BENZODIAZEPINE PREMEDICATION IN MINOR DAY-CASE SURGERY: COMPARISON OF ORAL MIDAZOLAM AND TEMAZEPAM WITH PLACEBO

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It is common anaesthetic practice not to offer premedication to day-case patients, in the belief that recovery is prolonged unnecessarily [1]. However, it is the author's experience that these patients frequently show high levels of anxiety on arrival in the anaesthetic room, suggesting a need for an oral premedicant drug with rapid onset and short duration of action.

Currently, benzodiazepines are the most popular premedicant drugs. Temazepam has been shown to be suitable for day-case patients [2,3]. It is absorbed rapidly when given by mouth, with a biological half-life of 3–6 h [4], and undergoes glucuronidation to inactive metabolites. Introduced initially as a water soluble i.v. or i.m. preparation with a half-life of 2–3 h [5], midazolam has potent amnesic and anxiolytic properties [6,7]. It is available in tablet form, but has not yet been granted a product licence. Limited clinical trials indicate a potential suitability for day-case surgery [8,9].

The aim of the present study was to evaluate premedication with oral midazolam 15 mg and temazepam 20 mg compared with placebo in the day-case patient. Temazepam has been used widely in a dose of 20 mg for day-case premedication [2]. The available preparation of oral midazolam was a 15-mg tablet with a break bar. Preliminary work suggests that temazepam 20 mg is comparable to midazolam 15 mg [10].

PATIENTS AND METHODS

Permission for the study was obtained from the Department of Health and Social Security and the local Ethics Committee. Ninety male and female patients, Grades ASA I and II, were studied during minor surgery as day- or short-stay patients. There were 30 patients in each group (age range 18–65 yr), the majority undergoing minor gynaecological surgery. Each patient gave written informed consent. Grossly obese and pregnant patients were excluded, as were those who had taken sedative drugs within the previous 72 h.

A brief history concerning previous general anaesthesia and premedication was elicited by the author, who performed all pre- and postoperative assessments. Measurements of heart rate, arterial pressure (Copal, printing, auto-inflation digital sphygmomanometer UA-251) and oral temperature (Life Watch LT-8) were made before operation, in the anaesthetic room and at 1 h and 3 h after operation. Anxiety was assessed using a 10-cm linear analogue scale (LAS) before premedication and again in the anaesthetic room. Sedation was assessed also at this time and graded as nil, mild, moderate or asleep. Awake patients were asked if they had slept or dozed since receiving premedication. Each patient was shown

SUMMARY

Ninety day-case or short stay patients were allocated to three groups in a double-blind study. The groups received oral midazolam 15 mg, oral temazepam 20 mg or placebo approximately 1 h before surgery. Midazolam was superior to temazepam regarding anxiolysis, sedation and amnesia, but temazepam was superior to placebo. However, delay in immediate and late recovery occurred significantly more often in the patients receiving midazolam than in those receiving temazepam or placebo.
a memory card and asked to recall it 3 h after operation. In the anaesthetic room each patient was questioned also on side effects, notably: headache, nausea and vomiting, dizziness and dryness of the mouth. The presence or absence of side effects was elicited again at 1 and 3 h after operation.

After baseline assessments had been obtained, each patient received premedication consisting of a white tablet and a green capsule at approximately 1 h before operation. This comprised an active and a dummy preparation for the two study groups and two dummy preparations for the placebo group.

Anaesthesia was standardized as far as possible and consisted of induction with a sleep dose of thiopentone and maintenance with nitrous oxide and halothane in oxygen, using the minimum concentration required of the volatile agent. For each patient, the maximum concentration of halothane was noted. The following were recorded: time from premedication to induction of anaesthesia; time from induction to end of surgery; time from end of surgery to eliciting a correct verbal response from the patient (TCR).

Two specialized tests were used to assess recovery. The Maddox Wing Test [11] records, in prism dioptres, the divergence of the eyes at rest. The digit-symbol substitution test [12] was used to assess hand co-ordination and mental function. The number of correct substitutions made in 2 min was scored. The tests were introduced and practised at the investigator's initial visit, and repeated at 1 h and 3 h after operation.

At the final visit (3 h after operation) the patient was questioned regarding memory for: (A) taking premedication tablets; (B) journey to theatre; (C) picture card; (D) i.v. injection; (E) location on awakening from anaesthesia. The patient was required to demonstrate ability to walk unaided.

Each patient was asked to assess quality of premedication, graded as very good, good, adequate or poor.

### RESULTS

In a preliminary survey, 70 of 105 patients (66.6%) felt that they would benefit from premedication; these are included in the 90 patients assessed.

Patient characteristics were similar in all three groups (table I). The majority of operations performed were dilatation and curettage: 80% of the placebo and temazepam groups and 73% of the midazolam group. Other procedures included minor orthopaedic surgery and cystoscopy. The distribution of operations was similar in all three groups.

**Anxiolysis**

Initial assessment of anxiety was comparable in the three groups (table II). However assessments before induction showed significant decreases in mean anxiety scores in the temazepam and midazolam groups compared with the placebo group. Within-group comparisons showed a marked decrease in both active treatment groups.

