COMPARISON OF SEDATION WITH TEMAZEPAM BY MOUTH AND DIAZEMULS I.V. FOR DENTAL SURGERY

Variability in Absorption may Influence Clinical Effect

H. E. HOSIE, I. M. BROOK AND W. S. NIMMO

Sedation, coupled with local anaesthesia, has been advocated as a safe alternative to general anaesthesia for dental surgery. The advantages of such a regimen are its minimal effects on vital signs, protective reflexes and patient co-operation, the minimal requirement for monitoring and rapid recovery to street fitness [1]. Sedatives administered by mouth can be as effective as those given i.v. and have the advantages of greater patient acceptability, ease of administration, safety and fewer sequelae [2, 3].

Temazepam, a safe and commonly-used benzodiazepine with a short duration of action and no active metabolites, has been reformulated as an elixir which is thought to be more rapidly absorbed than the original gelatin capsules. Significantly greater plasma concentrations of temazepam are found 20 min after the oral administration of the elixir when compared with the capsules [4].

We have compared temazepam elixir administered by mouth with i.v. Diazemuls in patients undergoing minor oral surgery and attempted to relate the plasma concentrations of temazepam with effect. The clinical effectiveness of temazepam by mouth has been reported elsewhere [5], and temazepam was shown to have a lesser amnesic effect than diazepam as judged by recall of operative events and picture cards. Reaction times on discharge 45 min after operation were shown to be significantly increased following the administration of diazepam when compared with pre-administration values. No significant changes in reaction times were demonstrated in the temazepam group [5].

SUMMARY

Temazepam elixir 30 mg by mouth was compared with i.v. Diazemuls titrated to a maximum dose of 20 mg in a double-blind study of 50 patients undergoing elective minor oral surgery. The treatments produced a similar reduction in anxiety score and similar degrees of patient relaxation and co-operation. The diazepam group had greater amnesia during surgery, but also showed significant slowing of reaction time at the time of discharge. Patients given temazepam elixir showed wide variations in plasma concentrations. Patients with low plasma temazepam concentrations at the time of surgery showed no significant reduction in anxiety scores.

PATIENTS AND METHODS

Fifty patients (ASA grade I) undergoing elective minor oral surgery and requesting sedation, gave written informed consent to take part in the study, which had local Ethical Committee approval. Patients already taking benzodiazepine preparations were excluded. On arrival, 1 h before surgery was expected, patients were allocated randomly to two groups. Group I received temazepam 30 mg in 15 ml of elixir by mouth and those in group II received placebo elixir 15 ml. Fifty minutes after taking the elixir, patients were transferred to the dental chair and those in group I were given an i.v. injection of Intralipid 4 ml (as placebo); those in group II received i.v. Diazemuls over 2 min to a maximum of 20 mg titrated to slurring of speech or ptosis. Both patient and dentist were unaware of the sedation used. The dentist performed the surgery under
local anaesthesia. Arterial pressure and heart rate were recorded using a Sears automatic digital sphygmomanometer on five occasions during the study: before taking the elixir; 45 min after the elixir but before transfer to the dental chair; after the i.v. injection and local block but before starting surgery; at completion of surgery and, finally, before discharge (normally 45 min after completion of surgery). Rate–pressure product was calculated by multiplying systolic arterial pressure by heart rate to provide an index of sympathetic activity.

Eleven patients re-attended for extraction of impacted third molars on the opposite side and were given the alternative sedation on their second visit, although both patient and dentist remained unaware of the sedation used. Data obtained from these patients were analysed separately.

Assessments

The type of surgery and its duration were noted. The dentist assessed the degree of difficulty of surgery as easy (a procedure involving raising a flap and elevating the tooth), moderate (where bone removal or sectioning the tooth was required) or difficult (where there was particular surgical difficulty). In addition he graded patient co-operation as excellent (relaxed), satisfactory (surgery completed) or unsatisfactory (surgery abandoned).

Anxiolysis was assessed using a 100-mm visual linear analogue scale (VAS) with anxiety/apprehension and relaxed/confident being the endpoints and measurement from the “relaxed” end. The VAS was completed by the patient before any sedation was given, after surgery and on follow-up at 1 week.

