I.V. TEMAZEPAM: THEORETICAL AND CLINICAL CONSIDERATIONS

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The repeated administration of diazepam to patients in an intensive care environment is associated with the accumulation of an hypnotically active metabolite (Gamble, Dundee and Gray, 1976). The discovery of a sub-population of patients with a prolonged midazolam half-life (Dundee et al., 1986)—although of little clinical importance following a single dose—may result in cumulation of the drug after repeated administrations, or when given by infusion. Thus, there is a clinical need for an injectable benzodiazepine which is intermediate in duration of action between these two and which does not possess any hypnotically active metabolite(s). Temazepam appears to fulfil these criteria: its elimination half-life is 7-10 h (Brittencourt et al., 1979; Fuccella, 1979) and biotransformation is to the inactive glucuronide. Recently, injectable preparations of temazepam were developed by the Department of Pharmacy, The Queen's University of Belfast (McCafferty et al., 1986): one in 90% propylene glycol (PG), the other in 40% sodium salicylate.

We report an evaluation of the use of these in clinical practice. Emphasis was placed on local venous tolerance, on attempts to find the sedative dose in adults, and on a 2-h comparative pharmacokinetic study. A large group of patients received temazepam in the 90% PG preparation, and a smaller volunteer group was given both i.v. formulations and the commercially available elixir and capsule. All studies were approved by the local medical Ethical Research Committee, and patients and volunteers had given verbal consent to participate.

### SUMMARY

Two injectable forms of temazepam, in 90% propylene glycol or 40% salicylic acid, were studied in volunteers, and before surgery in healthy patients. The volunteers also received two forms (capsule and elixir) by mouth. The salicylate preparation was painful on injection and both i.v. formulations caused an unacceptably high incidence of venous thrombosis. Temazepam was detected in plasma earlier following the elixir preparation than the capsule. Plasma concentrations were similar following both injectable preparations. The potency of i.v. temazepam in inducing drowsiness in patients was much less than expected and doses greater than 0.6 mg kg⁻¹ were required to produce adequate sedation. There was a significant reduction in thiopentone induction dose in patients receiving temazepam i.v.

### PATIENTS, SUBJECTS AND METHODS

**Volunteers**

Eleven fit, fasting, young, non-smoking students (mean age 22 yr, mean weight 68 kg) took part. They were not on any medication. In random order, each received temazepam 20 mg on four separate occasions either as the elixir (Euhypnos), a capsule (Euhynpos) or an i.v. preparation (two preparations). At least 2 weeks elapsed between administrations.

Injections were made to a large antecubital vein over 20 s. The occurrence of pain on administration was noted, and the vein inspected 14 days later. Arterial pressure (Riva Rocci), heart rate and ventilatory rate were measured at frequent intervals. Blood was drawn from an indwelling i.v. cannula in the contralateral arm at zero, 5, 10, 15, 30, 60, 90 and 120 min, centrifuged and samples stored at −20 °C until they were analysed. Plasma concentrations of temazepam were measured...
using high performance liquid chromatography with ultra-violet detection at 231 nm, based on the method of Ho and co-workers (1983). The within-batch coefficient of variation of a spiked sample of 800 ng ml$^{-1}$ was 3% and the between-batch coefficient of variation of the same sample was 5%.

Patients

All 72 patients were fit, unpremedicated women about to undergo routine gynaecological operations. They received only the PG preparation. An initial study in 10 patients receiving i.v. increments of temazepam 2.5 mg showed that, in doses smaller than 0.5 mg kg$^{-1}$, sedation was difficult to detect. The remaining patients received at random temazepam 0.5, 0.6, 0.75 or 1 mg kg$^{-1}$ given into a large antecubital vein over 20 s. Discomfort on injection was noted and graded as slight, moderate or severe. Vital signs were recorded as in the volunteer study. The degree of drowsiness was noted at 1-min intervals and graded on a recognized four-point scale ranging from 1 (slight) to 4 (asleep) (Brown and Dundee, 1968).

Ten minutes after the injection of the temazepam, anaesthesia was induced with thiopentone. A standard method of administration of thiopentone was used (Dundee et al., 1982) and the “induction” dose noted. Concurrently, thiopentone requirements were noted in a control group of 39 patients who received no other drugs.

