COMPARISON OF MIDAZOLAM AND DIAZEPAM IN DOSES OF COMPARABLE POTENCY DURING GASTROSCOPY

J. G. WHITWAM, D. AL-KHUDHAIRI AND R. F. MCCLOY

The water soluble benzodiazepine midazolam was compared with diazepam, in doses of 0.07 mg kg⁻¹ and 0.15 mg kg⁻¹ respectively, administered i.v. to 100 patients undergoing gastroscopy. The degree of sedation, ease of endoscopy and recovery were comparable in the two groups. The effects of both drugs on arterial pressure were similar. Compared with diazepam, midazolam had a faster onset of effect, caused virtually no pain on injection, and provided a greater degree of amnesia.

Midazolam is a water soluble benzodiazepine suitable for i.v. use (Conner et al., 1978; Dundee et al., 1980). The first report of its use in gastroscopy was restricted to a description of venous complications (Jensen, Huttel and Olesen, 1980).

In a previous study (Al-Khudhairi, Whitwam and McCloy, 1982), diazepam 0.15 mg kg⁻¹ (Valium, Roche) was compared with midazolam (Hypnovel, previously Dormicum (Roche)) 0.1 mg kg⁻¹ i.v. in 100 patients undergoing gastroscopy. It was found that the patients who received midazolam were more sedated than those receiving diazepam and that in four (8%) the degree of sedation was excessive. As a result the dose of midazolam was decreased to 0.07 mg kg⁻¹, and a further prospective comparison obtained with patients receiving diazepam 0.15 mg kg⁻¹. The results of this second study are reported here.

PATIENTS AND METHODS

In the present study 100 patients (ASA groups I and II) undergoing elective upper gastrointestinal endoscopy were allocated randomly to receive either midazolam 0.07 mg kg⁻¹ or diazepam 0.15 mg kg⁻¹.

The study was blind to the investigators assessing the patients. Five minutes after the application of a throat spray (lignocaine 50–100 mg) the drugs were injected to a large vein in the upper forearm, and followed by hyoscine-N-butyl bromide 40 mg (Buscopan) i.v. During recovery the degree of sedation, orientation in time, place and person, ability to walk without assistance and Rhomberg steadiness were observed every 5–10 min for 2 h. Patients were regarded as ready for discharge when fully orientated and Rhomberg steady even though several felt slight residual effects from the drugs. At the end of recovery they were asked if they could recall the throat spray, or the introduction or withdrawal of the endoscope.

Arterial pressure, and heart and respiratory rates were observed before and after the administration of each drug, every 5 min during the procedure and at intervals during recovery.

Subsequently, a questionnaire was sent to the patients asking if they could remember the journey home, their activities in the evening, when any "hangover" effect disappeared, whether they had a headache and when they felt ready for work. In addition they were asked whether they developed a red line, discolouration, tenderness or a "lump" at the site of the injection. Anyone with positive local signs was asked to revisit for examination. Statistical analysis was performed using either Chi-square or Mann–Whitney tests.

The methods used, for example the details of drug administration, and methods of assessment of the patients, have been described in detail in a previous paper (Al-Khudhairi, Whitwam and McCloy, 1982) and a preliminary report has been communicated to the British Society of Gastroenterology (Al-Khudhairi, McCloy and Whitwam, 1982).

RESULTS

The demography of the patients is shown in table I, and the primary and secondary diagnoses in table II.
In both groups the time from the throat spray to the injection of the drugs was approximately 5 min. The mean times to maximum sedation were 2.4 min (SD 0.48 min) for midazolam and 3.2 min (SD 0.48 min) for diazepam ($P < 0.001$). An additional dose of diazepam $0.07 \text{ mg kg}^{-1}$ was required in two patients.

Only one of the patients who received midazolam complained of pain on injection, compared with 18 in the diazepam group ($P < 0.001$).

The mean times between the onset of sedation and removal of the gastroscope were 13.4 min (SD 12.5 min) and 10.7 min (SD 8.9 min) for midazolam and diazepam respectively.