Amnesia was assessed by testing the patients’ recall of perioperative events. These included the administration of the local anaesthetic, the accurate recall of three picture cards shown to the patient during surgery and the ability to remember the number of times the heart rate and arterial pressure had been measured during the study.

Reaction times were measured using a BBC computer and a VDU. The response time between the presentation of a random audible and visual signal and pressing a button was measured electronically. After initial familiarization with the equipment 10 measurements were made on each of three occasions: before sedation, before surgery 45 min after taking the elixir and before discharge. The mean reaction time on each occasion was calculated.

Blood samples were taken during surgery and before going home, and plasma concentrations of temazepam were measured by high performance liquid chromatography. The chromatography consisted of a Model 302 pump (Gilson, Villiers le Bel, France) fitted to a Holochrome variable-wavelength ultraviolet detector (Gilson) operated at a maximum sensitivity of 0.02 a.u.f.s. and connected to a C-R1B chromatopac integrator (Shimadzu Corporation, Kyoto, Japan). Injection was made by syringe via a Rheodyne valve, Model 7125, with 20-µl loop (Rheodyne, CA, U.S.A.). The column was 150 × 4.6 i.d. and prepacked with 5-µm Microsorb C18 (Rainin Instrument Co. Inc. U.S.A.). Chromatography was performed in reverse-phase mode using a solvent system of methanol–water–acetonitrile (40:50:10 v/v/v) at a flow-rate of 1.5 ml min⁻¹ and the column effluent was monitored at 230 nm. The chromatograph was operated at 2200 p.s.i. and room temperature.

Reagents were of analytical grade and all inorganic reagents were prepared in freshly glass-distilled water. Chloroform was Distol grade, methanol and acetonitrile were HPLC grade (Fisons, Loughborough, U.K.). Borate buffer 0.2 mol litre⁻¹ containing sodium hydroxide 1 mol litre⁻¹ was adjusted to pH 9.4 with sodium hydroxide solution 0.1 mol litre⁻¹. A standard solution of temazepam was prepared in distilled water at a concentration of 10 ng ml⁻¹ and carbamezepine (the internal standard) at 20 ng ml⁻¹. Temazepam was supplied by Wyeth Laboratories and carbamezepine by Sigma Chemical Co. Ltd.

Plasma samples (0.5 ml) were spiked with internal standard (150 ng) and vortex-mixed with borate buffer 1.0 ml for 5–10 s. This mixture was extracted by shaking it with chloroform 4.0 ml for 15 min on an Orbital mixer, Model R100/TW (Luckham Ltd, Sussex, U.K.). After centrifugation (3000 rev min⁻¹) for 5 min the chloroform layer was transferred to a tapered test-tube and evaporated to dryness under a stream of oxygen-free nitrogen. The residue was redissolved in mobile phase (60 µl) and a 20-µl portion was injected to the chromatograph. Standard dilutions containing temazepam 500 ng ml⁻¹ in drug-free plasma were prepared as above for calibration.
Statistical analyses were performed using Student’s *t* test and Chi-squared analyses.

**RESULTS**

The two groups of patients did not differ significantly with respect to age, weight, sex distribution or in the time taken for surgery (table I). Most of the surgical procedures were extraction of impacted third molars, but included apicectomies and surgical removal of roots. The degree of difficulty of surgery did not differ significantly between the groups. The mean dose of i.v. diazepam was 16.6 mg. All procedures were completed, with co-operation being classified as excellent in the majority of the patients; there were no significant differences between the groups in this regard.

**Plasma concentrations of benzodiazepines**

Blood samples for assay of temazepam concentrations were obtained from 24 patients. One patient had an inadequate sample at the time of surgery and three samples taken at time of discharge home were insufficient for assay (fig. 1). Plasma concentrations of temazepam at the time of surgery (45 min after the elixir) varied widely—from 115 ng ml⁻¹ to 780 ng ml⁻¹. Concentrations at the time of discharge home (90–135 min after the elixir) were less variable. Plasma concentrations at the time of surgery were less than 200 ng ml⁻¹ in seven of the 23 patients. Subsequently, six of these individuals achieved concentrations similar to the other patients at 2 h. It would appear that these patients had delayed absorption of the elixir and that, at the time of surgery, plasma concentrations were low. Therefore, in addition to a comparison of the groups receiving diazepam and temazepam, the data from these seven individuals were analysed separately.

