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DOUBLE-BLIND STUDY OF THE REVERSAL OF MIDAZOLAM-SUPPLEMENTED GENERAL ANAESTHESIA WITH RO 15-1788†

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SUMMARY

The actions and side effects of the benzodiazepine antagonist Ro 15-1788 were evaluated in a randomized double-blind clinical study in which midazolam was used as an anaesthetic agent. Sixty women who underwent laparoscopy were treated with Ro 15-1788 or with placebo after the surgical procedure. Ro 15-1788 reversed the hypnotic effect of midazolam within a few minutes. The patients were alert, co-operative, oriented and had good recall of events after awakening. The effects were statistically better than placebo for up to 30 min after administration. Arterial pressure and heart rate remained stable and there were no significant side effects. The availability of Ro 15-1788 allows effective reversal of midazolam when this is used during general anaesthesia.

Several studies in animals have shown that the specific benzodiazepine antagonist Ro 15-1788 is highly effective in antagonizing the central effects of benzodiazepines by competitive inhibition (Möhler and Richards, 1983; Little and Bichard, 1984). Studies in healthy volunteers, and in patients, have shown that Ro 15-1788 can reverse benzodiazepine-induced sedation without producing toxic side effects (Darragh et al., 1982; Lauven et al., 1985). The purpose of this study was to evaluate the actions of Ro 15-1788 used to reverse midazolam given as part of a general anaesthetic technique for laparoscopy.

PATIENTS AND METHODS

Sixty women (ASA grades I and II) who were to undergo laparoscopy gave informed consent for inclusion in the study. Exclusion criteria were pregnancy, drug hypersensitivity or addiction to benzodiazepines. All patients were premedicated with midazolam 7.5 mg by mouth and anaesthesia was induced with midazolam 0.2 mg kg^{-1}. Suxamethonium was given to facilitate tracheal intubation. Anaesthesia was maintained with 50% nitrous oxide in oxygen and 0.6–1.5% enflurane. Supplements of midazolam 0.1 mg kg^{-1} were given when needed. Neuromuscular blockade was obtained with atracurium. At the end of surgery the enflurane and nitrous oxide were discontinued and neuromuscular blockade antagonized with neostigmine. After extubation of the trachea, 2 ml of a solution containing Ro 15-1788 0.2 mg or placebo was injected. Increments of 1 ml were given every 30 s until the patient was awake or a total of 10 ml had been given. The study was double-blind and patient allocation was random.

The patients were assessed before, and 5, 15, 30, 60 and 120 min after injection. The degree of sedation was graded on a scale of 0–3 (0 = sleepy not arousable; 1 = sleepy but arousable; 2 = drowsy and 3 = alert). Co-operation and comprehension, evaluated by orders to raise the head and to shake hands, were graded on a scale of 0–2 (0 = no execution of the order; 1 = imitation only and 2 = execution of the order). Orientation was graded from 0 to 2

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according to the patient's awareness of the day of the week and where she was (0 = disorientation; 1 = orientation in time *or* in space and 2 = orientation in time and in space). Amnesia (0 = none; 1 = slight; 2 = moderate and 3 = marked amnesia) was tested by showing the patients pictures and evaluating subsequent recall.

Arterial pressure, heart rate, side effects (graded as mild, moderate and severe) and the need for analgesics during the first 24 h after surgery were also monitored. Subjective assessment of awaking was evaluated 1, 2 and 4 h after injection and graded on a 4-point scale (0 = poor; 1 = satisfactory; 2 = good and 3 = excellent awakening).

Results were analysed using the two sided Mann–Whitney U test for evaluating the efficacy of Ro 15-1788 and for the haemodynamic variables. Fischer's exact test was used to compare the side effects. Values were considered significant when $P < 0.05$.

