The imidazobenzodiazepine derivative Ro 15-1788 (anexate) was first described by Hunkeler and colleagues (1981). Studies in animals and human volunteers have shown this compound to be an effective specific antagonist of the behavioural, neurological and electrophysiological effects of benzodiazepines (Darragh et al., 1981; Polc et al., 1981) which binds with high affinity ($K_D = 0.9 \text{ nmol litre}^{-1}$) to central benzodiazepine receptors (Mohler and Richards, 1981). In man, this drug is devoid of the typical behavioural effects of agonist benzodiazepines (Darragh et al., 1983), although it does exhibit anticonvulsant activity (Scollo-Lavizzari, 1984) and, possibly, an effect on stage 4 sleep (Gaillard and Blois, 1983). Its clinical efficacy as a benzodiazepine antagonist, recently reviewed by Lupolover and Amrein (1984), has been well demonstrated in human volunteers and in patients with benzodiazepine intoxication (Scollo-Lavizzari, 1983). This study was designed to determine dose requirements and the time-intensity profile of response, when anexate was administered in the postoperative period to patients sedated with midazolam.

**PATIENTS AND METHODS**

**Patient selection**

Patients selected were caucasian males scheduled for transurethral resection of the prostate (TURP), those excluded being patients already receiving benzodiazepine medication and patients with severe ventilatory disease. The study was approved by the Hospital Ethical Committee and informed consent was obtained from every patient. A total of 70 patients were entered in the trial, but five subjects were subsequently withdrawn and are not included in the results. Of these, two patients departed from the design of the study as a result of a requirement for concurrent opioid-induced pain relief, one antagonist-treated patient died 8 h after surgery because of non-drug related acute valvular heart disease (tricuspid incompetence), one patient was resuscitated from ventricular fibrillation before receiving drug/placebo, and one patient was excluded on the grounds of insufficient data.
Patients were premedicated with midazolam 7.5 mg by mouth given 30–60 min before operation, supplemented by a further 1–4 mg i.v. if patients were apprehensive before the start of anaesthesia. No hypnotics were given the evening before surgery. Spinal anaesthesia was produced, after crystalloid volume loading, using hyperbaric amethocaine solution 7–14 mg injected via a lumbar space. I.v. increments of midazolam 1–4 mg were given to maintain light to moderate sedation so that patients were drowsy with intermittent or sustained eyelid closure throughout the procedure until their transfer to the recovery ward. On arrival in the recovery ward, vital signs were observed, then patients were scored for degree of sedation, comprehension and collaboration, orientation in time and space, and anterograde amnesia, according to the scoring system given in figures 3, 4, 5 and 6. All scoring was performed by one of three people (D.J.S., R.A.B., A.C.). Anterograde amnesia scores were based on visual recall as follows. A board displaying five pictured items (e.g. animals) was shown to the subject for 1 min. These items were mixed with five similar items on the reverse of the board, which was shown to the subject 5 min later. If no errors were made by the patient in identifying the original five items from the new group of 10, the score was 0. One error scored 1, two errors scored 2 and three errors scored 3, corresponding to scores of slight, moderate and severe anterograde amnesia. For each patient, five different sets of pictures were used, rotated over the seven testing occasions so that the first two boards were used again for the last two testing occasions. Comprehension and collaboration were scored by assessing patients’ ability to blow into a hand-held Wright’s respirometer. Since vital capacity measured in this way in sedated patients does not truly reflect ventilatory function, the test was used as a means of scoring comprehension and task performance. The ability to complete the test unaided generated a score of 2, completion with assistance scored 1 and failure to complete the manoeuvre even with assistance scored 0. Orientation in time and space were assessed by direct questioning. Correctly stating the month, the days of the week, and date together scored 1, although 2 days either side of the correct date were accepted as correct. A score of 1 was also given when patients correctly identified their location; thus, a fully oriented subject scored 2.

Following these baseline measurements, drug or placebo was given i.v. in a random fashion, administered double-blind from coded ampoules that contained either active drug or a placebo consisting of drug vehicle only. Drug/placebo was given via a large vein in a freely running infusion. Patients 1–31 received anexate in its first formulation (a mixed-micelle solution, 1.0 mg ml\(^{-1}\)) and patients 31–65 received the second formulation (aqueous solution 0.1 mg ml\(^{-1}\)). In all patients an initial dose of 0.2 mg was given followed by increments of 0.1 mg at 1-min intervals to a maximum of 0.5 mg if the patient had not been restored to normal consciousness by the previous dose. Vital signs, degree of sedation, comprehension, orientation and short-term memory were observed 5 min after the injection of drug or placebo, and at 15, 30, 60, 120 and 240 min.

Statistical analysis was performed using unpaired Student’s t test on the demographic data and multivariate analysis of variance on the measures of drug efficacy and physiological response.

### RESULTS

The drug-treated and placebo groups were the same with regard to number of patients, age, weight, height and ASA class. Both groups required similar doses of amethocaine (subarachnoid) and midazolam i.v. (table I). The midazolam dose range (7.5–55.5 mg) was the total of both preoperative and intraoperative increments of the drug, the individual doses showing marked

| TABLE I. Details of 65 patients undergoing TURP: comparison of control and benzodiazepine antagonist-treated groups. Values are mean ± SD. \( *P < 0.01 \) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Placebo group   | Anexate group   |                 |
|                 | \((n = 33)\)    | \((n = 32)\)    |                 |
| Age (yr)        | 70±13           | 74±6            |                 |
| Weight (kg)     | 72±12           | 70±12           |                 |
| Height (cm)     | 174±6           | 170±14          |                 |
| Amethocaine dose (mg) (range 7–14) | 9.9±1.5 | 10.2±1.5 |                 |
| Total midazolam dose (mg) (range 9.5–55.5) | 16.3±8.2 | 16.1±6.1 |                 |
| Anexate/placebo dose (mg) (range 0.15–5) | 0.45±0.10* | 0.36±0.09* |                 |
variability as a result of considerable variation in the initial dose required to achieve sedation, as well as variation in duration of the operative procedure. Cognitive scores and measurements of vital signs immediately after operation, but before reversal, were the same for each of the two patient groups. The mean “dose” of placebo administered was equivalent to 0.45±0.10 mg of the antagonist (mean±SD). Mean placebo “dose” significantly exceeded mean anexate dose because of the requirement for the administration of 0.1-mg increments of the blinded drug until normal consciousness was restored.

