COMPARISON OF THE ACTIONS OF DIAZEPAM AND LORAZEPAM

J. W. DUNDEE, W. A. W. McGOWAN, J. K. LILBURN, A. C. MCKAY AND J. E. HEGARTY

SUMMARY

Diazepam and lorazepam differ in potency and in the time-course of their action. As a sedative, diazepam 10 mg is equivalent to lorazepam 2–2.5 mg. Diazepam is better absorbed after oral than after i.m. administrations but this does not apply to lorazepam. The clinical effect and amnesia begin more rapidly with diazepam, but last longer following lorazepam. Lorazepam is more effective than diazepam in blocking the emergence sequelae from ketamine. Lorazepam i.v. is followed by a lesser frequency of venous thrombosis.

Diazepam is widely used in anaesthetic practice as a premedicant and sedative-amnesic. In addition, it has been investigated as an induction agent although it is not used commonly for this purpose. Many new benzodiazepines have been studied, but apart from lorazepam most of these differ only slightly from diazepam and these differences relate only to their potency. There are minimal differences in duration of action.

This paper compares some facets of the actions of diazepam and lorazepam in anaesthetic practice. In some instances it summarizes data which have been published elsewhere and it includes new findings. The objective was to give an overall comparison of the two drugs.

Intravenous use

Diazepam has been used for the induction of anaesthesia (Dundee and Wyant, 1976). The onset of action takes 60–90 s, the response is variable and the effect is often too prolonged to be clinically acceptable. Full anaesthesia may require a dose in the range 1–1.5 mg kg\(^{-1}\). Dundee and others (1977) noted a delay of up to 40 min before the peak effect of lorazepam 4 mg and this would make it completely unacceptable for induction of anaesthesia.

We studied the rate of onset of sedation of the two drugs, using the “mean efficacy” score described by Dundee, Moore and Nicholl (1962). A score of 1 (unacceptable) to 5 (ideal) was allocated to the patient’s condition based on the degree of drowsiness and absence of apprehension. Groups of approximately 10 patients were given diazepam 10 or 20 mg or lorazepam 4 mg as i.v. preanaesthetic medication. Observations were made at 2, 5, 10, 15, 20 and 30 min after administration. With this method of assessment the peak sedative action of diazepam was reached within 5 min of injection, whereas that of lorazepam was still increasing at 30 min (fig. 1). The sedative effect of diazepam had started to diminish by 10 min, in contrast with the increasing effect of lorazepam at that time.

Figure 1 shows some of the problems of comparing the potency of two drugs with differing time-effect profiles. At 10 min a similar degree of sedation is produced by diazepam 10 mg and lorazepam 4 mg, while at 20 min the average effects of diazepam

![Mean efficacy score following i.v. injection of diazepam 10 mg = △, diazepam 20 mg = ▲, and lorazepam 4 mg = ○.](https://academic.oup.com/bja/article-abstract/51/5/439/248167)

© Macmillan Journals Ltd 1979
20 mg are similar to those of lorazepam 4 mg. However, the study shows that, in appropriate doses and allowing for the delay in onset of action, i.v. lorazepam is as good as diazepam as a sedative.

Thrombosis, with or without phlebitis, is a common complication of the injection of benzodiazepines. Hegarty and Dundee (1977) have reported a detailed 3–4 and 7–10-day follow-up of the frequency of venous sequelae following diazepam 10 mg and lorazepam 4 mg. Their findings (table I) show the superiority of lorazepam in this respect. The lorazepam was injected in the form available at that time (4 mg ml⁻¹) and not diluted to half this strength, as is now recommended by the manufacturers.