RESULTS

Volunteer study

The vital signs were stable throughout the study in all the volunteers. In the salicylate formulation group 6 complained of pain on injection and two developed a painless thrombosis in the antecubital vein. With the PG 90% preparation five experienced pain, nine developed thrombosis, one of which was painful to touch. None of the 11 volunteers receiving temazepam 20 mg i.v. developed more than slight drowsiness over the 2-h period of the study although both oral preparations produced a moderate degree of sedation in seven or eight subjects.

The mean plasma concentrations of temazepam, following the four administrations, are shown in figure 1, from which the SD is omitted for the sake of clarity, especially as it is of no significance. The drug was detected earlier with the elixir than with the capsule preparation, and average plasma concentrations were significantly greater with the former at 15 and 30 min ($P < 0.02$). Plasma concentrations appeared to be still increasing at 2 h, at which time there was no difference between the concentrations attained with the two oral preparations. There was no significant difference in mean temazepam concentrations with either i.v. preparation at any time during the study. By 2 h the mean concentrations achieved after temazepam 20 mg were similar in all four studies.

![Figure 1. Mean plasma concentrations following temazepam 20 mg by mouth either as Euhypnos elixir (▲) or Euhypnos capsule (○), or i.v. formulated in 90% propylene glycol (●) or 40% sodium salicylate (■).](http://bja.oxfordjournals.org/)

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Patient study

Table 1 shows that the mean ages and weights were comparable in all four dosage groups. With all doses, sedation was maximal at 3 min following injection. Figure 2 shows the level of sedation attained at this time in each group. The response to i.v. temazepam was variable with doses less than

<table>
<thead>
<tr>
<th>Dose (mg kg⁻¹)</th>
<th>n</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
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</thead>
<tbody>
<tr>
<td>0.5</td>
<td>15</td>
<td>31 ± 1.8</td>
<td>60 ± 2.7</td>
</tr>
<tr>
<td>0.6</td>
<td>16</td>
<td>33 ± 2.3</td>
<td>60 ± 3.7</td>
</tr>
<tr>
<td>0.75</td>
<td>15</td>
<td>34 ± 2.3</td>
<td>61 ± 2.8</td>
</tr>
<tr>
<td>1.0</td>
<td>16</td>
<td>31 ± 1.7</td>
<td>57 ± 2.8</td>
</tr>
</tbody>
</table>

Fig. 2. Sedation scores at 3 min, following i.v. temazepam in the four doses.

0.6 mg kg⁻¹. Adequate sedation (eyes closed but easily rousable), was achieved 3 min after injection in 15/31 patients receiving temazepam 0.5 or 0.6 mg kg⁻¹. There was a significant increase in adequate sedation to 26/31 in those receiving the higher (0.75-1.0-mg kg⁻¹) doses (P = 0.007). Only four of the 16 patients receiving the maximal dose, 1 mg kg⁻¹, showed marked sedation and required no thiopentone to induce anaesthesia.

With doses of 0.5-1.0 mg kg⁻¹, pain on injection occurred in 60% patients, being moderate to severe in 36%.

Thiopentone requirements were significantly lower (P < 0.001) in those patients who received i.v. temazepam than in the control group (no temazepam) with mean values of 2.4 ± 0.16 (SEM) mg kg⁻¹ and 4.6 ± 0.18 (SEM) mg kg⁻¹, respectively.

DISCUSSION

Circumstances limited the period of observation in our volunteers to 2 h and in the light of the findings it was decided not to continue with a more extensive evaluation. We have previously found that a 20-mg tablet is suitable for night sedation or preanaesthetic medication (Wilson et al., 1986); this study shows that a similar dose given i.v. produced a lesser effect. A possible explanation may be an altered initial distribution of the drug following i.v. administration, with a greater proportion being distributed to tissues outside the central nervous system. The two oral preparations behave similarly except for the slightly earlier onset of action with the less palatable elixir.

With both i.v. preparations of temazepam there was an unacceptably high incidence of pain on injection with some degree of discomfort associated with more than 50% of the administrations of these formulations. Despite the theoretical advantages of this injectable benzodiazepine, venous intolerance precludes further clinical use of either formulation.

ACKNOWLEDGEMENTS

The assistance of Farmitalia Carlo Erba for supply of temazepam and the Department of Pharmacy, The Queen's University of Belfast for making preparations for i.v. use are acknowledged.

REFERENCES