Vital signs

Differences between the treatment groups were not significant. Mean systolic and diastolic arterial pressures increased progressively after injection in each group as a result of the decreasing effect of the subarachnoid anaesthesia, and although mean systolic arterial pressures in the anexate-treated group were slightly higher than in the control group, the differences were not significant (fig. 1). Mean heart rate remained unchanged after the injection in both groups, and mean ventilatory rates showed slight decreases (1–2 b.p.m.) over the first 4 h after injection which were significant \( (P < 0.01) \)—ventilatory rates decreasing similarly in both groups (fig. 2).

Reversal of sedation

Dramatic awakening of many previously deeply comatose patients was reflected in the significant immediate reduction in mean sedation scores that
Anterograde amnesia

Severe anterograde amnesia was seen in both treatment groups immediately before injection. The anexate-treated patients showed an immediate improvement 5 min after injection which was maintained throughout the 4-h study period, whereas the placebo group took 2 h to achieve comparable levels of memory retention (fig. 4).

Orientation in time and space

Antagonist-treated patients became almost fully oriented immediately after injection when compared with the poor orientation of the placebo group, an effect that lasted for the remainder of the study. The placebo-treated patients exhibited a gradual improvement in orientation that equalled the drug-treated group by 120 min (fig. 5).
Comprehension and collaboration

Immediately following injection, anexate-treated patients showed marked increases in mean comprehension and collaboration scores that remained significantly greater than the placebo group for 60 min (fig. 6).

Haemoglobin and blood chemistry

Preoperative values for haemoglobin concentration, serum osmolality and the serum concentrations of sodium, potassium, urea, glucose and total protein were within normal limits and there were no differences between the two groups. By the 1st day after operation, all these values had changed but there were no significant differences between the groups in any of these variables.

Local reaction

There appeared to be no pain on injection of drug/placebo, but many subjects were heavily sedated at the time of injection. No venous irritation was observed immediately following the administration of anexate or vehicle in either formulation. At follow-up on the day after surgery, there were two cases of mild phlebitis which were attributed to blood transfusion and the administration of antibiotics i.v.

DISCUSSION

Anexate (Ro 15-1788), as used in this study to reverse sedation by midazolam, appears safe and effective. Changes observed in vital signs were consistent with the decreasing effectiveness of the subarachnoid anaesthesia rather than as consequences of the reversal of the effects of the benzodiazepine, and there was no evidence of immediate or delayed anxiety. Midazolam-induced sedation and impairment of comprehension were restored to normal values 5 min after the injection of anexate, indicating complete reversal of these effects of midazolam, but the less than complete orientation scores of 1.7-1.9, may reflect a residual orientation deficit in some anexate-treated patients or a general failing amongst the older patients in this study. Anterograde amnesia never returned to zero although, as with orientation, the true baseline performance in this test was not established in the preoperative period. Whereas placebo-treated patients tended to become gradually less sedated as a result of the offset of the action of the midazolam, exactly the opposite was true of the antagonist-treated patients who, following reversal, gradually became more sedated because of the offset of the antagonism produced by the anexate. The shorter acting effect of anexate compared with that of midazolam in the doses used is consistent with the difference in elimination half-lives (54–84 min (Klotz et al., 1985)) and 155 min (Lauven et al., 1985) for anexate and midazolam, respectively. The placebo-treated patients also showed spontaneous gradual improvement in orientation, comprehension and anterograde amnesia, again as a result of the offset of the action of the midazolam. However, in contrast to the re-sedation seen in the antagonist-treated group, no deterioration in performance could be demonstrated for the other indices of cognitive function over the 4 h of the study. This difference may be attributable to lack of sensitivity in the other tests of cognition or observer bias, or reflect a differential effect of anexate. Despite the use of a wide dose range of midazolam to achieve moderate sedation (eye closure), all patients had complete reversal of sedation with an antagonist dose of 0.5 mg or less (0.36±0.09 mg (mean ± SD)) when given incrementally over 5 min. The experience of Lauven and colleagues (1985) using much larger i.v. doses in volunteers, produced spontaneous eye-opening in 30 s following 10 mg given to unconscious subjects. Similarly, EEG changes in awake, mildly sedated subjects were abruptly reversed by 1 min after i.v. anexate 5 mg in a study by Laurian and co-workers (1984). In the elderly men in the present study, the time from the initial injection to eye-opening was often up to 5 min, perhaps as a result of the smaller doses of anexate used, and the probably longer arm–brain circulation times in these patients.

In conclusion, this study found anexate to be safe and effective in doses of 0.5 mg or less in reversing the sedation, disorientation and anterograde amnesia induced with midazolam in a routine clinical setting. As reported in volunteers (O’Boyle et al., 1983; Lauven et al., 1985), our study also showed that mild re-sedation could be seen after 1 h, suggesting that the reversal of long-acting or larger doses of benzodiazepines with anexate may be temporary or incomplete, depending on dose. Further investigation is required to confirm the safety and clinical utility of this drug.
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REFERENCES

BRITISH JOURNAL OF ANAESTHESIA