COMPARISON OF THE EFFICACY OF CHLORMETHIAZOLE AND DIAZEPAM AS I.V. SEDATIVES FOR SUPPLEMENTATION OF EXTRADURAL ANAESTHESIA

L. T. SEOW, L. E. MATHER AND M. J. COUSINS

Since many patients undergoing surgery under regional anaesthesia prefer to be asleep or sedated, and to have no recollection of the surgical procedure, a variety of adjuncts to local anaesthetic techniques have been recommended. These range from subanaesthetic infusions of anaesthetic agents i.v. (Coniam and Roberts, 1981; O'Callaghan et al., 1982), or combinations of analgesics and sedatives (Freedman, 1979) to an approach of distraction (Scott, 1975). Thus, there is a recognized need to optimize sedation for regional anaesthesia in order to achieve amnesia and to minimize the physiological insult.

Diazepam i.v. has been used increasingly for more than a decade as a sedative during surgery under regional anaesthesia. However, although it has enjoyed a long record of safety, it is not completely innocuous. Apnoea (Hall and Ovasapian, 1977) and cardiovascular depression (Jenkinson et al., 1974) have been reported. It has a low clearance and long half-life (Mandelli, Tognoni and Garattini, 1978) and these, undoubtedly, contribute to the reports of prolonged recovery (Brown and Dundee, 1968). In contrast, advantage has been taken of the high clearance of chlormethiazole (Seow et al., 1981; Seow, Mather and Roberts, 1981) and infusions i.v. have been designed to maximize control of sedation during the procedure, and to minimize postoperative sedation (Schweitzer, 1978; Marley and Ward, 1980; Mather and Cousins, 1980). In this study, we have compared the clinical efficacy of chlormethiazole and diazepam when used as sedative agents in patients undergoing surgery under extradural blockage.

SUMMARY

The clinical efficacy of two sedative agents was compared in 21 young healthy patients undergoing surgery under extradural blockade. A state of sedation and amnesia in which patients lapsed into a sleep-like state when left undisturbed, yet spontaneously opened their eyes to make comments and co-operate with verbal commands, was sought. This was achieved readily by careful titration of responses and required a diazepam loading dose of $20 (\pm 15) \text{ mg}$ given at a rate of $1 \text{ mg min}^{-1}$ or $0.8\%$ chlormethiazole edisylate infusion $10 \text{ ml min}^{-1}$ given over $16 (\pm 6) \text{ min}$. Control of this state was easier with chlormethiazole (by varying the rate of infusion) than by giving repeated doses of diazepam. Both agents provided good anterograde amnesia; there was no retrograde amnesia. Considerable postoperative somnolence with a high incidence of relapse into amnesic and sedated states were noted with both agents. However, if the total volume of chlormethiazole infused was less than $300 \text{ ml}$, then a distinct advantage of abrupt and lucid recovery was apparent. Blood concentrations producing the desired clinical state were more variable for diazepam than for chlormethiazole.

PATIENTS AND METHODS

Twenty-one young healthy (ASA I) patients, were studied. All were undergoing lower abdominal or lower limb surgery under extradural blockade. Informed consent was obtained after a detailed explanation on the night before operation. Patients were required to learn to do a simple mental arithmetic task called PASAT (Paced Auditory Serial Addition Task) (Gronwall and Sampson, 1974) the night before surgery. In this test a series of random digits from 1 to 9 was presented to the
Patient 2.5 s apart for 1 min. Patients were instructed to add each given digit to the one immediately preceding it. A baseline score for PASAT was recorded after four training attempts. PASAT has been used previously in a number of studies involving graded responses to central depressants (Mather et al., 1981; Seow, Mather and Roberts, 1981).

All patients were premedicated with pethidine hydrochloride 1.5 mg kg\(^{-1}\) i.m., 1 h before surgery. After baseline values of heart rate and arterial pressure were established, an infusion of electrolyte solution i.v. was commenced and a repeat PASAT performed. The extradural blockade was then performed with the patient in the lateral position. Two percent lignocaine hydrochloride 20 ml with 1:200000 adrenaline was administered through the extradural needle at the L2–3 space. An extradural catheter was placed for subsequent additional doses of 0.5% bupivacaine hydrochloride to provide postoperative analgesia. Patients were turned supine as soon as the extradural procedure was completed.