**Preanaesthetic medication**

Oral diazepam is now a popular premedicant, the usual adult dose being 10 mg. Dundee and others (1977) demonstrated the efficacy of lorazepam for this purpose, the optimum oral dose being 4 mg for adults. This study has been extended to include additional cases with the commercially available 2.5-mg tablet and the findings have been compared with diazepam in patients who are comparable with respect to average age and weight (table II). Again, the methodology was that described by Dundee, Moore and Nicholl (1962), which was used in previous studies of benzodiazepines (Assaf, Dundee and Gamble, 1975). This consists of an evaluation of the degree of drowsiness and apprehension at 20, 40, 60 and 90 min after administration, and a note of side-effects at these times. The doses of lorazepam studied were determined by the commercially available ampoules (4 mg) and tablets (1 and 2.5 mg) except for the 4-mg tablet which was prepared specially for the previous study.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Percentage of notable drowsiness (good and fair degrees) after diazepam 10 mg = △, lorazepam 4 mg = ○ lorazepam 2.5 mg oral or 2.0 mg i.m. = ●.

Table III shows the results with the commercially available 3.5-mg (1- and 2.5-mg) tablets of lorazepam and the specially prepared 4-mg tablets. The effects of 3.5 mg were almost identical with those of 4 mg. At 60 min significantly more patients had notable
drowsiness after 3.5 mg than after 2.5 mg ($\chi^2 = 3.96; P < 0.05$), but this difference was less marked at 90 min ($\chi^2 = 2.57; P < 0.20$).

In the doses used both diazepam and lorazepam were free from major side-effects and there was no hypotension, marked tachycardia or respiratory depression. However, lorazepam i.m. produced significantly more persistent pain at the site of injection than diazepam (table IV), but this had passed completely by 40 min with both drugs. Again, it should be pointed out that the injected lorazepam was more concentrated than that now currently recommended. Restlessness was also more frequent with i.m. lorazepam, and this persisted for 1 h. This was not a result of persistent injection-site pain as both occurred in only eight patients. Restlessness was not a problem with any oral dose of lorazepam.

**Ketamine sequelae**

I.v. administration of diazepam near the end of operation minimized the unpleasant sequelae from ketamine (Erbguth, Reiman and Klein, 1972; Coppel, Bovill and Dundee, 1973; Kothary and Zsigmond, 1975). However, premedication with diazepam only provided a limited degree of protection in patients undergoing minor surgery, but lorazepam in adequate doses was effective in this respect (Libburn et al., 1978). Dundee and Lilburn (1978) found a small frequency of emergence delirium and unpleasant dreams after operation in patients undergoing minor gynaecological operations under ketamine anaesthesia and premedicated with lorazepam 4 mg orally or i.m. but the published study did not include the commercially available tablet (2.5 and 3.5 mg). The effect of these has been studied in 75 women anaesthetized with intermittent ketamine (initial dose 2 mg kg$^{-1}$) for minor gynaecological operations, using the same routine as the study by Libburn and others (1978). The frequency of severe prolonged (10 min +) delirium and unpleasant dreams (as recalled 6 h later) is given in table V, which also shows the number of patients who would object to having the same anaesthetic on a subsequent occasion. Table V shows the efficacy of lorazepam 4 mg given i.v. This made ketamine very acceptable to patients as an induction agent. The same dose is effective when given by mouth, but the number of patients who would not like the same anaesthetic on a subsequent occasion was unacceptably high with the 2.5-mg tablet as premedication. However, it would appear that the findings with 3.5 mg (1- and 2.5-mg tablets) make this an acceptable premedication for ketamine anaesthesia and superior in this respect to an equivalent dose of diazepam.

**Table IV. Comparison of the percentage frequency of some side-effects of i.m. diazepam and lorazepam**

<table>
<thead>
<tr>
<th></th>
<th>Pain at site of injection</th>
<th>Restlessness</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam 4 mg</td>
<td>24</td>
<td>34</td>
<td>26</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Diazepam 10 mg</td>
<td>12</td>
<td>13</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>4.88</td>
<td>12.6</td>
<td>16.84</td>
<td>6.37</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;0.05</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&lt;0.025</td>
<td></td>
</tr>
</tbody>
</table>