**Sedation**

Significantly more midazolam and temazepam patients were found to be moderately sedated or asleep compared with placebo and there was a significant difference between the two active treatment groups (table III). Three of five sleeping midazolam patients were difficult to rouse and were considered to be sedated excess-

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**Table I. Demographic data (mean (SEM)) for the three groups of patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 30)</th>
<th>Temazepam (n = 30)</th>
<th>Midazolam (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.9 (2.1)</td>
<td>38.2 (1.9)</td>
<td>36.8 (1.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.8 (1.3)</td>
<td>63.2 (2.4)</td>
<td>65.0 (1.9)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>29/1</td>
<td>29/1</td>
<td>28/2</td>
</tr>
</tbody>
</table>

**Table II. Assessment of anxiety using LAS (mean (SEM)).**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 30)</th>
<th>Temazepam (n = 30)</th>
<th>Midazolam (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before premedication</td>
<td>42.3 (3.3)</td>
<td>46.4 (3.9)</td>
<td>44.3 (4.5)</td>
</tr>
<tr>
<td>Before induction</td>
<td>48.2 (4.8)</td>
<td>28.5 (4.3)</td>
<td>25.2 (4.2)</td>
</tr>
</tbody>
</table>
BENZODIAZEPINE PREMEDICATION

TABLE III. Observer assessment of sedation before induction of anaesthesia. *P < 0.05 (combined categories compared with placebo (χ² test)); †P < 0.05 placebo compared with each active treatment group (χ² test)

<table>
<thead>
<tr>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No sedation</td>
<td>25</td>
<td>83</td>
<td>10</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Mild sedation</td>
<td>5</td>
<td>17</td>
<td>16</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>Moderate sedation</td>
<td>0</td>
<td>—</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Asleep</td>
<td>0</td>
<td>—</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Slept/dozed on ward</td>
<td>2</td>
<td>2</td>
<td>15</td>
<td>50</td>
<td>23</td>
</tr>
</tbody>
</table>

TABLE IV. Anaesthetic data (mean (SEM)). *P < 0.05 (Student's t test); †P = 0.05 (Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Placebo (n = 30)</th>
<th>Temazepam (n = 30)</th>
<th>Midazolam (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of thiopentone (mg)</td>
<td>309 (7.6)</td>
<td>289 (8.0)</td>
</tr>
<tr>
<td>Premedication to induction (min)</td>
<td>74 (3.1)</td>
<td>80 (2.4)</td>
</tr>
<tr>
<td>Induction to end of surgery (min)</td>
<td>15 (0.4)</td>
<td>18 (1.8)</td>
</tr>
<tr>
<td>End of surgery to patient's correct response (min)</td>
<td>6 (0.9)</td>
<td>8 (0.9)</td>
</tr>
</tbody>
</table>

Anaesthetically. More patients in the two active treatment groups had slept or dozed on the ward than in the placebo group.

Anaesthetic data

Patients in both active treatment groups required smaller doses of thiopentone and halothane than placebo patients, but this was significant only for thiopentone in midazolam patients (table IV). The times from premedication to induction and the duration of surgery were comparable in all three groups. However, awakening from anaesthesia was significantly longer in the midazolam group compared with placebo and temazepam groups.

Cardiovascular data

Mean baseline measurements of heart rate and systolic arterial pressure were comparable in the three groups (table V). There was an increase in heart rate before induction in all groups which was significant in the placebo group. One hour after anaesthesia, mean heart rate was significantly lower in temazepam and placebo groups and similar to baseline values in all groups at 3 h. Mean pre-induction measurement of systolic arterial pressure was greater than baseline in the placebo group and significantly lower in the midazolam group.

Tests of recovery

There was significantly more eye divergence in midazolam patients than in placebo patients at 1 h after anaesthesia and in both active treatment groups compared with placebo at 3 h after operation (table VI). Mean scores for the digit-symbol substitution test were significantly decreased in all groups at 1 h after operation, but were similar to baseline values at 3 h, except in the midazolam group (table VII). At 1 h, two patients in each active treatment group were too drowsy to perform the test, and at 3 h one midazolam patient felt too unwell to complete the test. There were no differences between the groups in ability to walk unaided at 3 h after operation, one temazepam and six midazolam patients being unable to walk without support.
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The main objectives of premedication are relief of anxiety together with some degree of sedation. In addition to these properties, any drug prescribed for day-case patients must have rapid onset of action and must not prolong recovery or produce impairment of psychomotor skills [1,15,16].

Diazepam, lorazepam, flunitrazepam and oxazepam have been used as premedication for minor surgery [2,17], but have been found to be inappropriate for day-case patients, because of slow onset of action and prolonged effect resulting partly from formation of active metabolites. Of the benzodiazepines with a short elimination half-life, triazolam has been found to be a poor anxiolytic, and results in impaired psychomotor performance at 3 h after operation [18]. Currently, temazepam is the most popular benzodiazepine for day-case patients, producing peak plasma concentrations in 20–40 min and having a short elimination half-life of 3–6 h, with no active metabolites [19]. Midazolam, with an even shorter half-life for both oral and parenteral preparations [20], appears to be a promising alternative to temazepam.