I.v. sedation was started simultaneously with the start of the extradural procedure. Patients were allocated randomly to receive either diazepam or chlormethiazole. The sedative was administered to produce moderate sedation, with the patient lapsing into a sleep-like state when left undisturbed, yet able to co-operate and converse with the anaesthetist when awoken. This corresponded to the more objective measure of approximately 50 % PASAT errors. Diazepam was administered at a rate of 1 mg min\(^{-1}\) i.v. until this clinical state was achieved and was maintained with further doses i.v. (at the same rate) as required, during surgery. Chlormethiazole edisylate 0.8% (Heminevrin, CTZ) was administered via a 100-ml burette, initially as a loading dose at a rate of 10 ml min\(^{-1}\) i.v. until the desired clinical state was achieved, and then with varying rates of infusion as required to maintain that state.

PASAT was used as an objective test of the level of sedation during surgery by testing every 15 min after the start of sedation, and for the degree of recovery from sedation during the first 4 h after infusion, and again at 8 and 24 h after surgery. Amnesia is an important property of drugs used during surgery. The time sequence of amnesia to auditory, visual and tactile stimuli was established by recording the times of procedures performed on patients, events happening during and following surgery, and visual cards were shown to patients at 15-min intervals for 4 h following the procedure. Specific comments and conversations with patients were also recorded at regular 10-min intervals and patients were questioned as to their ability to recall these cards, events, procedures and conversations at a later visit, 24 h after surgery.

Consumer satisfaction with the anaesthetic technique was assessed at 24 h, by means of a questionnaire.

A sample of peripheral venous blood was obtained 30–45 min after the start of i.v. sedation when the clinical state was satisfactory (corresponding to 50 % PASAT error rate). Diazepam and chlormethiazole edisylate concentrations in whole blood were measured by gas–liquid chromatography (Mather and Tucker, 1974) and nitrogen selective detection. Diazepam was analysed on OV-17 liquid phase at 270 °C with cyproheptadine internal standard. Chlormethiazole was analysed on an OV-225 column operated at 150 °C with bromothiazole as internal standard.

**RESULTS**

The physical characteristics of the patients studied and the duration of surgery were comparable in the two groups (table I). There were no correlations between the doses of either diazepam or CTZ and age or body weight.

Ten out of 11 patients in the diazepam group, and all 10 patients in the CTZ group, were easily sedated to the desired clinical state for supplementation of extradural blockade. Patients' comments and questions asked were usually about surroundings, personnel or surgery, seemingly relating to patients' subconscious thoughts or uncertainties about which they had wanted to enquire before operation. Throughout the study, patients were able to answer questions rationally and accurately,

<table>
<thead>
<tr>
<th>Table I. Physical characteristics of patients and dose regimens (mean±SD). CTZ = 0.8% chlormethiazole edisylate solution</th>
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<tbody>
<tr>
<td><strong>Diazepam</strong></td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<tr>
<td>Loading dose</td>
</tr>
<tr>
<td>Rate of initial loading dose</td>
</tr>
<tr>
<td>Maintenance dose</td>
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<tr>
<td>Total dose</td>
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<tr>
<td>Duration of operation (min)</td>
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as well as to co-operate with various procedures such as pressing on a swab after blood sampling. Control over this state, however, was much easier with CTZ by varying the infusion rate. After the initial loading dose (10 ml min⁻¹) was given over a period (mean ± SD) of 15.5 ± 5.8 min, the maintenance rate had to be reduced to 2.6 ± 1.1 ml min⁻¹ for the 1st hour, 2.0 ± 1.1 ml min⁻¹ for the 2nd hour, and 1.4 ± 0.6 ml min⁻¹ for the 3rd hour, to maintain this state. The initial loading dose of diazepam was 20 ± 15 mg with total subsequent top-up doses of 15 ± 7 mg. Diazepam administered this way caused more fluctuating levels of sedation, which tended to become lighter about 20–30 min after each dose. Greater variability in the doses required to achieve the same clinical state was observed for diazepam than for CTZ (table I). Postoperative sedation was marked in both groups. Four of the 11 patients who received diazepam and five of the 10 patients who received CTZ, remained sedated for up to 4 h following the procedure.

