

## CLINICAL EVALUATION OF A SPECIFIC BENZODIAZEPINE ANTAGONIST (RO 15-1788)

*Studies in Elderly Patients after Regional Anaesthesia under Benzodiazepine Sedation*

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Several drugs have been administered to patients in an attempt to antagonize the clinical effects of the benzodiazepines (BZD). Of these, physostigmine seemed to be the most effective (Caldwell and Gross, 1982), although it was not totally reliable (Garber et al., 1980). The efficacy of naloxone (Jordan et al., 1980; Forster, Morel et al., 1983) and aminophylline (Stirt, 1981; Meyer, Weis and Müller, 1984) remains controversial.

Recently, a new class of BZD, the imidazodiazepines, have been developed, some of which specifically antagonize the action of the BZD by competition at BZD-receptors in the central nervous system (Hunkeler et al., 1981). Of these, RO 15-1788 (RO) has been selected for clinical trials because of its lack of toxicity and its efficacy in antagonizing the effects of BZD in man (Darragh et al., 1981). The anticonvulsant action of RO (Scollo-Lavizzari, 1984) and the electrophysiological modifications described by Schöpf and colleagues (1984) are the only objective evidence of agonist effect in man. However, subjective symptoms such as drowsiness and dizziness have been described in volunteers when RO was administered alone (Darragh et al., 1983) and other objective agonist properties have been demonstrated in animals (Dantzer and Perio, 1982). Depending on the details of the investigation and dose given, inverse agonist effects of RO, such as anxiety, have been described in man (Louis et al., 1984) and animals (File, Lister and Nutt, 1982).

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### SUMMARY

*The efficacy, usefulness and side effects of RO 15-1788 (RO), a specific benzodiazepine (BZD) antagonist, have been evaluated. Sixty-two patients (ASA I-III, mean age 72 ± 9 yr) scheduled for urological surgery under regional anaesthesia and BZD sedation received placebo or RO in a randomized, double-blind fashion at the end of the procedure, following sedation with midazolam. When compared with placebo, RO improved alertness and collaboration for 15 min, and suppressed anterograde amnesia for 60 min. No major side effect was noted, although five patients became anxious after administration of RO. Two cases of a paradoxical reaction to midazolam were treated successfully by RO.*

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Transurethral resection of tumours of the bladder or prostate is usually performed under regional anaesthesia, because it allows earlier recognition of complications such as water intoxication (Desmond, 1970) and permits better monitoring of the patient's clinical state (Marx and Orkin, 1962).

Nevertheless, adequate preoperative and perioperative sedation is desirable since it permits the use of regional anaesthesia in a relaxed and co-operative patient (Greenblatt, Shader and Abernethy, 1983). In addition, it improves operative conditions and the acceptability of these procedures for the patients, who must lie immobile in an uncomfortable position (lithotomy) on a hard operating table, for more than 1 h.

Sedation can be obtained easily with a non-analgesic sedative agent such as a BZD, which produces good anxiolysis and anterograde amnesia

without inducing major cardiorespiratory depression, even in elderly patients (Pearce, 1974). However, at the end of surgery it is desirable to have an awake, well-orientated and collaborative patient so that better understanding and participation in postoperative care can be obtained. Since the intensity and the duration of the BZD sedation are difficult to predict—particularly in elderly patients (Kanto et al., 1979; Greenblatt, Sellers and Shades, 1982; Greenblatt et al., 1984)—the reversal of the sedation with a specific BZD antagonist could be useful.

The purpose of the present study was to confirm the efficacy of RO in a clinical situation, to assess its duration of action and its side effects, and to determine whether its routine administration in elderly patients after regional anaesthesia under BZD sedation was of any value.

#### PATIENTS AND METHODS

After approval by the Hospital Ethical Committee, 62 patients of both sexes, ASA classes I–III, scheduled for transurethral resection of tumours of the prostate or bladder, gave their informed consent and participated in the study.

All patients with hypersensitivity to BZD, impairment of consciousness, behaviour or memory, hepatic or renal insufficiency (diagnosed on biochemical tests), or who were receiving prolonged treatment with sedative or psychotropic drugs were excluded from the study.

#### *Preoperative sedation and anaesthetic technique*

On the evening before operation, all patients received chloral hydrate 20 ml by mouth. On the day of the operation, 1 h before the arrival of the patient in the operating room, midazolam 7.5 mg was administered by mouth to patients of less than 60 kg, and midazolam 15 mg to those weighing more than 60 kg.

