) as the diazepam by an independent technician and injected by an anaesthetist not involved with data collection. Injections were given into the saline infusion and were made double-blind for the volunteer and observer by masking both syringe and i.v. tubing. Each study was separated by an interval of at least 3 weeks and was performed in the same environment controlled for temperature and light intensity with the same observer performing the tests of recovery and sedation.

A battery of psychomotor/sedation tests (see below) was performed by each subject before, and at 10, 30, 60, 120 and 180 min after injection. During the first 10 min after injection, sedation was assessed by the observer using a seven-point scoring system (table I), each change in score being recorded on a small microcomputer system with timing function. This observer assessment was chosen because psychomotor tests could not be performed because of the degree of sedation.

To examine long-term memory, a series of simple line diagrams were shown to the subjects for 20 s before, and at 1, 5, 10, 20 and 30 min after drug administration. Recall was tested at 24 h.

Heart rate, arterial pressure (Dinamap), rate of ventilation, end-tidal carbon dioxide concentration (nasal cannulae with Datex CO₂ analyser) and oxygen saturation (Biox ear oximetry) were recorded during the first 30 min of the study period.

SUMMARY

A double-blind crossover comparison of efficacy and recovery from midazolam 5 mg and diazepam (in propylene glycol) 10 mg was undertaken in eight volunteer subjects. It was found that midazolam was significantly more potent in this dose ratio than diazepam, helping to explain the finding of previous studies that the recovery from midazolam and diazepam in a 1:2 dose ratio is comparable.
TABLE I. Sedation scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No subjective or objective sedative effects</td>
</tr>
<tr>
<td>1</td>
<td>Onset of first observable drug effect</td>
</tr>
<tr>
<td>2</td>
<td>Drowsy, partial lid closure</td>
</tr>
<tr>
<td>3</td>
<td>Upper lid bisects pupil or full lid closure,</td>
</tr>
<tr>
<td></td>
<td>responds to verbal command</td>
</tr>
<tr>
<td>4</td>
<td>Unresponsive to verbal command,</td>
</tr>
<tr>
<td></td>
<td>responds to mild physical stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Responsive only to painful stimulus</td>
</tr>
<tr>
<td></td>
<td>(trapezius squeeze)</td>
</tr>
<tr>
<td>6</td>
<td>Unresponsive</td>
</tr>
</tbody>
</table>

Psychomotor/sedation tests

Five simple assessments were chosen to encompass a range of benzodiazepine effects, relevant to the clinical recovery of function: subjective sedation, cognition, short term memory and visuo–motor performance.

Visual analogue sedation scale—a subjective measure of perceived sedation. Subjects were asked to assess their degree of sedation by marking a 10-cm linear visual analogue scale (VAS). The extremes were denoted “wide awake, alert” and “drowsy, dull.”

Letter deletion test. Thirty lines of 25 randomly typed upper and lower case letters were given and subjects deleted as many letters g or G as possible in a 2-min interval. This form of simple pen and paper test is sensitive to the effects of benzodiazepines and is an adaption of that described by Dixon and Thornton [9]. The letter g/G was chosen because of the dissimilarity between the upper and lower case characters. This test has a saccadic eye movement component in addition to motor co-ordination and cognition.

Simple Reflex Time—a robust measure of sensory–motor performance [10]. Reflex time was assessed as the time taken to press a button after a visual light stimulus. The mean reflex time was taken as the averaged value for the last 30 of 35 attempts.

Simple addition. A cognitive task in which 25 pairs of two-digit numbers were given for addition, each requiring an answer to be given within a 5-s interval onto a microcomputer keyboard.

Seven-digit recall—a test of short term memory. Thirty consecutive seven-digit numbers were presented on a microcomputer screen for recall. Each number was shown to the subject for 4 s, and after a 7-s interval subjects entered the memorized number onto the keyboard.

Reflex time, simple arithmetic and seven-digit recall were each performed on an Apple Ile microcomputer.

Statistical analysis

t Tests were used for parametric comparisons and Chi-square tests for non-parametric comparisons, where appropriate. A Wilcoxon Signed Rank test was used to analyse the between-group differences in sedation score during the first 10 min, by comparing for each subject and drug the area under the curve of the sedation–time plot.

The changes in the psychomotor/sedation test battery were analysed as a whole using a multivariate analysis of variance [7] with treatment, time, subject and interaction terms. Tests of significance of effects were made with the Lawley–Hotelling trace statistic. As there were significant treatment-time and treatment-subject interactions, the treatments were compared at each time and for each subject using canonical variates analysis. Comparisons were made using the Bonferroni inequality to give an experimental level of significance less than or equal to 0.05 [8].