The frequency of amnesia for various events is shown in table II. No retrograde amnesia was recorded with either diazepam or CTZ. A very high incidence of anterograde amnesia was obtained with both agents 10 min after commencement of sedation. The durations of amnesia for events and conversations are given in table III. The difference in the duration of amnesia between the two agents was not significant (P > 0.05). However, a significant finding was the relationship of dosage of CTZ to duration of amnesia after operation. Four patients required less than 300 ml and six patients required more than 300 ml. Postoperative amnesia was brief (9 ± 6 min) in those patients recovering and awakening abruptly when the total dose of CTZ was less than 300 ml, but prolonged (114 ± 70 min) when the total dosage exceeded 300 ml. No relationship between duration of action and total dose was evident with diazepam. For example, the longest duration of postoperative sedation and amnesia was observed in five patients who received less than 40 mg total dose of diazepam (303 ± 138 min and 71 ± 44 min, respectively), but one patient who received a total of diazepam 80 mg had negligible sedation after operation, without any amnesia. Duration of amnesia for recognition of cards was consistently shorter than that for conversation and events (table III) with both diazepam and CTZ.

In the recovery room, four patients receiving diazepam became amnesic 95–300 min after the start of the diazepam injection, while seven patients relapsed into amnesic states in the postoperative period 105–345 min after start of CTZ infusion.

Venous blood concentrations obtained at the required level of sedation (corresponding to 50% PASAT errors) were 0.58 ± 0.60 mg litre⁻¹ and 8.3 ± 2.9 mg litre⁻¹ for diazepam and CTZ, respectively. The range of diazepam blood concentrations was wide (from 0.13 to 2.23 mg litre⁻¹) (table IV).

The level of extradural analgesia obtained in both groups varied from T6 to T10. Mild hypertension was seen in patients receiving both sedative agents (mean decrease 15 ± 10 mm Hg). Chlormethiazole caused more tachycardia (mean increase 41 ± 17%) than diazepam (26 ± 12%) (P < 0.05; Student's t test).

Minor side effects were noted with both

<table>
<thead>
<tr>
<th>TABLE II. Frequency of amnesia for events and procedures. * I.v. sedation commenced with extradural administration</th>
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<tbody>
<tr>
<td>Combined groups</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Transport to induction room</td>
</tr>
<tr>
<td>Insertion of i.v. infusion</td>
</tr>
<tr>
<td>Positioning of extradural block</td>
</tr>
<tr>
<td>Extraludal procedure*</td>
</tr>
<tr>
<td>Testing extradural blockade (10 min post-extradural)</td>
</tr>
<tr>
<td>Move into theatre</td>
</tr>
<tr>
<td>Surgical incision</td>
</tr>
<tr>
<td>Blood sampling</td>
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<tr>
<td>End of operation</td>
</tr>
<tr>
<td>Transport to recovery</td>
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<tr>
<td>Transport to ward</td>
</tr>
</tbody>
</table>

**TABLE III. Amnesic period (min) (mean ± SD). *Not significantly different between drugs (P > 0.05, Student's t test). **When total volume of CTZ infused exceeded 300 ml (n = 6), post-infusion amnesic period = 114 ± 70 min; when total volume CTZ was less than 300 ml (n = 4), post-infusion amnesic period = 9 ± 6 min. No relationship between dose and post-infusion amnesic period was found with diazepam**

<table>
<thead>
<tr>
<th>Diazepam</th>
<th>CTZ</th>
</tr>
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<tbody>
<tr>
<td>Total duration*</td>
<td></td>
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<tr>
<td>Recall of conversation/events</td>
<td>114 ± 88</td>
</tr>
<tr>
<td>Recognition of cards</td>
<td>80 ± 42</td>
</tr>
<tr>
<td>Post-infusion period*</td>
<td></td>
</tr>
<tr>
<td>Recall of conversation/events</td>
<td>37 ± 44</td>
</tr>
<tr>
<td>Recognition of cards</td>
<td>42 ± 29</td>
</tr>
</tbody>
</table>
TABLE IV. Blood concentrations of sedative agents during clinically ideal sedation and corresponding to a 50% PASAT error rate