**Amnesia**

The i.v. administration of most benzodiazepines affected the patient's ability to remember objects shown or events occurring for a short period after injection. The duration and intensity of this varied with dose and individual drugs. Figure 3 summarizes our findings with i.v. diazepam and lorazepam. This is based on the subject's ability to recall objects shown at varying times after administration. Amnesia

**Table V. Percentage frequencies of sequelae following ketamine 2 mg kg$^{-1}$ after various premedicants, and the patient's opinion of the anaesthetic**

<table>
<thead>
<tr>
<th>Premedicant</th>
<th>Route</th>
<th>$n$</th>
<th>Severe emergence delirium</th>
<th>Unpleasant dreams</th>
<th>Anaesthesia unacceptable to patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>I.v.</td>
<td>50</td>
<td>32</td>
<td>38</td>
<td>64</td>
</tr>
<tr>
<td>Diazepam 15 mg</td>
<td>I.v.</td>
<td>20</td>
<td>45</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Lorazepam 4 mg</td>
<td>I.v.</td>
<td>50</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lorazepam 4 mg</td>
<td>Oral</td>
<td>50</td>
<td>0</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Lorazepam 3.5 mg</td>
<td>Oral</td>
<td>20</td>
<td>0</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Lorazepam 2.5 mg</td>
<td>Oral</td>
<td>55</td>
<td>2</td>
<td>34</td>
<td>44</td>
</tr>
</tbody>
</table>
 occurred quickly after diazepam, with recovery by 30 min, by which time the amnesic action of lorazepam was becoming marked (George and Dundee, 1977).

The i.m. injection of diazepam 10 mg caused an insignificant degree of amnesia, but this was enhanced by the addition of hyoscine or opiates. The amnesic action of i.m. lorazepam has not been studied.

Since many patients take both diazepam and lorazepam orally as tranquillizers during the day, it was felt necessary to study their amnesic action following oral administration. Diazepam 10 or 20 mg or lorazepam 2 or 4 mg were given before operation to patients who were shown 10 cards over the next 90 min. Their ability to recognize these was tested 6 h later. Significant failure to identify a card was only found (with either drug) when the patient was notably drowsy at the time of presentation; in this respect there is a difference between the effects of oral and i.v. administration of both drugs. Figure 4 shows the percentage frequency of failure to identify objects after approximately equivalent sedative doses of diazepam and lorazepam. This shows the slower onset of action of lorazepam. Not included in this figure is that lorazepam 1 mg did not appear to affect the memory. However, it should be noted that, in our studies, a 10-mg tablet of diazepam did cause more impairment of memory than an inert tablet (McKay, Dundee and George, 1978).

**Plasma concentrations**

These have been reported for clinical doses of both diazepam (Gamble, McKay and Dundee, 1973; Gamble, 1975; Gamble, Dundee and Assaf, 1975) and lorazepam (Dundee et al., 1978) following i.m. injection to the thigh.

The rate of uptake of the two drugs is similar and the slower onset of clinical effect of lorazepam cannot be explained on these grounds. A second peak in plasma concentration has been found 6–8 h after oral administration with both drugs, and clinically this may lead to a second period of drowsiness. Whereas the plasma concentrations increase sooner after diazepam 10 mg orally compared with i.m.

---

**Fig. 3.** Percentage frequency of loss of ability to recall objects shown at various intervals following i.v. administration of lorazepam 4 mg and diazepam 10 mg (George and Dundee, 1977).

**Fig. 4.** Percentage frequency of loss of ability to recall objects shown at various intervals following oral administration of two doses of diazepam and lorazepam.
COMPARISON OF DIAZEPAM AND LORAZEPAM

