COMPARISON OF LORAZEPAM AND DIAZEPAM AS PREMEDICANTS

S. GALLOON, G. D. GALE AND W. J. LANCEE

SUMMARY
A double-blind random study compared lorazepam with diazepam as i.m. premedicants in 84 healthy women undergoing uterine curettage. Anxiety, assessed by a self-rating test by the patient and by a trained observer, was reduced 90 min after both lorazepam (P<0.001) and diazepam (P<0.01). There was more sedation and a longer recovery time after lorazepam than after diazepam. Amnesia at 24 h after operation (lack of recall rather than lack of recognition) was greater after lorazepam. There was transient local discomfort at the site of the injection in most patients in both groups, but no serious effects. Local erythema was present in 12 patients who received lorazepam and 10 who received diazepam 90 min after the injection, disappearing after 24 h in the former group but remaining in the latter. The incidence of nausea, vomiting and headache in both groups was small and similar, but there was more restlessness and dizziness after diazepam in the early recovery period.

Lorazepam (Ativan, Wyeth Ltd) is one of the newer compounds in the benzodiazepine series and had recently been shown to provide greater relief of anxiety and more amnesia than papaveretum BPC (Pantopon, Omnopon) when used i.m. as a premedicant (Gale and Galloon, 1976). Diazepam (Valium, Hoffmann-La Roche Ltd) is probably the most widely used drug of the benzodiazepine group and therefore it seemed appropriate to compare these two drugs.

METHODS
The method used was similar to that of a previous study to compare lorazepam with papaveretum (Gale and Galloon, 1976) in a double-blind and randomized study, with both drugs injected i.m. Healthy women, admitted for uterine curettage, were studied and their informed written consent was obtained by the anaesthetist on the day before operation. Each patient was allocated a number on a random list. No drugs were given on the night before operation.

Approximately 2½ h before the operation, a trained nurse visited the patient and assessed her state of sedation and reusability (on a scale of 1 = alert to 6 = fast asleep) and her anxiety (1 = no anxiety to 5 = very anxious). At this time the patient also completed a self-assessment test for anxiety using an adaptation of the Multiple Affect Adjective Check List (MAACL), which is a self-rating scale performed by the patient (Zuckerman, 1960; Wassenaar et al., 1977). The scoring scale is from 0 to 21, the higher numbers reflecting more anxiety. Two hours before the operation each patient was given either lorazepam or diazepam i.m. in a dose related to weight. The doses used were lorazepam 5 mg and diazepam 10 mg per 70 kg body weight (table I). Neither the patient, the nurse giving the injection, the trained nurse doing the tests, nor the anaesthetist, knew which drug had been injected. Ninety minutes after premedication, the trained nurse visited the patient and repeated the observations. The self-rating anxiety test (MAACL) was repeated also.

When the patient arrived at the operating room the anaesthetist assessed her sedation and anxiety, examined the injection site and asked about it, and measured the heart rate and arterial pressure. He also showed the patient three cards, with one black and white object drawn on each, and asked her to identify each of the three objects. Anaesthesia was then induced with sodium thiopentone and maintained with nitrous oxide in oxygen and intermittent thiopentone. The nurses in the recovery room were asked to record the progress of recovery, vital signs and any adverse effects. On the morning following

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Lorazepam (mg)</th>
<th>Diazepam (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>55-64</td>
<td>4</td>
<td>7.5</td>
</tr>
<tr>
<td>65-74</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>&gt;74</td>
<td>6</td>
<td>12.5</td>
</tr>
</tbody>
</table>
the operation the patient was again assessed by the trained nurse for anxiety and behaviour, and the MAACL test was repeated. The patient was asked if she remembered any picture cards; if she did not, she was shown a nine-picture composite containing the three pictures on it and asked if she remembered any. She was also asked nine specific questions to test her recall of events from the time of premedication to induction of anaesthesia and a further question dealing with events after the operation. Short-term memory was tested by showing the patient three coloured blocks at the beginning of the interview and asking her to name the colours at the end of the interview. Enquiry was also made regarding nausea, vomiting, headache and dizziness at any time.

RESULTS

Forty-three patients received lorazepam and 41 received diazepam. The groups were similar in respect of age, weight and duration of operation (table II).

The patients’ self-rating tests of anxiety (Multiple Affect Adjective Check List, MAACL) showed a high degree of anxiety just before premedication (fig. 1). Sixty to ninety minutes after the injection, there was a mean reduction of anxiety score of 2.9 following lorazepam ($P<0.001$) and of 1.3 following diazepam ($P<0.01$). The difference between the two groups was not statistically significant. Both groups showed a further significant reduction, to the normal range, when tested at 24 h after operation.

Anxiety, as assessed clinically by the trained nurse, was reduced significantly in both groups after premedication and a further significant reduction was observed 24 h after operation, correlating well with the changes in the scores of the self-rating MAACL. The anaesthetists’ assessment of anxiety also indicated a significant reduction after premedication in both groups.

