NITRAZEPAM IN PREMEDICATION

BY

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SUMMARY
The sedative effects of nitrazepam in a dose of 5 mg and 10 mg have been compared with Mandrax, a combination of methaqualone 250 mg with diphenhydramine 25 mg. Studies were carried out in gynaecological patients undergoing minor surgical operations using the scoring system previously described. The degree of sedation obtained after administration of the two dose levels of nitrazepam was comparable to that obtained after the administration of Mandrax and the changes in heart rate and blood pressure were similar. There was a significantly higher incidence of postoperative emetic sequelae with the larger dose of nitrazepam.

Among the variety of drugs studied in the search for the ideal premedicant agent have been those of the benzodiazepine group. These are claimed to have a specific anxiolytic effect and chlordiazepoxide and diazepam in small doses are used in the treatment of anxiety states. The use of chlordiazepoxide as a pre-anaesthetic medication was reported by Brandt, Lui and Briggs (1962) and diazepam was used by Brandt and Oakes (1965) and Tornetta (1965). Both drugs were studied by Haslett and Dundee (1968) and their properties compared with other groups of drugs commonly used in premedication. Murray, Bechtold and Berman (1968), in a study of oral psychosedative drugs for pre-anaesthetic medication, concluded that it was difficult to detect sedative activity unless drowsiness was also produced. In this study we have, therefore, chosen nitrazepam (Mogadon; Roche), a member of the benzodiazepine group commonly used as a hypnotic, and compared its activity with that of Mandrax (Roussel) with which we have previously had considerable experience. Since nitrazepam is recommended as a hypnotic in a dose of 5 or 10 mg we compared each of these doses with our standard drug.

METHOD
The method of study was that previously described (Nisbet and Norris, 1963) and again by Norris and Telfer (1968, 1969). All measurements were made on patients undergoing minor gynaecological procedures. The patients were otherwise healthy and were studied from one ward unit. A total of 150 patients was studied; 50 were given Mandrax one tablet, 50 nitrazepam one tablet (5 mg) and 50 nitrazepam two tablets (10 mg). In order to satisfy the requirements for a double-blind trial, when only one tablet of the active drugs was used a placebo tablet (lactose) was included. This means that each patient received two tablets with a sip of water normally at 8 a.m., the theatre operating list being due to commence at 9 a.m. The assessment of sedative activity was made using the scoring system previously described and in a few cases the arterial pulse wave velocity was also measured.

RESULTS
From table I it can be seen that the patients studied were comparable in age but that those patients receiving nitrazepam 10 mg were significantly lighter in weight than those receiving one tablet of Mandrax. This chance finding despite the randomization of the series, while of statistical significance, we feel to be of no clinical significance in view of the small actual weight difference involved and the fact that there is little evidence to show that, even if it were possible, relating the dose of this type of drug to body weight is of any value (Campbell, Masson

and Norris, 1965; Morrison, Hill and Dundee, 1968).

It can be seen that the mean time from administration of the drug to the time when readings were taken in the anaesthetic room is similar for all three groups. In addition, adequate sedation was provided over a period of 1–5 hours in each group.

**Sedation.**

Table II shows the sedation scores obtained with the three drug groups. There is no significant difference in the mean scores obtained or in the proportions of patients considered to show good, fair, or poor sedation.

**Arterial pulse wave velocity.**

This part of the study is still in a preliminary stage and the results are not reported here. The performance of this test had no statistically significant effect on the sedation scores obtained.

**Circulatory side effects.**

The changes in systolic and diastolic blood pressure and in heart rate from the readings taken the day before operation to those taken in the immediate pre-operative period are shown in table III. The changes following each drug are not great and are not significantly different one from the other. Slight falls in blood pressure of the order noted here are to be expected when patients are well sedated and such changes have been noted in our previous studies.

**Postoperative sequelae.**

Table IV shows the incidence of postoperative emetic sequelae in the period up to 9 p.m. when the nursing staff change, i.e. a period of 9–12 hours postoperatively. The incidence of postoperative restlessness is similarly recorded. There is no significant difference between the drug groups. The higher incidence of postoperative emetic sequelae after nitrazepam 10 mg was a surprise finding and this figure is significantly higher than after 5 mg of the drug. In our studies we have not recorded the duration of anaesthesia nor the total amount of halothane administered as we rely on randomization to level out any differences between cases. There may be additional factors unaccounted for in this respect but the study was designed principally to assess the sedative effects of the drugs.