The results of the present study showed that both midazolam and temazepam produced anxiety compared with placebo, midazolam being superior. Both drugs were also more sedative than placebo, but three of the midazolam patients were considered to be too heavily sedated. Observations by nurses on the ward indicated rapid onset of action of midazolam, many patients falling asleep within 15 min of premedication.

Midazolam was found to produce marked anterograde amnesia compared with both temazepam and placebo. This has been found also with i.m. midazolam [6,7] and in sedation techniques using i.v. midazolam [21–23].

Midazolam and temazepam patients did not show a significant increase in the number of side-

### Table VII. Digit–symbol substitution scores (mean (SEM)).*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 30)</th>
<th>Temazepam (n = 30)</th>
<th>Midazolam (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>67 (3.6)</td>
<td>60 (3.3)</td>
<td>67 (3.2)</td>
</tr>
<tr>
<td>1 h post-op.</td>
<td>55 (3.2)†</td>
<td>45 (2.9)†</td>
<td>48 (3.3)†</td>
</tr>
<tr>
<td>3 h post-op.</td>
<td>70 (3.7)</td>
<td>61 (3.0)</td>
<td>63 (3.1)†</td>
</tr>
</tbody>
</table>

*P < 0.05 (t test compared with placebo); †P < 0.05 (Wilcoxon matched pair signed ranks lest)

### Amnesia

All patients recollected taking the premedication tablets, indicating that there was no retrograde amnesia (table VIII). Significant numbers of midazolam patients were found to be amnesic for events B, D, E and especially for C, compared with placebo and temazepam patients.

### Side-effects

The incidence of minor side-effects was similar in all groups. The only significant side-effect was nausea in eight patients who received temazepam (P < 0.05, χ² test) compared with the placebo group.

### Patient preference

Significantly more patients in both active treatment groups rated their premedication as good or very good compared with placebo patients. There were more poor ratings in the placebo group than in each of the active treatment groups (table IX).

### Discussion

The majority of patients entering hospital for major or minor surgery are anxious or afraid [13,14]. Sixty-six percent of day case patients questioned in the present study expressed a positive need for premedication.

### Table VIII. Assessment of amnesia. Temazepam v. placebo: B, C, D, E ns; midazolam v. placebo (B, C, D, E) and midazolam v. temazepam (B, C, D, E): *P < 0.05 (χ² test)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 30)</th>
<th>Temazepam (n = 30)</th>
<th>Midazolam (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Complete</td>
<td>None</td>
</tr>
<tr>
<td>(A) Taking tablets</td>
<td>30</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>(B) Journey to theatre</td>
<td>30</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>(C) Card</td>
<td>30</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>(D) i.v. injection</td>
<td>30</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>(E) Recovery ward</td>
<td>30</td>
<td>—</td>
<td>5</td>
</tr>
</tbody>
</table>
effects compared with placebo patients, although more actively premedicated patients complained of dizziness. This is a well recognized side-effect of benzodiazepines [18].

In both immediate recovery after operation and the three tests of late recovery at 3 h, midazolam patients showed delayed return to preoperative status, but there was little difference between placebo and temazepam patients. Ability to walk unaided proved to be an insensitive test of return to street fitness. The bullseye walking test [24] may be a more sensitive test for day-case patients. The slower recovery in the midazolam patients was disappointing in view of its short elimination half-life. This lack of correlation between half-life and clinical recovery has been found also when i.v. midazolam and diazepam are compared in sedation techniques [21,25]. Midazolam patients required significantly smaller doses of thiopentone than placebo or temazepam patients. Previous studies have shown that, for short procedures, the effects of i.v. induction agents are longer lasting than those of the volatile agent [26]. Therefore, in this study the delayed recovery in the midazolam patients presumably resulted from the effects of midazolam itself.

Significantly more patients in the active treatment groups rated their premedication as good or very good compared with placebo. The amnesia provided by the premedication was liked by those patients who experienced it. Thirty-seven percent of the placebo group requested the same premedication again, although only 20% rated premedication as good or very good. This favourable placebo response was probably a result of the combination of receiving tablets and the extra patient attention involved in carrying out the assessments.

In conclusion, this study showed the anxiolytic and sedative properties of midazolam were superior to those of temazepam or placebo, with a rapid onset of action which is appropriate for day-case patients, but the delay in recovery in the midazolam group was considered to be undesirable in this situation. Midazolam shares the variability in response characteristic of the benzodiazepines, especially in this age group of patients [26]. Midazolam 15 mg tablets can be broken easily into 7.5 mg tablets, which might provide a more appropriate dose for patients weighing less than 60 kg. However, in a study [27] comparing oral midazolam 15 mg and 7.5 mg with placebo, the lower dose did not produce significantly more anxiolysis and sedation than placebo. Both doses of midazolam resulted in significant impairment of performance in the digit-symbol substitution test for duration of the investigation, which finished at 2 h after operation. The results of the present trial indicate that oral midazolam 15 mg is less suitable for day-case patients than temazepam 20 mg, but would be an excellent premedication for in-patients with high patient acceptability.

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REFERENCES


