EFFECTS OF TEMAZEPAM PREMEDICATION ON COGNITIVE RECOVERY FOLLOWING ALFENTANIL-PROPOFOL ANAESTHESIA

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Anaesthesia for day case surgery requires a technique which allows rapid recovery and a swift return to street fitness [1]. The i.v. induction agent propofol and the short acting opioid alfentanil have been shown to produce rapid recovery and minimal residual effects [2-5]. They would appear, therefore, to be ideally suited for day-case anaesthesia. However, recent attention has focused on the degree of preoperative anxiety in day-case patients and it has been suggested that temazepam, a short acting benzodiazepine, produces satisfactory anxiolysis without altering long term recovery [6].

A recent review of the literature identified no study which had used computerized assessments to measure cognitive recovery from anaesthesia. However, in a recent study with healthy volunteers, a series of microcomputerized cognitive tasks was able to measure a profile of cognitive decrements following hyoscine [7] which previous work had failed to identify. This suggests that computerization may increase greatly the sensitivity of cognitive assessment and may potentially identify effects of anaesthesia and premedication which have been overlooked previously. The present study was designed to use microcomputerized tasks to identify the degree of impairment in cognitive function on recovery from propofol-alfentanil anaesthesia and any additional effects of premedication with temazepam 20 mg.

SUMMARY

The effects of temazepam 20 mg and placebo were compared for premedication in patients anaesthetized with propofol and alfentanil and undergoing day surgery. Temazepam 20 mg significantly reduced preoperative anxiety and increased recovery time. A series of computerized cognitive tasks revealed significant deficits in attention and memory following anaesthesia, which were increased in range and magnitude by temazepam, which were apparent 30 min after surgery and had largely, but not completely, recovered at 4 h. This study has demonstrated that computerized cognitive testing can identify a wider profile of impairments produced by temazepam than has been found in previous work using non-computerized techniques.

PATIENTS AND METHODS

The patients studied were ASA I or II females, age 16-75 yr, scheduled for routine minor gynaecological surgery not involving tracheal intubation. Patients with significant cardiovascular disease, a history of allergy, or receiving therapy likely to modify the response to the agents used, were excluded from the study. All patients gave verbal consent to inclusion in the study.

On admission, all patients performed the cognitive tests, and completed the State and Trait scales of the State-Trait Anxiety Inventory (STAI [8]). The STAI was used as it has been found previously to be sensitive to the effects of temazepam as a premedication [9]. The Trait scale of the STAI gives a score which reflects the anxiety-proneness of the individual, while the State scale yields a score reflecting the level of anxiety of the individual at the time of completion.
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of the scale. All the operations were performed during the morning of the day following admission. One hour before surgery, patients completed a further State scale and then received premedication. The hospital pharmacist, who was not involved in the study, had previously allocated them to one of two groups: group 1 received temazepam 20 mg orally and group 2 received an identical placebo capsule. All cognitive assessments were conducted by one of the authors (NP). No maximum number of patients was planned, as many as possible being recruited during a 5-month period. Because of a delay in obtaining matched placebo capsules, the first 26 of the 65 patients were allocated to group 1. This was unknown to the researcher undertaking the cognitive assessments and to those conducting the initial evaluation of data. All testing and initial evaluation of data was conducted double-blind.

On arrival in theatre, all patients completed a further questionnaire immediately before induction of anaesthesia. All anaesthetics were administered by the same anaesthetist (RB). Anaesthesia was induced with alfentanil 10 μg kg⁻¹ i.v. followed by propofol 2 mg kg⁻¹ and maintained with an infusion of propofol 12 mg kg⁻¹ h⁻¹ and alfentanil 0.5 μg kg⁻¹ h⁻¹. All patients received 100% oxygen at a flow rate of 140 ml kg⁻¹ via a Bain circuit. Apnoea of more than 90 s duration occurred following induction in 50% of patients, and was easily managed by manual ventilation. Apnoea did not extend after the end of surgery in any patient and no postoperative respiratory depression occurred. At the end of surgery the infusion was discontinued and the patients transferred to the recovery ward.

The time taken from the end of the infusion to the patient being able to give name, age and ward was recorded. The patients completed the cognitive tests 30 min after the end of the infusion and again 4 h after operation.

All patients were discharged from hospital on the day of operation when both anaesthetist and gynaecologist were satisfied with their condition.