TABLE VI. Plasma concentrations (ng ml⁻¹) following the oral administration of diazepam 10 mg (D) and lorazepam 4 mg (L) with or without previous i.v. injection of metoclopramide 10 mg (M). (Mean values ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>65 ± 22.3</td>
<td>122 ± 18.2</td>
<td>205 ± 22.9</td>
</tr>
<tr>
<td>D + M</td>
<td>10</td>
<td>218 ± 53.6</td>
<td>240 ± 27.7</td>
<td>233 ± 21.9</td>
</tr>
<tr>
<td>L</td>
<td>20</td>
<td>12.6 ± 7.9</td>
<td>22.55 ± 10.41</td>
<td>39.85 ± 16.22</td>
</tr>
<tr>
<td>L + M</td>
<td>8</td>
<td>12.8 ± 18.32</td>
<td>17.38 ± 14.58</td>
<td>28.00 ± 21.25</td>
</tr>
</tbody>
</table>

Injection, this relationship was not found with lorazepam—in fact there was a slight delay in the increase of plasma concentrations after the oral administration of the drug.

Gamble and others (1976) found that the i.v. injection of metoclopramide 10 mg hastened the uptake of diazepam from the gastrointestinal tract. The average plasma concentration was significantly greater at 15 (P<0.05) and 30 (P<0.005) min when metoclopramide had been given compared with a control series (table VI). A similar study with lorazepam 4 mg showed no significant difference in average plasma concentrations with or without metoclopramide. No explanation can be offered for this.

Gamble, Dundee and Gray (1976) also studied plasma concentrations in patients receiving diazepam 5 mg and 10 mg at 4-h intervals for periods of 6–22 days. There was an accumulation of both diazepam and its metabolite for about 8 days, by which time the plasma diazepam concentration reached a plateau while the major metabolite (n-desmethyl diazepam) continued to increase during the period of administration.

A similar study was carried out in seven patients who received lorazepam 4 mg every 4 h for periods of 2–15 days. There was a small accumulation in plasma concentration (measured at the same time after injection) for about 8 days, again followed by a plateau. A typical finding (fig. 5) shows a plateau effect with rapid decrease in plasma concentration on discontinuing the drug with its disappearance from the blood over the next 6 days. In this respect
diazepam and lorazepam behave very similarly. No metabolite of lorazepam was detected in this study.

In our premedicant studies, it was often possible to estimate plasma concentrations for up to 2 days after administration. By 4–6 h the plasma concentrations were similar irrespective of whether the drugs were given orally or i.v., and this applied to both diazepam and lorazepam. In view of the prolonged soporific effects of the benzodiazepines, the plasma concentrations were estimated at 24 and 48 h after administration of diazepam 10 mg or lorazepam 4 mg in patients who received no medication after operation. The average findings in a small number of patients show the persistence of an appreciable amount of both drugs in the plasma for 48 h (table VII). These values represent 35–40% of peak plasma concentrations still present at 24 h and 25–30% at 48 h. Lorazepam was eliminated from plasma slightly more slowly than was diazepam but the difference was not statistically significant.

TABLE VII. Plasma concentrations (ng ml$^{-1}$) of diazepam and lorazepam at 24 and 48 h after oral administration. (Mean values ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam 2.5 mg</td>
<td>13</td>
<td>17.40 ± 1.7</td>
<td>10.3 ± 2.6</td>
</tr>
<tr>
<td>Diazepam 10 mg</td>
<td>10</td>
<td>90.30 ± 10.8</td>
<td>67.9 ± 8.9</td>
</tr>
</tbody>
</table>

DISCUSSION

There is no published detailed comparison of the actions of diazepam and lorazepam with which to compare this study. However, reports on various facets of these drugs (Galloon, Gale and Lancee, 1977) are in agreement with the present findings.

Our results show that diazepam and lorazepam differ quantitatively, rather than qualitatively in their actions and they indicate certain respects in which there is a preference for one or other drug.

Both drugs cannot be recommended as injectable premedicants because of local irritation. By mouth, diazepam requires more precise timing than lorazepam. The latter is particularly useful for "later cases" on an operating list where a delay of a few hours will not result in recovery from sedation. However, the prolonged effect of lorazepam may be a disadvantage for minor operations when rapid recovery is desirable. It has proved particularly useful as a reliable sedative in doses of 2.5–3.5 mg for the night before operation and can be recommended for this purpose. One may hesitate to use lorazepam on both the night before and the morning of operation, and diazepam can be substituted in the latter occasion.