RESULTS

Table I shows that the two groups of patients were comparable in respect of age, weight and height as well as duration of operation and of anaesthesia. The dose of midazolam (mean ± SD) used was 17.3 mg ± 6 in the test group and 16.6 mg ± 4.6 in the placebo group. In both groups midazolam 0.27 mg kg^{-1} was required. Figure 1 shows the results in the two groups. Before the injection of Ro 15-1788 there was no difference between the groups: all patients were asleep, unrousable and

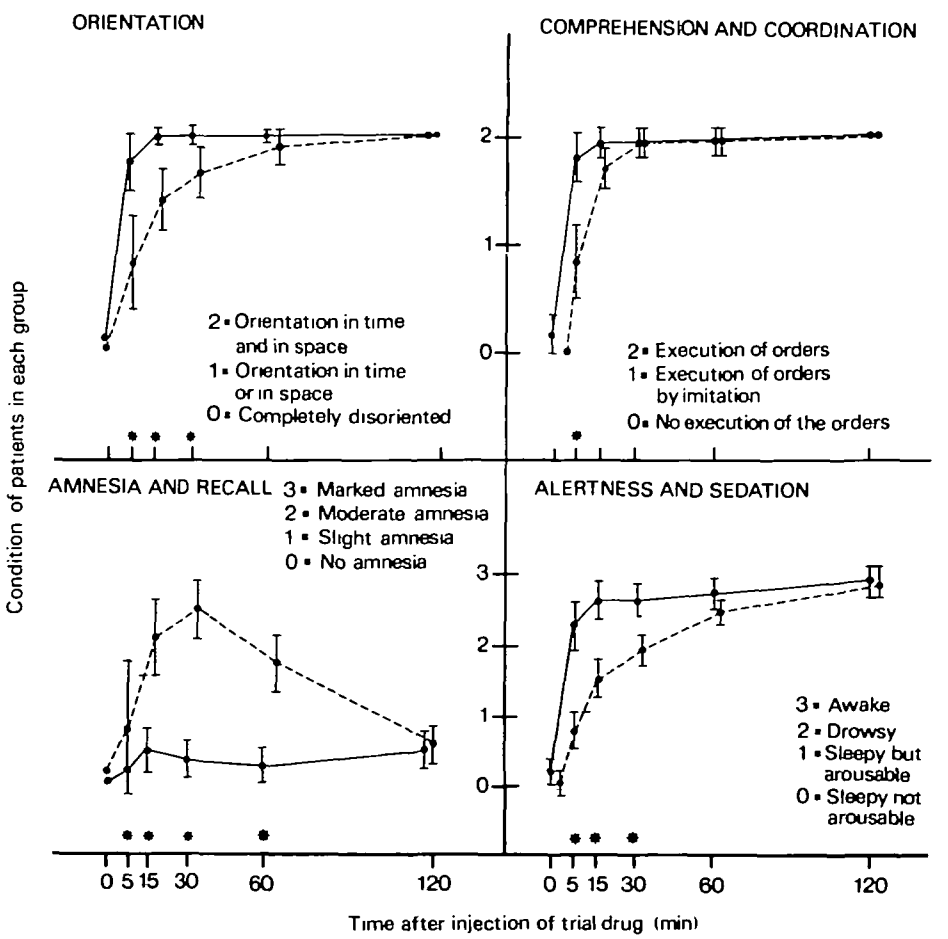

FIG. 1. Patients' clinical condition after injection of trial drug or placebo (mean ± confidence intervals). *Statistically significant ($P < 0.05$). ●——● = Ro 15-1788; ●---● = placebo.

TABLE I. *Details of patients included in the study, duration of surgery and duration of anaesthesia in both groups of patients (mean ± SD)*

	Ro 15-1788	Placebo
Age (yr)	30.7 ± 6.3	35.9 ± 6.8
Weight (kg)	62.0 ± 22.5	60.2 ± 9.5
Height (cm)	157.8 ± 16.8	164.2 ± 6.7
Duration of surgery (min)	38.4 ± 15.7	43.0 ± 15.1
Duration of anaesthesia (min)	56.7 ± 16.9	58.3 ± 14.6

TABLE II. *Side effects after injection of trial drugs in both groups of patients. *Statistically significant difference (P < 0.05)*

Side effects	Ro 15-1788	Placebo
Nausea*	11	3
Vomiting	5	4
Tremor	6	4
Involuntary movements	5	4
Headache	1	3

unco-operative (graded 0). Orientation and amnesia were therefore graded 0. Five minutes after the injection the differences between the groups were statistically significant and at 15 and 30 min the patients given Ro 15-1788 were fully awake, co-operative, oriented in time and space and had no amnesia. In contrast, patients who received placebo remained sleepy, unco-operative and disoriented, with slight to moderate amnesia. By 2 h, performance was similar in both groups: all patients were awake. The amount of Ro 15-1788 required varied between 0.3 and 1 mg (mean dose 0.6 mg; SD 0.27).