Cognitive Test System

An automated microcomputer-based system for the assessment of drug effects on cognitive function has been developed [10, 11] and shown to have drug sensitivity in both laboratory settings with young volunteers [12] and applied settings with the elderly [13]. A version of the system which has been developed for use with mildly demented patients was the subject of a pilot study to determine its sensitivity in the recovery room [Wesnes, Simpson and Restall, unpublished data]. Twelve patients of both sexes (age range 19–69 yr) performed the tasks in a recovery room a few minutes after waking from a variety of surgical procedures. All were able to perform the tasks, but at a significantly lower level of efficiency than a control group of theatre staff. This pilot study indicated that the system was practical for use in this environment, and suggested that it was sensitive to residual impairments following anaesthesia. The Cognitive Drug Research Cognitive Assessment System, comprising a BBC Master Microcomputer, disk drive, colour monitor and response module, was used, therefore, in the present study. The software was written in BASIC with machine code subroutines included to permit response times to be recorded to the nearest millisecond. All information was presented via the monitor and all responses made by pressing one of two buttons on the response module.

The following tasks were used:

(a) Word recognition: A list of 12 words is presented on the monitor. Afterwards, these 12 words plus 12 new words are presented singly, and the patient indicates whether or not she recognizes each word by pressing either a YES or a NO button.

(b) Picture recognition: The procedure is the same as for word recognition, a series of 14 pictures being presented and 14 distractors included for forced choice recognition.

(c) Memory Scanning Task: A series of three digits is presented for the patient to remember, followed by a series of 18 digits. For each digit in the second series, the patient must identify whether or not it was in the original series and respond by pressing the YES/NO button.

(d) Number Vigilance Task: In this task, a digit is constantly displayed in the right hand side of the screen. A series of digits is displayed in the centre of the screen at a rate of 80 per minute, and the patient is required to press the response button when the digit in the centre matches that displayed on the right.

(e) Choice Reaction Task: Either the word NO or the word YES is presented on the screen and the volunteer has to press, as quickly as possible, either the button marked NO or that marked YES as appropriate. There are 20 trials.
The sequence of the stages of the test administration was:

- Presentation of word list — 30 s
- Immediate recognition testing of word list — 30 s
- Presentation of picture sequence — 60 s
- Number Vigilance Task — 75 s
- Choice Reaction Task — 75 s
- Memory Scanning — 45 s
- Delayed recognition testing of word list — 30 s
- Recognition testing of picture sequence — 60 s

The total time to complete the computerized tests varied between 10 and 15 min.

During the course of the trial, it was decided to introduce additional recognition testing to be completed by all new recruits. After the first postoperative performance of the tests, a further list of words and a series of pictures were presented and recognition testing was carried out on these immediately before the final test session.

Statistical analysis procedures

A test for normality [14] was used to determine the suitability of parametric analysis. Statistical comparisons between the groups were made with t tests if there were single data points per volunteer, or using planned t ratios [15] where repeated measures were made, as with performance measures. Split plot ANOVA, using the unweighted means solution because of the different sizes of the two groups, were conducted both on the complete set of the performance data and on difference from preoperative baseline scores. The planned t ratios utilized the appropriate error terms from the ANOVA. Where parametric analysis was not appropriate, Mann–Whitney and Wilcoxon testing was used.

RESULTS

Sixty-five patients entered the study and were given the opportunity to withdraw at any time. Six patients in the placebo group were withdrawn: three were too sleepy to perform the 30-min assessment, and three were not available for the 4-h assessment. Four patients in the temazepam group were withdrawn: two were not awake for the 30-min assessment, one was unwell 30 min after operation and one was not available for the 4-h assessment. No patient withdrew because of nausea or vomiting. Nineteen patients receiving placebo and 36 receiving active medication satisfactorily completed all stages of cognitive testing.

The two groups were matched for age and weight (table I). On admission, there was no significant difference between the two groups for either State or Trait scale scores of the STAI. The infusion times for the two groups were not significantly different (table II). The first postoperative assessment took place, on average, at 35.3 min (range 19–53 min) in the placebo group and 36.9 min (range 22–54 min) in the temazepam group. The second assessment took place, on average, at 243.7 (range 224–262) min in the placebo group and at 243.9 (range 234–268) min in the temazepam group. The two groups did not differ significantly in the times that these assessments were made.

Effects of temazepam on anxiety and immediate recovery

Figure 1 shows the effect of premedication on the anxiety levels measured using the State scale of the STAI. There was no difference between the groups before medication, whereas before induction the placebo group had a significantly higher level of anxiety than the temazepam group ($t(90) = 2.13, P < 0.05$). Further, testing over time indicated that the slight reduction in anxiety following temazepam was not significant, whereas the increase in anxiety in the placebo group was significant ($t(45) = 2.43, P < 0.02$).
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Early recovery was significantly longer in the temazepam group, both in time to eye opening ($t(52) = 3.56, P < 0.01$) and in time to giving name, age and ward ($t(52) = 3.97, P < 0.01$) (table II).

Effects on cognitive function

Application of normality testing indicated normality of distribution for all data sets except for that of the accuracy of picture recognition (table III). Thus non-parametric statistical procedures were used only for this measure.