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diazepam (mg litre(^{-1})) ((n = 11))</th>
<th>CTZ (mg litre(^{-1})) ((n = 10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.35</td>
<td>9.9</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>5.4</td>
</tr>
<tr>
<td>4</td>
<td>0.13</td>
<td>8.4</td>
</tr>
<tr>
<td>5</td>
<td>0.16</td>
<td>4.9</td>
</tr>
<tr>
<td>6</td>
<td>2.23</td>
<td>9.1</td>
</tr>
<tr>
<td>7</td>
<td>0.46</td>
<td>9.0</td>
</tr>
<tr>
<td>8</td>
<td>0.46</td>
<td>10.2</td>
</tr>
<tr>
<td>9</td>
<td>0.52</td>
<td>14.2</td>
</tr>
<tr>
<td>10</td>
<td>0.75</td>
<td>5.3</td>
</tr>
<tr>
<td>11</td>
<td>0.15</td>
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</tr>
</tbody>
</table>

Mean ± SD 0.58 ± 0.60 8.3 ± 2.9

sedatives. These consisted of six instances of pain on injection of diazepam and six of nasal irritation with CTZ. The latter took the form of an itchy or hot sensation in the nose, usually mild and transient, occurring 5 min after commencement of CTZ infusion and lasting a mean period of 16 ± 9 min. Two patients in the CTZ group also had transient watery eyes, headache and flushed face.

All patients expressed satisfaction with the regional blockade plus sedation. Among the reasons volunteered were absence of dry mouth, absence of postoperative nausea and vomiting, amnesia during the operation and analgesia following the procedure.

DISCUSSION

The ideal sedative state with which to supplement regional blockade during surgery is that in which patients maintain their own airway, are sedated and amnesic, will lapse into a sleep-like state if left undisturbed, yet can be aroused easily to communicate and co-operate with verbal commands, and are able to communicate any untoward sensations. This state was easily achieved with both of the regimens used in this study. A high total body clearance coupled, preferably, with a short half-life are important pharmacokinetic properties for i.v. sedative agents. These properties allow blood concentrations (and hence clinical responses) to be altered quickly, as well as minimizing the problems of cumulation during surgery and prolonged postoperative recovery. Although benzodiazepines (notably diazepam) have been advocated as sedation for regional anaesthesia (Pearce, 1974; Scott, 1975; Gjessing and Tomlin, 1977), it was pointed out recently (Seow et al., 1981) that, because of its low clearance (0.02–0.03 litre min\(^{-1}\)) and long elimination half-life (20–90 h) (Mandelli, Tognoni and Garattini, 1978), diazepam may not allow the same flexibility of response as can be obtained with a high clearance agent. However, limited flexibility still can be obtained with low clearance agents if the blood concentrations remain constantly in the region where they are dominated by redistribution. Hence, limited flexibility can be obtained with diazepam by using the fast redistribution half-lives of 10–15 min (Kaplan et al., 1973). This is the reason that supplementary doses were required throughout surgery in the present study. However, continued redistribution to tissues occurs over many hours, but at a slower rate (half-lives 1–3 h) (Kaplan et al., 1973) and this, coupled with the low rate of elimination, accounts for the slow recovery. Redistribution undoubtedly contributes to the dissipation of the effects of chlormethiazole, but its clearance is so high that it can be given safely by infusion for short periods. Of course, once redistribution effects have equilibrated the drug into the tissue mass, infusion rates need to be decreased to avoid excessive sedation in those patients requiring prolonged infusions (Schweitzer, 1978; Scott et al., 1980).

The use of diazepam is complicated by its metabolism to compounds known to have central depressant activity. However, recovery from chlormethiazole is rapid only with infusions of less than 300 ml. Infusions of greater than 300 ml led to prolonged postoperative sedation and it is possible that this may have been the result of the formation of active metabolites (Seow et al., 1981), or non-linearity in the rate of metabolism. It is not possible to differentiate between these mechanisms in the present study, since both necessitate reductions in dose rate with prolongation of infusion. However, the advantage of using chlormethiazole over diazepam is lost when the infusion is prolonged.