Systolic and diastolic arterial pressures and heart rate remained stable and did not differ significantly between the two groups. Mild to moderate pain at the site of i.v. injection was reported by eight patients who received Ro 15-1788 and five in the placebo group, a difference which was not statistically significant. No local irritation and no signs of thrombophlebitis were observed in any of the patients. Side effects are shown in table II. The difference between the groups was statistically significant only for nausea, which was graded as only mild or moderate. The postoperative requirement for analgesics was the same in both groups.

All patients reported good to excellent subjective impressions of awakening.

DISCUSSION

This study was undertaken to evaluate Ro 15-1788 and its side effects when given after midazolam-supplemented general anaesthesia. Previously, Lauven and colleagues (1985) administered Ro 15-1788 10 mg i.v. in the presence of a stable concentration of midazolam and demonstrated its prompt effect in an open study. Doenicke and colleagues (1984) showed that Ro 15-1788 0.1 mg kg^{-1} could antagonize an anaesthetic dose of flunitrazepam. This study demonstrated that Ro 15-1788 0.01 mg kg^{-1} could antagonize an anaesthetic dose of midazolam.

The effectiveness of Ro 15-1788 was demonstrated by comparing with placebo its effect on alertness, orientation, comprehension of and co-operation with commands, and recall at the end of anaesthesia. The results indicated that recovery was much faster after the administration of Ro 15-1788. No rebound effects were encountered, probably because of the relatively small amount of benzodiazepine administered. Reports on patients comatose as a result of benzodiazepine intoxication have shown that repeated doses of Ro 15-1788 may be required (Geller, Niv and Silbiger, 1985).

In an animal experiment Glisson and Falinski (1984) showed that Ro 15-1788 reversed the effect of midazolam on catecholamines without adversely affecting haemodynamic stability and, in the present study, haemodynamic stability was maintained. Local tolerance of the drug was good and no potentially serious side effect occurred. There was more nausea in the Ro 15-1788 group and there were a few patients in both groups who reported a mild or moderate degree of tremor and involuntary movement. These results suggest that Ro 15-1788 may be a useful addition to the armamentarium of any anaesthetist using benzodiazepines.

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REFERENCES

Darragh, A., Lambe, R., Kenny, M., Brick, I., Taaffe, W., and O'Boyle, C. (1982). Ro 15-1788 antagonises the central effects of diazepam in man without altering diazepam bioavailability. *Br. J. Clin. Pharmacol.*, 14, 677.

Doenicke, A., Suttmann, H., Kapp, W., Kugler, J., and Ebenthener, H. (1984). Zur Wirkung des Benzodiazepin-Antagonisten Ro 15-1788. *Anaesthesist*, 33, 343.

Geller, E., Niv, D., and Silbiger, A. (1985). Ro 15-1788 a benzodiazepine antagonist in the treatment of 34 intoxicated patients. *Anesthesiology*, **63**, (Suppl.), A157.

Glisson, S. N., and Falinski, B. S. (1984). Reversal of midazolam's effect on autonomic responses in dogs by the benzodiazepine antagonist Ro 15-1788. *Anesthesiology*, **61**, (Suppl.) A324.

Lauven, P. M., Schwilden, H., Stoeckel, H., and Greenblatt, D. J. (1985). The effect of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. *Anesthesiology*, **63**, 61.

Little, H. J., and Bichard, A. R. (1984). Differential effects of the benzodiazepine antagonist Ro 15-1788 after "general anaesthetic" doses of benzodiazepines in mice. *Br. J. Anaesth.*, **56**, 1153.

Möhler, H., and Richards, J. G. (1983). Benzodiazepine receptors in the central nervous system. Benzodiazepine antagonists; in *The Benzodiazepines: From Molecular Biology to Chemical Practice* (ed. E. Costa). New York: Raven Press.