Without discussing the indications for the use of benzodiazepines for induction of anaesthesia, it is obvious that lorazepam is unsuitable for this purpose. However, it can produce a useful degree of sedation and can be used in conjunction with regional analgesia techniques, provided the anaesthetist appreciates the slow onset of action. For outpatient dental procedures, diazepam is preferred.

Amnesia may be regarded as either desirable or undesirable. It is important to appreciate the consistency of amnesia with both drugs and particularly the prolonged amnesia which follows lorazepam. If a short period of amnesia is desired, for example in childbirth or for performance of a nerve block, diazepam is preferred. Diazepam accumulates in the fetus (Gamble et al., 1977) in contrast with lorazepam, following which a maternal/fetal ratio greater than unity has been found (unpublished observations). We have found lorazepam 2–3 mg to be very effective when given i.v. early in labour and there appears to be no deleterious effects on the fetus.

The persistence of such high concentrations of both drugs in the plasma for up to 48 h was unexpected. It shows the need for caution in outpatients and the danger of drug interactions in the period soon after operation.

We have summarized the important differences between diazepam and lorazepam below. These are intended as a guide in deciding which drug is preferable in differing clinical situations.

(1) As a premedicant, diazepam 10 mg produces a degree of sedation comparable with 2.0–2.5 mg lorazepam.

(2) The duration of action of lorazepam is three to four times greater than that of equivalent doses of diazepam.

(3) Oral diazepam produces earlier effects than the equivalent dose given i.m., but this does not apply to lorazepam.

(4) These effects occur in parallel with plasma concentrations of the drugs.

(5) There is a slow excretion of both drugs from the body and plasma concentrations remain increased for 24–48 h.

(6) The main metabolite of diazepam, n-desmethyl diazepam, has an appreciable hypnotic action and accumulates following repeated administrations. This does not apply to lorazepam.
ACKNOWLEDGEMENTS

This paper represents clinical studies carried out over a 6-yr period and our thanks are given to our many colleagues who co-operated at various stages. These include the staffs of Belfast City, Musgrave Park and Royal Victoria Hospitals and our own laboratory staff. Dr T. V. A. Harry supplied lorazepam before this became commercially available and Wyeth International supported the study financially.

REFERENCES


COMPARAISON DES ACTIONS DU DIAZEPAM ET DU LORAZEPAM

RESUME

Le diazépam et le lorazépam diffèrent du point de vue efficacité et durée d'action. En tant que sédatif, le diazépam à raison de 10 mg équivaut à 2-2,5 mg de lorazépam. Le diazépam est mieux absorbé après administration par voie orale que par voie intramusculaire, mais cela n'est pas applicable au lorazépam. L'effet clinique et l'amnésie commencent plus rapidement avec le diazépam, mais durent plus longtemps avec le lorazépam. Le lorazépam est plus efficace que le diazépam pour bloquer les séquelles provenant de la ketamine. Le lorazépam administré par voie intraveineuse est suivi d'une plus faible fréquence de thrombose veineuse.

VERGLEICH DER WIRKUNGEN VON DIAZEPAM UND LORAZEPAM

ZUSAMMENFASSUNG

COMPARACION ENTRE LAS ACCIONES DE DIAZEPAM Y LORAZEPAM

SUMARIO
Diazepam y lorazepam difieren en potencia y en el transcurso de tiempo de su acción. Como sedante, 10 mg de diazepam equivale a 2-2,5 mg de lorazepam. El diazepam es mejor absorbido por administración oral que intramuscular, aunque no es así con el lorazepam. El efecto clínico y la amnesia comienzan más rápidamente con diazepam, pero duran más tras lorazepam. El lorazepam es más efectivo que el diazepam en el bloqueo de la secuela que se presenta al emerger de los efectos de ketamina. El lorazepam intravenoso es seguido por una menor frecuencia de trombosis venosa.