Retrograde amnesia was not observed with either drug and this is consistent with other reports on diazepam (Gregg, Ryan and Levin, 1974; Pearce, 1974; Shira, 1978; Gelfman et al., 1978) and chlormethiazole (Schweitzer, 1978; Seow et al., 1981). Intense anterograde amnesia has been noted in volunteers (Clarke et al., 1970; Kortilla and Linnoila, 1975) and patients (Dundee...
and Pandit, 1972) and would appear to be dose-dependent. In the present study, a relationship between dosage and predictability of amnesia with diazepam was not evident, marked variation occurring in the response to diazepam. In contrast, amnesia was predictable with chlormethiazole when the volume of infusion exceeded 300 ml and the duration of amnesia after operation was related to the total volume of chlormethiazole infused. Relapse of amnesia, 1.5–6 h into the postoperative period occurred with diazepam (four out of 11 patients) and in all six patients who had more than chlormethiazole 300 ml. This reinforces the current practice of insisting that patients who have received sedative drugs be accompanied home after day-case surgery.

In this study, the duration of amnesia for conversation and events was consistently longer than that for recognition of cards, regardless of the sedative used. A relationship between amnesia and the type of stimuli presented was not found by Gregg, Ryan and Levin (1974), but was found by Gelfman and colleagues (1978) and Cherkin and Harroun (1971), where more amnesia was obtained for cutaneous-tactile stimuli than for visual stimuli. The need to decrease the noise in the operating theatre and conversation during regional blockade under sedation has been emphasized previously (Scott, 1975). The role of visual input to patients has not been as well recognized, but the present results suggest that any visual stimuli should be made as pleasant as possible, and this includes appropriate screening of the patient from potentially disturbing visual stimuli.

Various studies have demonstrated a relationship between clinical effects of diazepam and blood or plasma concentrations (Hillestad et al., 1974; Dasberg et al., 1974; Ghoneim, Newaldt and Ambre, 1975). These indicate that a minimum blood concentration of diazepam of 0.4 mg litre\(^{-1}\) is required to control acute anxiety states. This value would appear suitable for the provision of sedation in association with regional blockade, although others have suggested that no simple correlation exists between clinical response and plasma concentrations of diazepam (Mandelli, Tognoni and Garattini, 1978). In the present study, blood diazepam concentrations varied widely (0.13–2.23 mg litre\(^{-1}\)) at the same clinical state of sedation, and this tends to support the latter viewpoint. The total blood or plasma concentration, therefore, appears to be a poor predictor of clinical effects. Since diazepam is highly bound to plasma proteins and many factors such as increased concentration of non-esterified fatty acids can alter this (Desmond et al., 1980), it is possible that the variable effects result from variability in the unbound drug concentration.

Blood concentrations of chlormethiazole correlate well with its central depressant effects (Seow, Mather and Roberts, 1981; Seow et al., 1981) and showed much less variability in producing the desired effect than did diazepam. Studies (Seow, Mather and Roberts, 1981; Seow et al., 1981) have shown that a blood chlormethiazole concentration of 9.2–10.3 mg litre\(^{-1}\) corresponded to the ideal clinical state of sedation (approximately 50% PASAT errors) in unpremedicated volunteer subjects. The slightly lower blood concentration associated with sedation obtained in this study may be attributed to the addition of premedication with pethidine decreasing the amount of sedative required during surgery.

In the absence of regional blockade, tachycardia, stable or increased arterial pressure (Wilson, Stephen and Scott, 1969; Seow et al., 1981; Seow, Mather and Roberts, 1981) may occur with chlormethiazole infusion. In the present study involving an analgesic level to T6, tachycardia was still evident. This property of chlormethiazole could be more important if a higher level of central neural blockade was obtained. The bradycardia induced by high neural block then may be counteracted by the tachycardia caused by the chlormethiazole.

In summary, both diazepam and chlormethiazole provided useful sedation to supplement regional blockade in the regimens used. However, control of the sedative state and predictability of the sedation and amnesia was easier with chlormethiazole. As far as recovery was concerned, there was no difference between either agent when surgery was prolonged and the dose of either agent was high — since there was prolonged somnolence and amnesia after operation, with a tendency to relapse into a clinical state of sedation after apparent recovery. With short surgical procedures when total volume of 0.8% chlormethiazole infused was small (that is, less than 300 ml), there was a distinct advantage of chlormethiazole over diazepam, manifested in a rapid and lucid recovery.

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