The effects of anaesthesia were evaluated by analysing the performance of the placebo group over time (table IV). At 30 min after surgery, significant decrements were found in the total number of pictures correctly identified, the speed of picture recognition, the speed of number matching and choice reaction time (figs 2–4). At 4 h after operation, only the speed of number matching was still impaired, although the accuracy of delayed recognition had decreased from the 30 min level, the only measure of any task in each group to do this.

In contrast, the temazepam group showed significant decline in all tasks in the speed of performance 30 min after operation, and decreases in the numbers of items identified correctly in the verbal and picture tasks. These impairments were highly significant (table IV).

Comparing the two groups at 30 min, the temazepam group performed consistently worse than placebo (table V). They were significantly slower at number matching, choice reaction, memory scanning, immediate verbal recognition and delayed verbal recognition. Significant impairments were found also in the total number of items recognized correctly on immediate verbal recognition and picture recognition. The impairments in accuracy of delayed verbal recognition and the speed of picture recognition just failed to reach statistical significance ($P < 0.1$). None of these differences was significant at the 4-h post-operative assessment.

An additional test was performed by 15 patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo ($n = 19$)</th>
<th>Temazepam ($n = 36$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-dose 30 min 4 h</td>
<td>Pre-dose 30 min 4 h</td>
</tr>
<tr>
<td>Immediate verbal recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number correct (total = 24)</td>
<td>21.53 (1.3) 20.74 (2.6) 21.47 (1.9)</td>
<td>21.78 (1.4) 19.19 (2.3) 20.64 (1.9)</td>
</tr>
<tr>
<td>Speed (ms)</td>
<td>811.8 (385) 798.9 (190) 688.2 (126)</td>
<td>784.7 (191) 1013.8 (293) 773.0 (200)</td>
</tr>
<tr>
<td>Delayed verbal recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number correct (total = 24)</td>
<td>21.21 (2.4) 20.89 (1.7) 19.37 (3.2)</td>
<td>20.39 (1.9) 18.75 (2.5) 18.86 (2.0)</td>
</tr>
<tr>
<td>Speed (ms)</td>
<td>854.5 (338) 837.9 (228) 773.5 (165)</td>
<td>866.1 (230) 1021.9 (254) 851.6 (133)</td>
</tr>
<tr>
<td>Picture recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number correct (total = 28)</td>
<td>26.58 (2.0) 25.05 (2.1) 26.05 (1.9)</td>
<td>26.89 (1.2) 23.31 (3.4) 25.92 (2.2)</td>
</tr>
<tr>
<td>Speed (ms)</td>
<td>723.5 (136) 827.6 (176) 745.2 (136)</td>
<td>736.1 (116) 916.7 (249) 778.2 (157)</td>
</tr>
<tr>
<td>Number matching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed (ms)</td>
<td>368.4 (56) 434.8 (87) 404.1 (51)</td>
<td>362.4 (47) 460.9 (69) 405.9 (57)</td>
</tr>
<tr>
<td>Choice reaction</td>
<td></td>
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<tr>
<td>Speed (ms)</td>
<td>411.7 (57) 460.1 (78) 433.9 (60)</td>
<td>410.6 (45) 498.3 (100) 444.8 (60)</td>
</tr>
<tr>
<td>Memory scanning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed (ms)</td>
<td>606.7 (114) 608.2 (119) 586.6 (118)</td>
<td>605.6 (139) 704.2 (157) 629.1 (124)</td>
</tr>
</tbody>
</table>
TABLE IV. Significant impairments in performance compared with baseline

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>Temazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>P</td>
</tr>
<tr>
<td>Immediate verbal recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>30 min</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Speed</td>
<td>30 min</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Delayed verbal recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>30 min</td>
<td>&lt; 0.0097</td>
</tr>
<tr>
<td>Speed</td>
<td>30 min</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Picture recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>30 min</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Speed</td>
<td>30 min</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Number matching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed</td>
<td>30 min</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Choice reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed</td>
<td>30 min</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Memory scanning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed</td>
<td>30 min</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Fig. 2. Cognitive effects of anaesthesia, with (---) or without (—) temazepam premedication. Speed of performance of tasks involving differing levels of information processing (means and SEM bars).

in the temazepam group and 20 in the placebo group. This measured their ability, 4 h after operation, to recognize information presented 40 min after operation. Both groups performed only minimally above chance levels for verbal recognition and, while performance on the picture recognition task was better, it was considerably inferior to performance at 30 min after operation. However, there were no significant differences between the groups in any of these scores.
Relationship between infusion time and time to eye opening

The time of infusion was correlated with the early waking times. For the placebo group significant negative correlations were found between infusion times and both time to eyes open ($r = -0.49$, df = 18, $P < 0.05$) and time to state name, age and ward ($r = -0.46$, df = 18, $P < 0.05$). For the temazepam group, the corresponding coefficients were $r = -0.26$ (df = 33, $P < 0.1$) and $r = -0.05$, respectively.