**Endoscopic assessment (table III)**

There were no significant differences between the two groups. In 43 who received midazolam and 39 in the diazepam group, endoscopy conditions were described as excellent.

**Recovery**

On entry into the recovery room 16 of the patients who received diazepam were not drowsy, compared with eight in the midazolam group. However, thereafter recovery was similar in the two groups (table IV), including their responses to the questionnaire on their symptoms and activities in the subsequent 24 h.

**Vital signs**

There were no serious respiratory or cardiovascular complications. No patient became apnoeic and the airway was maintained without assistance. In one patient the arterial pressure decreased by 20% after the administration of midazolam, whereas in the other patients decreases of 5–15% were observed with both drugs.

**Amnesia (table V)**

All patients remembered the throat spray. In the midazolam group 64% did not recall the passage of the gastroscope and 74% could not remember its removal compared with 30% and 44% respectively in the diazepam group.

**Venous complications**

One patient who received midazolam developed local thrombosis at the injection site. Of those who received diazepam, two developed an extended thrombophlebitis, two a local thrombosis and three complained of tenderness, pain and discolouration lasting several days.
TABLE IV. Mean recovery times (from the end of injection of the benzodiazepine) (min (SD))

<table>
<thead>
<tr>
<th></th>
<th>Orientated in time, place and person</th>
<th>Rhomberg steady</th>
<th>Ready for discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>14.6 (5.7)</td>
<td>49.8 (17.3)</td>
<td>75.3 (23.2)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>12.9 (5.2)</td>
<td>46.2 (25.4)</td>
<td>76.4 (30.9)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

TABLE V. Number of patients recalling the throat spray and the passage and removal of the gastroscope

<table>
<thead>
<tr>
<th></th>
<th>Throat spray</th>
<th>Gastroscope passed</th>
<th>Gastroscope removed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Midazolam</td>
<td>50</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Diazepam</td>
<td>50</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td><em>P</em></td>
<td>n.s.</td>
<td></td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

DISCUSSION

As with all benzodiazepines there is a considerable variability in the response to midazolam (Gamble et al., 1981) and the more rapid onset of sedation following this drug is advantageous since it allows a patient to be “titrated” more quickly to any particular degree of sedation. The mean times to maximum sedation for both drugs in this study and the previous one where a larger dose of midazolam (0.1 mg kg\(^{-1}\)) was used (Al-Khudhairi, Whitwam and McCloy, 1982), were comparable.

Diazepam causes a high frequency of venous complications (Hegarty and Dundee, 1977), whereas for midazolam the frequency is low (Jensen, Huttel and Olesen, 1980). The present study confirmed these findings.

In the previous study (Al-Khudhairi, Whitwam and McCloy, 1982) using a dose of 0.1 mg kg\(^{-1}\), between 88% and 92% of the patients had amnesia for the procedure compared with 64–74% in the present study when the dose was decreased to 0.07 mg kg\(^{-1}\). However, this is still much greater than the degree of amnesia achieved with diazepam 0.15 mg kg\(^{-1}\) (44–54% in the first study and 30–44% in the present study in which the mean dose of diazepam was 9.9 mg). In a previous study, Douglas and colleagues (1980) administered diazepam 12.1 mg (mean dose) for gastroscopy and...
found that total amnesia for the procedure occurred in only approximately 17% of patients, but that when partial amnesia was included in the assessment this figure increased to 55%. In view of the larger doses of diazepam used it is difficult to draw strict comparisons with the present study, but their data are not inconsistent with those reported here for diazepam.

The high degree of amnesia associated with the use of midazolam has also been reported previously, by Dundee and Wilson (1980), and appears to be maximal 2–5 min after the injection of the drug. These workers observed also that the degree of amnesia appeared greater in the more heavily sedated patients. This amnesia is anterograde with very little retrograde component, since most patients can remember the injection of the drug but not the subsequent events (Gamble et al., 1981). However, the response to the questionnaire in the present study revealed that the amnesia is relevant to the procedure, concurrent with the sedative effects of the drug, and hence is not a potentially dangerous problem during subsequent ambulation of the patients.