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**Table I**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean age (yr)</th>
<th>Mean weight (lb.)</th>
<th>Mean time from administration of drug to test (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandrax tab. 1</td>
<td>34.72</td>
<td>138.4</td>
<td>156.9</td>
</tr>
<tr>
<td>Nitrazepam 5 mg</td>
<td>34.74</td>
<td>134.0</td>
<td>158.5</td>
</tr>
<tr>
<td>Nitrazepam 10 mg</td>
<td>33.3</td>
<td>126.9</td>
<td>154.0</td>
</tr>
</tbody>
</table>

Weights: Mandrax v. nitrazepam 10 mg; $t = 2.28$; $P < 0.05$.

**Table II**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean score</th>
<th>Good sedation (7-10)</th>
<th>Fair sedation (5, 6)</th>
<th>Poor sedation (0-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandrax tab. 1</td>
<td>6.48 ± 2.27</td>
<td>28</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Nitrazepam 5 mg</td>
<td>6.46 ± 2.16</td>
<td>24</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Nitrazepam 10 mg</td>
<td>7.14 ± 2.06</td>
<td>32</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table III**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean change in systolic BP (mm Hg)</th>
<th>Mean change in diastolic BP (mm Hg)</th>
<th>Mean change in heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandrax tab. 1</td>
<td>119 – 112 = –7 66.5 – 65.2 = –1.3</td>
<td>83 – 84 = + 1</td>
<td></td>
</tr>
<tr>
<td>Nitrazepam 5 mg</td>
<td>122 – 112 = –10 66.2 – 66.4 = + 0.2</td>
<td>83 – 81 = –2</td>
<td></td>
</tr>
<tr>
<td>Nitrazepam 10 mg</td>
<td>116 – 106 = –10 63.8 – 65 = + 1.2</td>
<td>82 – 76 = –6</td>
<td></td>
</tr>
</tbody>
</table>

**Table IV**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Emetic sequelae</th>
<th>Restlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandrax tab. 1</td>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>Nitrazepam 5 mg</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Nitrazepam 10 mg</td>
<td>34%</td>
<td>24%</td>
</tr>
</tbody>
</table>
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DISCUSSION

These studies suggest that nitrazepam in doses of either 5 or 10 mg will produce sedation roughly equivalent to that obtained with one tablet of Mandrax. The figures show some increase in sedative activity with the higher dose of nitrazepam but in the numbers tested this difference is not statistically significant. Again the higher dose of nitrazepam shows a higher incidence of postoperative emetic sequelae and restlessness, and since the sedation achieved was not significantly greater than with the smaller dose, it would seem that 5 mg is preferable.

It appears, therefore, that the use of nitrazepam, belonging as it does to a class of drugs claimed specifically to relieve anxiety, produces sedation no better and no worse than a drug used specifically as a hypnotic. While these conclusions apply to the series tested, viz. patients undergoing minor gynaecological procedures, it is considered that the potential advantages of methaqualone in potentiating codeine (Cass and Fredrik, 1958; Becker and Hayes, 1958) and the anti-emetic effects of diphenhydramine may show to greater advantage in a wider range of cases.

REFERENCES


NITRAZEPAM EN PREMEDICATION

SOMMAIRE

Les effets sédatifs d'une dose de 5 et 10 mg de nitrazepam ont été comparés avec Mandrax, une association de methaqualone 250 mg avec diphenhydramine 25 mg. Les études ont été faites chez des patientes gynécologiques, subissant des interventions chirurgicales mineures, en utilisant le système de scores décrit antérieurement. Le degré de sédation obtenu après l'administration des deux doses différentes de nitrazepam, fut comparable à celui obtenu à l'aide de Mandrax, avec similitude des modifications de la fréquence cardiaque et de la pression sanguine. Les vomissements postopératoires furent significativement plus fréquents avec la dose la plus élevée de nitrazepam.

PRÄMEDIKATION MIT NITRAZEPAM

ZUSAMMENFASSUNG