The time course of antirecall effect and grades of sedation after the oral administration of diazepam and lorazepam were determined in 120 patients. Three standard doses of each drug were employed. Grades of sedation following oral diazepam were dose related, with a latency of 30–60 min and duration of 120–150 min. All three doses of lorazepam produced significantly more sedation with a similar latency (30–60 min) but longer duration (more than 240 min). Peak frequencies of the antirecall effects of diazepam 10, 15, and 20 mg were 3, 20, and 30 per cent, respectively. The duration was about two hours. Peak frequencies of the antirecall effect after lorazepam 2, 3, and 4 mg were 30, 45, and 72 per cent, respectively. Latency of peak action was about 60–90 min for all the doses, but the duration, especially with 3 and 4 mg doses, was long (4 h). (Key words: Hypnotics: benzodiazepines, diazepam, lorazepam. Memory. Premedication.)

BENZODIAZEPINES, especially diazepam and the newly introduced lorazepam, are commonly used premedicants. Diazepam and lorazepam have excellent sedative and anxiolytic effects, and patient acceptance of both these agents is very high.1,2 One of the intriguing properties of these drugs is their antirecall effect. Knowledge of this unique property of diazepam and lorazepam is based almost entirely on studies of parenterally administered drugs.3,4 Since oral administration of premedicants is becoming more common, it is important to know the time course of the antirecall effects, if any, of these two agents when given orally. Dundee et al.5 have studied the amnesic effects of these two drugs when given orally. However, their study was restricted to only 90 min following the drug administration. Thus, we still do not know either the peak effect or the duration of effect following commonly used doses of these two drugs.

The grades of sedation and the frequency and the duration of the anterograde amnesia (lack of recall) following oral administration of diazepam and lorazepam at three clinically useful doses for up to four hours has been studied and is reported.

Materials and Methods

The subjects of the study were 120 healthy patients between the ages of 18–55 years, of either sex (ASA class I–II) scheduled for elective operations and requiring premedication. None of the patients were mentally retarded and all had negative psychiatric histories. Drug-dependent individuals were excluded from the study. The Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University Hospital approved the study. The patients were interviewed the day prior to operation, the details of the procedure were explained, and a written informed consent was obtained.

The doses of diazepam studied were 10.0, 15.0, and 20.0 mg and of lorazepam 2.0, 3.0, and 4.0 mg. Each was given in a single dose as a premedicant. No other premedication was administered during the observation period. Dispensing of the medication was done on a random basis. There were twenty patients in each dose group. Five observations were made in patients receiving diazepam, starting at 30 min and then continuing at 30-min intervals for 2½ h. Five observations were also made in patients who received lorazepam, again starting at 30 min but continuing for 4 h.

Because of the known difference in the duration of the clinical effects of diazepam and lorazepam, it was assumed that a double blind study would not be possible. The patients were not aware of the nature of the medication, but the observer was. By using a different duration of study (2.5 hours for diazepam, and 4 h for lorazepam), the authors tried to obtain maximum information about the time course of these two agents.

At each observation period, the patient was visited by the same observer and the grade of sedation was recorded on a scale of 1 to 5 where:

Grade 1: No sedation
Grade 2: Calm but not asleep
Grade 3: Sleepy but easily arousable
Grade 4: Asleep and not easily arousable
Grade 5: Unable to communicate.

For the purpose of determining the frequency of anterograde amnesia (lack of recall) to a visual stimulus, a large memory card depicting a black and white sketch of an object or animal was shown to each patient at each
observation period. The same five memory cards were shown to each patient, but the sequence was randomized.

The patients in this study underwent various kinds of operations, mainly gynecologic, e.g., dilatation and curettage, laparoscopic tubal ligation, cervical conization, radium implantation in the cervix, oopherectomies, and hysterectomies. Some minor non-gynecologic operations, e.g., inguinal hernia repair, thyroidectomy were also included. All patients (except 13 patients whose surgery was cancelled for reasons unrelated to this study) received either general, regional or combination anesthesia.

Each patient was visited 24 h after the operation by the same observer (SPK) and was interrogated. The patient was asked to recollect the pictures shown on the previous day. If he/she could not recollect all of the pictures, he/she was shown ten similar cards (as a composite, including the pictures shown on the previous day). The failure of both the recollection and recognition of the memory cards shown the previous day was considered an indication of drug induced anterograde amnesia.

Postoperative pain medications received by each of these 120 patients were not standard. However, potent narcotic analgesics and tranquilizers were avoided within four hours before the postoperative interrogation.

**Statistical Analysis**

**SEDATION**

One-way analysis of variance was performed using the drug group as the stratifying variable. As part of the analysis, pairwise comparisons of the individual drug groups were examined using a t test to determine if there was a significant difference in the grade of sedation between the two groups. Scheffe confidence levels were used to adjust for the large number of t tests calculated at each time point.