Amnesia for the procedure is important since it helps patients to accept repeated endoscopies, when these are necessary.

There were no gross differences in the cardiovascular and respiratory effects of the two drugs. Both groups of patients showed a slight gradual decrease in arterial pressure and increase in heart rate. Samuelson, Reves and Kouchoukos (1981) reported that the effects of midazolam on the cardiovascular system were similar to those of diazepam, apart from slightly greater decreases in arterial pressure and increases in heart rate immediately after injection. The effects of the two drugs on respiration were comparable (Forster et al., 1980). A few patients undergoing endoscopy may develop partial reflex closure of the larynx. This occurred in three patients in the midazolam group in this study and in one patient who received diazepam in our previous study (Al-Khudhairi, Whitwam and McCloy, 1982). There were no gross differences between the two drugs in terms of endoscopic management and recovery, which suggests that the doses reported here are approximately equipotent. However, previous work by Dundee and co-workers (1980) and Gamble and colleagues (1981) suggests that, when large doses of midazolam and diazepam are compared, although the degree of sedation is greater following midazolam the rate of recovery from its effects is more rapid, possibly because of the very rapid elimination half-life of midazolam (approximately 2.3 h), which also applies to its principal metabolites (Heizmann, Eckert and Ziegler, 1983).

ACKNOWLEDGEMENTS
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REFERENCES

COMPARAISON DU MIDAZOLAM ET DU DIAZEPAM A DES DOSES EQUIPOTENTES AU COURS DE LA GASTROSCOPIE

RESUME
Le midazolam, benzodiazépine hydrosoluble, a été comparé au diazepam, aux doses de 0,07 mg kg⁻¹ et 0,15 mg kg⁻¹ respectivement, en administration i.v. chez 100 patients subissant une gastroscopie. Le degré de sédation, la facilité de l'endoscopie et le
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réveil étaient comparables dans les deux groupes. Les effets des deux agents sur la pression artérielle étaient semblables. Par rapport au diazépam, le midazolam a un début d'action plus rapide, est pratiquement indolore à l'injection et entraîne un degré d'amnésie plus grand.

VERGLEICH ZWISCHEN MIDAZOLAM UND DIAZEPAM IN ÄQUIPOTENTEN DOSEN BEI GASTROSKOPIE

ZUSAMMENFASSUNG

Das wasserlösliche Benzodiazepin Midazolam wurde bei 100 Patienten zur Gastroskopie mit Diazepam in Dosen von 0,07 mg kg\(^{-1}\) bzw. 0,15 mg kg\(^{-1}\) verglichen. Bei beiden Gruppen war die Stärke der Sedierung, die Leichtigkeit der Endoskopie und die Erholungszeit vergleichbar. Der Effekt beider Präparate auf den arteriellen Druck war ähnlich. Verglichen mit Diazepam hatte Midazolam eine kürzere Wirkungseintrittszeit, verursachte keinen Injektionsschmerz und erzeugte einen größeren Grad an Amnésie.

COMPARACION DEL MIDAZOLAM Y DEL DIAZEPAM EN DOSIS DE POTENCIA COMPARATIVA DURANTE LA GASTROSCOPIA

SUMARIO

El midazolam, benzodiazepina soluble en agua, se comparó con el diazepam, en dosis de 0,07 mg kg\(^{-1}\) y de 0,15 mg kg\(^{-1}\) respectivamente, administrados por vía intravenosa a 100 pacientes sometidos a gastroscopía. El grado de sedación, facilidad de endoscopia y recuperación fueron comparables en los dos grupos. Los efectos de ambas drogas en los dos grupos fueron comparables en los dos grupos. En comparación con el diazepam, el midazolam presenta un periodo de comienzo de su actividad que es más corto, no ocasiona, prácticamente, dolor alguno al inyectarse y provee un mayor grado de amnesia.