TABLE II. Mean change in physiological variables from preinjection value. M = Midazolam, D = diazepam

<table>
<thead>
<tr>
<th></th>
<th>1 min M</th>
<th>1 min D</th>
<th>3 min M</th>
<th>3 min D</th>
<th>5 min M</th>
<th>5 min D</th>
<th>10 min M</th>
<th>10 min D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>-6</td>
<td>3</td>
<td>-11</td>
<td>-2</td>
<td>-13</td>
<td>-4</td>
<td>-13</td>
<td>-9</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>1</td>
<td>5</td>
<td>-1</td>
<td>2</td>
<td>-7</td>
<td>-4</td>
<td>-8</td>
<td>-8</td>
</tr>
<tr>
<td>Ventilatory rate (b.p.m.)</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>ECO₂ (%)</td>
<td>0.1</td>
<td>-0.1</td>
<td>0.1</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
RESULTS

After the injection of the relevant drugs there were no significant between-group differences in heart rate, arterial pressure, ventilatory rate, end-tidal carbon dioxide concentration or oxygen saturation. Mean changes are shown in table II.

The mean times to onset of drug effect did not differ significantly (diazepam 28±SD 15, midazolam 32±SD 22 s).

During the first 10 min the observed degree of sedation was found to be significantly greater with midazolam (P < 0.05) (fig. 1). Similarly, as assessed by the psychomotor tests, recovery was better in the diazepam group at 10 (P < 0.0001),
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30 ($P < 0.0001$) and 60 min ($P = 0.001$). This trend was consistent for all subjects at these times. At 180 min the midazolam group performed slightly better than the diazepam group (ns). Figure 2 is a summary of the psychomotor test battery, representing the mean number of the five tests that had returned to the control values at the given time. The mean change in the visual analogue sedation score is shown in figure 3.

Amnesia for picture recall, analysed for the complete 30-min test period, was significantly greater in the midazolam group ($P < 0.01$).

**DISCUSSION**

The potency of midazolam relative to diazepam has been estimated to be 1.5–2:1:1 [11] and several clinical studies of diazepam with midazolam in this dose ratio have found the recovery characteristics to be comparable. In a study of dental sedation with subjects who received a mean dose of diazepam 26 mg or midazolam 13 mg, Skelly and colleagues [3] found no difference between the groups when six psychomotor tests were used to assess recovery. Whitwam, Al-Khudairi and McCloy [12] found similar recovery characteristics in gastroscopy patients who received diazepam 0.15 mg kg$^{-1}$ or midazolam 0.07 mg kg$^{-1}$, but noted that the midazolam group were more sedated on arrival in the recovery room and had a greater degree of amnesia.

The apparent discrepancy between the recovery and pharmacokinetic characteristics of midazolam and diazepam has been attributed to the presence of active metabolites [5] and to their similar distribution half-lives [13].

It is unlikely, however, that the principal active metabolite of midazolam, alpha hydroxy midazolam, plays an important part in delaying recovery as its own elimination half-life (< 1 h) is considerably shorter than that of the parent drug [14]. Alpha hydroxy midazolam probably exerts its most significant clinical effect after oral administration of midazolam (because of the high first-pass effect) when it potentiates rather than prolongs the action of midazolam [15].

Although midazolam is classified as a short-acting benzodiazepine, on the basis of its elimination half-life, it is the distribution half-life which determines initial recovery. The distribution half-life of diazepam is 0.3 h (SD 0.1 h) [16], comparable to some values found for midazolam (0.31 h (SD 0.08 h) [17]).

Our results indicate that midazolam 5 mg is significantly more potent than diazepam 10 mg, in terms of both subjects’ and investigators’ assessments of sedation, amnesia and objective psychomotor testing. However, by 3 h this effect showed signs of reversal, with the results in the midazolam group beginning to improve beyond those of the diazepam group.

We believe, therefore, that the doses used in our study were not equipotent, and that the relative potency of the two drugs is significantly greater than 2:1 (perhaps nearer 3:1). This would help explain the findings of those other studies which demonstrated that midazolam has a similar recovery and more intense amnesia than that of diazepam. If the newer formulations of diazepam (mixed micelle or lipid emulsion) were to be compared with midazolam, the discrepancy between their relative potencies are likely to be even greater [18].

In summary, midazolam 5 mg was found to be significantly more potent than diazepam (in propylene glycol) 10 mg and to be associated with delay in recovery. Our results indicate that comparisons of recovery from the two drugs should not be made with a dose ratio of 2:1 and that the advantageous pharmacokinetic profile of midazolam may be apparent only if its considerably greater potency is taken into account.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