The nurse’s assessment after premedication showed significantly increased drowsiness after lorazepam ($P<0.05$ compared with control) although all the patients were still easily rousable. There was no significant difference between the two groups in the nurse’s assessment of drowsiness. Using a three-point scale, the anaesthetists found more drowsiness outside the operating room after lorazepam than after diazepam ($P<0.001$) with 17 and two patients, respectively, in the “sleepy” category.

Heart rate, arterial pressure and respiratory frequency were virtually unchanged in all patients, with a trend towards slightly greater values in all three measurements in the first 90 min after operation. The dose of thiopentone (mean 7.4 mg kg$^{-1}$) and the duration of operation (mean 14 min) were similar in both groups.

Observations in the recovery room showed that patients who received diazepam recovered more quickly than those who received lorazepam (table III). However, the initial response to the stimulus of a nasal catheter and the total time in the recovery room were not significantly different between the two groups.

There was a low frequency of adverse effects in the recovery room in both groups, although dizziness and restlessness occurred more often in the diazepam group.
**TABLE III.** Time required for recovery with SD and significance of the difference between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Mean time (min)</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening of eyes</td>
<td>Lorazepam</td>
<td>46.6</td>
<td>29.4</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>26.9</td>
<td>15.6</td>
</tr>
<tr>
<td>Response to command</td>
<td>Lorazepam</td>
<td>48.9</td>
<td>32.5</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>27.9</td>
<td>15.7</td>
</tr>
<tr>
<td>Total time in recovery room</td>
<td>Lorazepam</td>
<td>80.3</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>74.0</td>
<td>24.4</td>
</tr>
</tbody>
</table>

n.s. = not significant.

Twenty-four hours after operation each patient was asked if she recalled seeing any picture cards before the operation. Only 12 of 43 in the lorazepam group (28%) could recall all three pictures compared with 27 of 41 in the diazepam group (68%) (P < 0.01) (table IV). Where memory was incomplete or inaccurate a composite picture was presented to the patient and most patients then recognized the cards. Short-term memory was shown to be intact in all patients by showing the patients three coloured blocks at the beginning of the interview and obtaining complete recall for them at the end of the interview.

**DISCUSSION**

The measurement of anxiety by clinical observation has the disadvantage that a patient’s emotions may be concealed. The use of a self-evaluating anxiety test (MAACL) overcomes this problem because it enables the patient to indicate how she herself feels regardless of outward appearances. The MAACL test is also likely to be more sensitive than a retrospective questionnaire because memory of anxiety before operation is likely to be diminished with the benefit of hindsight and the successful completion of surgery.

In this study the MAACL test showed a reduction of anxiety which was significant after both diazepam and lorazepam, but the magnitude of the change was not significantly different between the two drug groups. The anxiety scores by the nurse decreased after premedication in both groups but the change as a proportion was smaller than that in the MAACL. MAACL has been shown to be a reliable test of anxiety (Gale and Galloon, 1976; Wassenaar et al., 1977). When used in doses which provided a similar degree of drowsiness, lorazepam in a dose of 5 mg per 70 kg was shown to provide superior relief of anxiety compared with papaveretum in a dose of 20 mg per 70 kg (Gale and Galloon, 1976). The reduction of anxiety by 2.45 points after lorazepam in the previous study and by 2.9 points after lorazepam in this study suggests that MAACL provides a measure of change in anxiety which is superior to clinical impressions.

The frequency of amnesia was significantly greater after lorazepam than after diazepam in this study. In both groups amnesia was mainly a lack of recall because the patients recognized the composite picture and then memory of the pictures was the same in both groups. Clarke and others (1970) considered that the amnesic action of diazepam was a result of impairment of memory input or consolidation processes because both recall and recognition were affected equally. Our results show that recall was impaired more than recognition, particularly in the lorazepam
group. This suggests that lorazepam impairs retrieval of information rather than input and consolidation. Duarte (1976) noted more amnesia after lorazepam than after diazepam, although he used a larger dose of diazepam than that in our study (10 mg orally at night and 10–20 mg i.m. before operation). Hyoscine, used alone, is a weak amnesic (Hardy and Wakely, 1962) but its effect is potentiated when combined with diazepam (Dundee and Haslett, 1970). It is likely, therefore, that the amnesic action of lorazepam would be potentiated if it were combined with hyoscine.

Lorazepam has been shown to provide more sedation than diazepam, both in this study and in others (Duarte, 1976; Gomez et al., 1976). Thus it may be a better premedicant than diazepam, which has been shown to produce more recall for unpleasant dreams when compared with atropine (Turner and Wilson, 1969). The long recovery times for opening the eyes and responding to command in our lorazepam group suggest that the sedative effects of lorazepam persist into the recovery period.

The incidence of restlessness and dizziness was more common after diazepam than after lorazepam, but this was not a significant difference 24 h later.