Although the difference in the average duration of infusion time for the placebo and temazepam groups (7.3 and 9.7 min, respectively) was not significant, it was decided to investigate its relevance. The difference was the result, not of a general trend but, as an inspection of the data indicated, of a few volunteers in the temazepam group having longer infusion durations than was typical. Removal of the six temazepam patients who had longer operation times than any in the placebo group decreased the average for the group to 7.48 min. It was decided to determine if the
pattern of the results had been influenced by the inclusion of these six patients. Their data were removed and a number of parameters re-examined. Time to eyes open was unaffected (11.8 min for the 29 volunteers compared with 11.5 min for the whole group), as was time to state name, age and ward (13.45 min, compared with 13.48 min when the six patients were excluded). Finally, the cognitive data were re-analysed with the six patients excluded, but an identical pattern of changes between and within the groups was detected. It is safe to conclude that the inclusion of the patients with the longer induction times has no bearing on the outcome of the study results and does not warrant their exclusion from the analysis.

**DISCUSSION**

This study has shown that anaesthesia produced a clear pattern of cognitive decrements which was more extensive when temazepam 20 mg was given as premedication. At 30 min after anaesthesia, information processing was impaired, as indicated both in the increased time to detect the targets in the number matching task, representing decreased vigilance, and the slowing of choice reaction performance, representing slowing of the processing of the stimuli and the selection of relevant responses. Impaired memory was seen in the decreases in the speed and accuracy of object recognition. At 4 h after operation these impairments were reduced by varying amounts, performance on several measures returning to the preoperative levels. However, in the absence of a control group and an opportunity to conduct practice sessions on the tasks, it is not possible to specify whether these apparent recoveries by 4 h were solely a recovery from drug-induced impairments or were partially the result of improvement in efficiency resulting from repeated performance on the tasks. Nonetheless, performance on two tasks did not recover by 4 h (speed of vigilance and accuracy of delayed verbal recognition).

A further effect detected was the failure of both groups to show long term verbal learning for the words presented at 40 min after operation. The inclusion of this testing in a subset of patients was made because of the frequently observed phenomenon that, soon after surgery, patients may answer questions and appear coherent and alert, but later they deny any knowledge of the episode. Clear evidence of verbal learning was evident at 30 min after operation, delayed verbal recognition being at the same level as immediate recognition for both groups at this time, indicating that such information could be maintained over a 7–10 min period. Thus anaesthesia appeared to produce a selective “long term” anterograde amnesia which was not indicated over an “intermediate term”, and consequently reflected a failure to store or retrieve information rather than a failure to attend to or to register the information. A practical implication of this is that any precautionary information (e.g. avoiding driving) which is given during the immediate postoperative period is unlikely to be retained.

Temazepam significantly affected performance in all the tasks, either by increasing the decrements following anaesthesia at 30 min, or by impairing aspects of performance which were unaffected by anaesthesia at this time. At 4 h the effects of temazepam could no longer be differentiated from those of placebo. In considering the differences detected between the two groups, the lack of initial randomization must be acknowledged. However, this did not affect the double-blind nature of the trial.

Previously, impairments following premedication with temazepam 20 mg have been found in the accuracy of delayed recall [6] but have not been found for performance on the Digit Symbol Substitution task [16] or for reaction time [17]. Further, temazepam 20 mg given without an-
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The study was supported financially by Cognitive Drug Research who also provided the software, equipment and recovered completely by this time.

The increased time to open eyes following temazepam 20 mg has been found in some previous studies [6, 17], but not others [16, 19]; the reasons for this disparity are not clear. An interesting and unexpected finding of the present study was the negative correlation between wake up time and duration of anaesthesia in the placebo group.

The alleviation of preoperative anxiety assessed by the Spielberger questionnaire is in accordance with similar effects of temazepam which have been detected using visual analogue scale techniques [6, 16, 19, 20], indicating that both techniques are sensitive to these effects.

Overall, the findings of this study are consistent with previous work, in that temazepam 20 mg produces anxiolysis before operation at the expense of longer times to opening eyes and impaired cognition 30 min later. The general recovery of these cognitive impairments induced by temazepam is suitable for day-case surgery. However, the residual decrease in vigilance in both groups at 4 h indicates that patients have not recovered completely by this time.

ACKNOWLEDGEMENTS

The study was supported financially by Cognitive Drug Research who also provided the software, equipment and personnel for conducting the cognitive assessments.

REFERENCES

9. O'Boyle PA, Ogg TW, Gilks WR. Temazepam 20 mg has been found in some studies [6, 17], but not others [16, 19]; the increased time to open eyes following temazepam is suitable for day-case surgery. How-ever, the residual decrease in vigilance in both groups at 4 h indicates that patients have not recovered completely by this time.