**Table 1. Diazepam Groups—Demography (Mean ± SE)**

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Age (Years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Sex</th>
<th>Mg/Kg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam 10.0 mg</td>
<td>32.7 ± 2.23</td>
<td>60.7 ± 2.56</td>
<td>162.2 ± 1.60</td>
<td>F = 18</td>
<td>0.17 ± 0.01</td>
</tr>
<tr>
<td>Diazepam 15.0 mg</td>
<td>38.3 ± 2.17</td>
<td>73.4 ± 2.48</td>
<td>167.2 ± 2.08</td>
<td>M = 2</td>
<td>0.21 ± 0.01</td>
</tr>
<tr>
<td>Diazepam 20.0 mg</td>
<td>31.7 ± 2.09</td>
<td>72.7 ± 3.33</td>
<td>166.2 ± 2.26</td>
<td>F = 13</td>
<td>0.29 ± 0.01</td>
</tr>
</tbody>
</table>

**Table 2. Lorazepam Groups—Demography (Mean ± SE)**

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Sex</th>
<th>Mg/Kg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam 2.0 mg</td>
<td>32.4 ± 2.18</td>
<td>63.05 ± 2.95</td>
<td>162.6 ± 2.05</td>
<td>F = 13</td>
<td>0.03 ± 0.002</td>
</tr>
<tr>
<td>Lorazepam 3.0 mg</td>
<td>36.4 ± 2.06</td>
<td>73.3 ± 3.72</td>
<td>164.4 ± 2.58</td>
<td>M = 7</td>
<td>0.04 ± 0.002</td>
</tr>
<tr>
<td>Lorazepam 4.0 mg</td>
<td>31.6 ± 1.97</td>
<td>66.4 ± 2.98</td>
<td>164.9 ± 1.77</td>
<td>F = 14</td>
<td>0.06 ± 0.002</td>
</tr>
</tbody>
</table>

**ANTI-RECALL EFFECT**

Due to the binomial nature of the response (did suffer recognition failure, did not suffer recognition failure), chi-square statistics were used to analyse the recognition failure tables. The frequency of recognition failure tables arise from product binomial sampling in which the row totals (number of patients in each treatment) are fixed and the column total (number of patients with recognition failure and number of patients without recognition failure) are not fixed. The null hypothesis for this sampling design is that the proportion response in each row is identical.

When all six groups were compared (30, 60, 120 min), the resulting test statistic was $\chi^2$ with 5 df. Pairwise comparisons of the individual groups were examined using a chi-square statistic to determine if there was a significant difference in the number of patients suffering recognition failure between the two groups. To adjust for the non-independence of the chi-square statistics, each statistic was compared to the $\chi^2$ with 5 df.

When only three groups were compared (90, 150, 180, 240 min), the resulting test statistic is $\chi^2$ with 2 df. Pairwise comparisons of the individual groups were calculated and the resulting test statistics were compared to the $\chi^2$ with 2 df.

**Results**

The demography of the patients in the diazepam and lorazepam subgroups is shown in tables 1 and 2. There were no statistically significant differences except in the weight of the groups (one-way analysis of variance). The largest difference was found between diazepam 10.0 mg versus diazepam 15.0 mg and diazepam 10.0 mg versus lorazepam 3.0 mg groups. All patients were cooperative and pain did not appear to influence their responses.
As expected, the duration of the sedation was shorter after diazepam as compared to lorazepam (fig. 1). While the three doses of diazepam produced dose-related sedation for up to 2 h, the three doses of lorazepam produced approximately the same high grades of sedation, which lasted for a long period (4 h). Compared with 10 mg diazepam, a statistically significant difference ($P < 0.01$) was obtained for 20 mg diazepam at 60 min. The grades of sedation after lorazepam 2, 3, and 4 mg at 120 min were also statistically significant ($P < 0.01$) compared with both 10 and 15 mg diazepam at the corresponding time. Comparison between all other groups, at the corresponding times, revealed no significant differences (fig. 1).

All patients did remember receiving the medication (no retrograde amnesia). The anterograde amnesic effects of diazepam and lorazepam were quite different. As expected, 10.0 mg diazepam produced virtually no amnesia (5 per cent peak frequency). Although higher doses of diazepam did produce some antirecall effect, there was no statistical difference between the peak effects of the three doses of diazepam (fig. 2). The amnesic effects of lorazepam were quite different. There was a latency of about 60 min in both the 3.0 and 4.0 mg dose groups (fig. 2). The peak frequencies obtained at 2 and 3 h following lorazepam 4.0 mg were about 70 and 72 per cent, respectively. With 3.0 mg lorazepam, the peak frequency was about 45 per cent at 2 h. The peak frequency obtained with 2.0 mg lorazepam was about the same as that obtained with 20.0 mg diazepam (30 per cent). Antirecall effect with 3 mg lorazepam at 120 min and 4 mg lorazepam at 60 min were statistically different ($P < 0.05$), compared with 10 mg diazepam at the corresponding times. Similarly, the antirecall effect after 4 mg lorazepam at 120 min was statistically different ($P < 0.01$), compared with both 10 and 15 mg diazepam. Also, the antirecall effect after lorazepam 4 mg at 180 min was significantly different ($P < 0.01$), compared with both 2 and 3 mg lorazepam at the corresponding time (fig. 2).