Both groups had similar anxiety scores before taking the elixir. Patients given diazepam and those with high plasma temazepam concentrations showed a significant decrease in anxiety score which persisted 1 week later at review (fig. 2). Patients with low plasma concentrations of temazepam had lower initial anxiety scores and showed no significant change at any time.

Rate–pressure product (RPP) was used as an index of sympathetic activity and an indirect estimation of anxiolysis (fig. 3). Before random allocation to groups, those who subsequently received temazepam had a significantly lower RPP (*P* < 0.05); thereafter, these patients showed a significant increase in RPP at the time of surgery compared with initial values (*P* < 0.05), with RPP decreasing on completion of surgery and then decreasing further before discharge. Those with low temazepam concentrations showed the same pattern of changes, but higher values. Patients given i.v. Diazemuls showed a different pattern, with no increase in RPP at the time of surgery and a significant reduction in RPP before being allowed home compared with pretreatment values (*P* < 0.01).

**FIG. 1.** Plasma concentrations of temazepam following oral administration of elixir.

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**TABLE I.** Sex distribution, age and weight of patients (mean (range)), mean (SEM) dose of sedative and mean (range) duration of surgery

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>F</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Dose (mg)</th>
<th>Time taken (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam elixir</td>
<td>5</td>
<td>20</td>
<td>24.2</td>
<td>65.5</td>
<td>30</td>
<td>12.5 (2–30)</td>
</tr>
<tr>
<td>(n = 25)</td>
<td></td>
<td></td>
<td>(16–51)</td>
<td>(45–91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam i.v.</td>
<td>5</td>
<td>20</td>
<td>26.2</td>
<td>65.3</td>
<td>16.6</td>
<td>14.5 (1–30)</td>
</tr>
<tr>
<td>(n = 25)</td>
<td></td>
<td></td>
<td>(17–50)</td>
<td>(45–105)</td>
<td>(0.6)</td>
<td></td>
</tr>
</tbody>
</table>
SEDATION FOR DENTAL SURGERY: VARIABLE ABSORPTION

Anxious/Apprehensive

Relaxed/Confident

Before After At Before After At Before After At
elixir surg. review elixir surg. review elixir surg. review

FIG. 2. Mean anxiety scores (± SEM) before sedation, after surgery and at follow-up. ***P < 0.005. □ = Diazepam; △ = temazepam, high concentration; ○ = temazepam, low concentration.

Paired data

The degree of difficulty of the procedure and patient co-operation were similar at both visits. Seven of the patients received temazepam elixir at their first visit and diazepam i.v. at the second operation.

Anxiety scores in those attending for surgery on the second occasion were significantly lower than their initial anxiety scores, and were similar to those found following the first postoperative review. A further small but insignificant reduction in anxiety score was seen subsequent to the second procedure (fig. 4). At the first operation the RPP showed a significant increase at the time of surgery with a decrease to pre-operative values during recovery, but during the second operation RPP remained virtually unchanged (fig. 5).

At review, following the second procedure, patients were asked which sedation they preferred. Eight of the 11 preferred diazepam, two temazepam and one was happy with either. Four patients preferred the first sedative and six preferred the sedation given on the second occasion. The differences were not significant.
DISCUSSION

We have previously reported that a fixed dose of temazepam elixir administered by mouth in patients undergoing minor oral surgery is acceptable as a sedative agent to both patient and dentist [5]. Our finding that temazepam elixir 30 mg is comparable to a mean dose of Diazemuls 16.6 mg i.v. agrees with work of Douglas and colleagues [2] who found that temazepam 20 mg in gelatin capsule formulation 1 h before operation was comparable to a mean dose of diazepam 12 mg in propylene glycol in patients having endoscopy. O'Boyle, Harris and Barry [3] compared temazepam 40 mg in capsule formulation with a maximum of Diazemuls 10 mg i.v. in minor oral surgery. In their study, surgery started 40 min after the oral administration of the capsules and plasma concentrations were not measured. A bioavailability study by Pickup, Rogers and Launchbury [4], comparing temazepam in capsules with the elixir, showed that higher plasma concentrations were reached 20 min after the elixir and suggested that a more rapid onset of activity was possible using the elixir. It may be that the discrepancy in comparability between these studies is attributable to a combination of the different drug formulations and the timing of surgery.