Propylene glycol is used as a solvent for benzodiazepine drugs and this may be the cause of the transient pain on i.m. injection in both groups; alternatively, precipitation of the drug may have occurred at the injection site. Lorazepam is well absorbed when given by the i.m. route, with an absorption half-life of 21.2 min and a peak plasma concentration within 3 h of injection (Greenblatt et al., 1977). In this respect lorazepam may be different from diazepam, because Assaf, Dundee and Gamble (1975) showed that blood concentrations of diazepam are less predictable after i.m. compared with oral administration.

ACKNOWLEDGEMENTS

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REFERENCES


COMPARAISON DU LORAZEPAM ET DU DIAZEPAM EN TANT QUE PREMEDICATIONS

RESUME

On a comparé, au cours d'une étude à double inconnue effectuée au hasard sur 84 femmes en bonne santé subissant un curetage utérin, le lorazépam et le diazépam administrés par voie intra-musculaire en tant que pré-médications. L'automatie, estimée par un test effectué par la malade elle-même et par un observateur formé, a diminué, 90 min après l'administration de lorazépam (P < 0,001) et de diazépam (P < 0,01). La sédation a été plus profonde et le temps de récupération plus long après le lorazépam qu'après le diazépam. L'amaîsé (manque de souvenirs plutôt que difficulté de reconnaissance) 24 h après l'intervention a été plus forte après le lorazépam. Il y a eu une douleur locale transitoire au point d'injection sur la plupart des malades des deux groupes, mais on n'a constaté aucun effet grave. Il y a eu un érythème localisé sur 12 personnes ayant reçu du lorazépam et sur 10 personnes ayant reçu du diazépam 90 min après l'injection; celui-ci disparait à 24 h plus tard dans le premier groupe, mais restant dans le second. L'incidence des cas de nausées, de vomissements et
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de maux de tête a été faible et similaire dans les deux
groupes, mais il y a eu davantage de nervosité et de malaises
après le diazépam au début de la période de récupération.

EINE VERGLEICHUNG VON LORAZEPAM UND
DIAZEPAM ALS PREMEDIKATIONEN

ZUSAMMENFASSUNG
Eine wahllose Doppelblinduntersuchung verglich Lorazepam und Diazepam als i.m. Premedikationen in 84 gesunden Frauen, die Gebärmutterkürettage erlitten. Nach 90 min liess sich eine von der Patientin selbst in einer Veranschlagungsprobe und von einem unterrichteten Beobachter abgeschätzte Beklemmungsverminderung sowohl nach Lorazepam ($P < 0,001$) wie auch nach Diazepam ($P < 0,01$) merken. Nach Lorazepam war die Beruhigung grösser und die Wiederherstellungszeit länger als nach Diazepam. Vierunzwanzig Stunden nach der Operation war die Amnesie bedeutsamer nach Lorazepam, bestand aber mehr aus Zurückkunftsschwierigkeit als aus Erkennungsschwierigkeit. Eine vorübergehende örtliche Beschwerde an der Einspritzungsstelle ergab sich in den meisten Patientinnen beider Gruppen, hatte aber keine gefährliche Einwirkung. Neunzig min nach der Einspritzung war ein örtliches Erythem bei 12 Patientinnen zu sehen, die Lorazepam empfangen hatten, und bei 10 Diazepam-Patientinnen; nach 24 Stunden war es in der ersten Gruppe verschwunden, bestand aber noch in der zweiten. Das Auftreten von Brechreiz, Erbrechen und Kopfschmerzen war in beiden Gruppen gering und auch gleichartig, nach Diazepam waren jedoch die Unruhe und der Schwindel am Anfang der Wiederherstellungszeit bedeutsamer.

COMPARACION ENTRE LORAZEPAM Y
DIAZEPAM COMO PREMEDICAMENTOS

SUMARIO
Un estudio fortuito de doble anonimato comparó lorazepam con diazepam como premedicamentos intramusculares en 84 mujeres saludables sometidas a raspado uterino. El grado de ansiedad, determinado mediante una prueba de autoclasificacion realizada por la paciente y por un observador instruido se redujo al cabo de 90 min tanto después de lorazepam ($P<0,001$) como después de diazepam ($P<0,01$). Se produjo una mayor sedación y un periodo más largo de recuperación después de lorazepam que después de diazepam. La amnesia a 24 h de la operación fué por olvido en vez de falta de reconocimiento. Sintieron una incomodidad local transitoria en al lugar de la inyección la mayoría de las pacientes en ambos grupos, pero no efectos serios. Se presentó eritema local en 12 pacientes que recibieron lorazepam y en 10 que recibieron diazepam, 90 min después de la inyección y desapareciendo al cabo de 24 h en el primer grupo, pero durando en el último. La incidencia de náusea, vómito y dolor de cabeza en ambos grupos resultó pequeña y similar, pero hubo mayor intranquilidad y mareo después de diazepam al principio del periodo de recuperación.