**Discussion**

The main purpose of premedication is the reduction of perioperative anxiety. Several agents, particularly benzodiazepines, are known for their anxiolytic properties. Many anxious patients, seem to benefit if they do not recall much of the perioperative events. This is most predictably obtained with either intravenous diazepam$^3$ or lorazepam.$^4$ Intravenous diazepam$^3$ provides an antirecall effect which has a short latency, high predictability and rather short duration, whereas intravenously administered lorazepam produces antirecall effect with a longer latency, high predictability and fairly long duration of action.$^4$

Interesting differences were found between the effects of these two commonly used benzodiazepines when administered orally. The dose-response of the sedative effects with diazepam is clear in figure 1. Expected higher blood levels with higher doses should explain this difference. The duration of sedation also appears to be slightly longer with 20 mg diazepam compared with 10 and 15 mg. However, it is evident from the figure that significant sedation cannot be expected with any of the three doses of diazepam after three hours.

The sedative effects of the three standard doses of lor-
azepam show no clear dose-response. Latency (about 60 min), the peak effects (grades 2.85 to 3.25) and the duration of effect (more than four hours) with the three doses appear close. The blood level of lorazepam producing optimum sedative effect is not known. However, from the present observations, it would appear that as far as sedative effects are concerned, there is no real benefit of using a dose higher than 2 mg, when given orally. The authors' clinical experience would tend to support this observation.

Differences were also observed between the antirecall effects of diazepam and those of lorazepam. The finding that 10.0 mg diazepam given orally produces little antirecall effect (peak frequency 5 per cent) was not unexpected, since similar results were found in an earlier unpublished study. On this basis, 10.0 mg diazepam was used as an active placebo (control), and all other observed effects were compared with the effect of 10.0 mg diazepam at the corresponding time.

The latency of the antirecall effect of both diazepam and lorazepam appears to be similar (30–60 min). The peak antirecall effects of various doses of both diazepam and lorazepam are quite different and clear dose responses are obvious in figure 2. The peak antirecall effect with the highest dose of diazepam (50 per cent) is about the same as that with the lowest dose of lorazepam studied. A frequency of 30 per cent antirecall effect, may not be clinically significant. This is also less than the peak antirecall frequency after 0.6 mg intravenous scopolamine (50 per cent).³

The peak antirecall effect of both lorazepam 3 and 4 mg (45 and 72 per cent, respectively) appears both statistically and clinically significant. Thus, if antirecall effect is desired (rather than only sedation) there is a clear justification for using higher doses of lorazepam. The duration of this antirecall effect is quite long. The frequency of antirecall effects is still 40 and 22 per cent at 4 h after 4 mg lorazepam and 3 mg lorazepam, respectively. As was found when given intravenously,³ the sedative and antirecall effects of neither diazepam nor lorazepam are parallel. This might indicate a differential depressant effect of benzodiazepines on various areas of the brain. Although the antirecall effects of oral versus intravenously administered diazepam³ are remarkably different, this is not the case for 4.0 mg lorazepam. The drug pharmacokinetics would explain these observations. Baird and Hailey⁴ showed that the peak blood level of intravenous diazepam 10–20 mg varies from 0.8–1.1 µg/ml during the first half hour. It is known that the duration of amnesia after intravenous diazepam is about 30 min.³ After oral administration of 10 mg diazepam,³ however, a peak blood level of only 0.3 µg/ml is obtained in 90 min. This, clearly, is not sufficient to produce a significant antirecall effect. Dundee et al.⁷ measured plasma levels of lorazepam following oral, intramuscular and intravenous administration of 4.0 mg. They found that the blood level of lorazepam reached a peak at 90 min after oral administration, 120 min after intramuscular administration and immediately (first sampling at 2.5 min) after intravenous administration. However, irrespective of the route of administration, the blood level of lorazepam was 0.05–0.06 µg/ml by about 90 min. Almost the same blood level persisted for another 4–5 h. This finding does explain the latency of the effect after oral administration (60 min) and also the similar peak frequency and the duration of the antirecall effect after 4.0 mg lorazepam given either orally or intravenously. However, the blood level alone does not explain the relatively long latency (15–30 min) after intravenous administration.⁸ Korttila et al.⁸ recently reported no statistically significant amnesia after intramuscular administration of approximately 4.0 mg lorazepam. They made their observations about 90 min after the drug administration, possibly before the peak effect was achieved.

There is no controlled study of the antirecall effect after chronic administration of diazepam or lorazepam. However, clinical impression would lead us to believe that a higher blood concentration in these patients⁹ does not produce significant antirecall effects. The pharmacologic mechanism of this is not understood.

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