It is of interest that seven out of 23 patients given temazepam elixir had plasma concentrations less than 200 ng ml\(^{-1}\) at the time of surgery. All patients were ASA grade I and were not receiving drugs or other medications. There was no history of any gastrointestinal disease that would delay gastric emptying. Although patients had not been instructed to fast before surgery, on direct questioning it appeared that some had fasted for several hours, whereas others had had a light meal within the previous 4 h. However, there was no correlation between fasting and non-fasting patients and plasma concentrations of temazepam. Similarly, there was no correlation between age, sex or weight and plasma temazepam concentration at the time of surgery.

A number of factors can affect drug absorption, including the formulation of the drug and the degree of anxiety experienced by the patient. Nakano, Ogawa and Kawazu [6] found that a high neurotism score was associated with higher plasma diazepam concentrations and suggested that an increase in anxiety was associated with more rapid absorption of benzodiazepines. Our patients with low plasma temazepam concentrations at the time of surgery did not differ significantly from the other patients in terms of anxiety score, although their initial score was lower and numbers are small. Patients given temazepam had a lower rate-pressure product than those given diazepam. The correlation coefficient between anxiety score before treatment and temazepam concentration was poor \((r = 0.0754)\).

Attempts have been made to relate plasma concentrations of benzodiazepines with effect. However, Nakano, Ogawa and Kawazu [6] found poor correlation coefficients between sedation—as measured using Choice Reaction Time Test—and plasma diazepam concentrations after diazepam by mouth. In the seven patients with low temazepam concentrations at the time of surgery, the decrease in anxiety score following surgery was not significant and they showed a marked increase in rate-pressure product at that time—although, once again, the difference was not significant. Despite the numbers being small it may be that plasma concentrations greater than 200 ng ml\(^{-1}\) are associated with more marked anxiolysis.

Bioavailability studies by Fucella [7] in four fit volunteers suggested that peak plasma concentrations were achieved 20–40 min after the administration of temazepam by mouth in solution and in soft gelatin capsules. However, in the study by Pickup and co-workers [4] in 10 fit volunteers, peak plasma concentrations were reached after 95 min for both elixir and capsules. From our study of 25 fit patients awaiting surgery we find plasma concentrations less variable at the second sample 90–135 min after the elixir. If the effects of sedation and anxiolysis are related to the plasma concentration of the drug, then increased effects may be seen if surgery takes place at a time when peak plasma concentrations could be anticipated.

Comparing temazepam and diazepam overall, our findings support the findings of previous studies. Both drugs reduce anxiety and provide satisfactory conditions for the surgeon and the patient. We have previously reported the lack of amnesic effect of temazepam. The flattened rate-pressure product graph (fig. 3) suggests that i.v. diazepam may obtund the sympathetic response to surgery, whereas temazepam may only reduce it. Although more patients receiving both sedatives expressed a preference for diazepam, this may have been related to the order of adminis-
tration of the sedation. Both sedatives reduced anxiety to similar values for repeat procedures. The “paired patients” in our sample had lower anxiety scores at their second presentation and these scores correlated well with their scores after the first procedure. This could be attributed to the good effect of the sedative previously given, or simply to having experienced the surgery before.

Anxiety scores did decrease at the second visit, but not to any significant extent. During the first visit the rate-pressure product showed a significant increase at the time of surgery, whereas at the second operation there was no change throughout the study. However, seven of the 11 patients had been given temazepam at the first visit and diazepam at the second, and this could account for the differences seen.

Temazepam is a drug with a good record of safety and efficacy. Certainly, the oral route of administration has many factors to commend it, especially to those not proficient in i.v. cannulation and to patients who do not wish injections or residual effects. However, it would appear that further investigation is merited of the absorption of temazepam in patients about to undergo surgery.

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REFERENCES