On arrival of the patient in the operating room, a cannula (Venflon 17-gauge) was inserted to a peripheral vein, and an infusion of lactated Ringer's solution was started. Spinal anaesthesia was performed with amethocaine in 58 patients, and in one patient in each group extradural anaesthesia was instituted with lignocaine or bupivacaine (segmental level of T8–10.).

Once the quality of the regional anaesthesia had been assessed, midazolam 0.05 mg kg<sup>-1</sup> followed by incremental doses of 1.5 mg was injected i.v. to obtain the desired state of sedation (patient asleep,

but rousable on command). When the degree of sedation became insufficient, a further dose of midazolam 1.5 mg was injected to maintain the desired state of sedation (unless it appeared likely that the operation would be completed within the next 15 min).

At the end of surgery, either RO 0.1 mg kg<sup>-1</sup> or placebo (solvent = glycolic acid, 40% NaOH, lecithin, HCl, H<sub>2</sub>O) was injected over 30 s, in a double-blind and randomized fashion.

#### *Measured variables*

Routine laboratory tests were performed before and after the operation to exclude an impaired state of consciousness resulting from water intoxication. Routine haemodynamic variables were measured throughout the study.

In order to assess the effects of RO on the central nervous system, the degrees of sedation, of comprehension and collaboration and temporospatial orientation were evaluated the day before surgery, on arrival in the operating area, 15 min after the injection of midazolam, and at 5, 15, 30, 60, 120 and 240 min after the administration of RO or placebo. No determination was made just before the end of surgery, in order to avoid any stimulation of the patients, which could have modified their response to the injection of the test drug (placebo or RO). The evaluation of the central nervous system was scored as indicated in table I. Sedation was evaluated as described elsewhere (Nisbet and Norris, 1963) and degrees of comprehension and collaboration were determined by asking the patients to execute simple gestures such as inflating the cheeks or raising their hands.

TABLE I. *Scoring of tests for CNS evaluation*

Sedation	
0	= awake and tense.
1	= awake and relaxed
2	= drowsy
3	= asleep but arousable
4	= asleep, not arousable
Comprehension and collaboration	
0	= order executed on command
1	= order executed on imitation
2	= order not executed at all
Temporo-spatial orientation	
0	= totally disorientated
1	= orientated in one of the two modes
2	= orientated in both modes

Vital capacity, measured with a Wright spirometer, was considered more as an objective test of comprehension and collaboration, than as an evaluation of respiratory volume. Presence and duration of anterograde amnesia were evaluated by standard methods (Benton, 1953) and by asking patients to recall the different events of the day of the operation such as arrival in the operating room, the anaesthetic procedure and the surgery.

The results are presented as mean values  $\pm$  standard deviation (SD). Data from the same group were statistically analysed by paired *t* test or one-way analysis of variance; when the two groups were compared, either unpaired *t* test or Wilcoxon rank sum test was used depending on the distribution. The Chi-square test was utilized for non-parametric data. The differences were considered statistically significantly if  $P < 0.05$ .

#### RESULTS

Thirty patients received the antagonist RO 15-1788 (group RO) and 30 the placebo (group PL). Two other patients at first included in the study had to be excluded because of an unexpected reaction to midazolam.

Physical characteristics were similar in both groups (table II). There were no differences in medication or reasons for operation between the groups.

The total dose of midazolam injected during the operation was comparable in both

TABLE II. Physical characteristics of the patients (mean values  $\pm$  SD)

	PL group (n = 30)	RO group (n = 30)
Age (yr)	71.5 $\pm$ 8.6	70.2 $\pm$ 9.6
Sex (F/M)	3/27	3/28
Weight (kg)	73.1 $\pm$ 11.2	76.6 $\pm$ 12.8
Height (cm)	169 $\pm$ 8	170 $\pm$ 7

groups:  $4.33 \pm 1.86$  mg in the PL group and  $4.77 \pm 2.44$  mg in the RO group. The time interval between the first injection of midazolam and placebo or RO was similar being, respectively,  $58.1 \pm 25.7$  min and  $59.46 \pm 26.7$  min.

Apart from an increase in blood glucose concentration and a decrease in serum sodium concentration which were not clinically important, no significant changes occurred in the other laboratory variables. All the haemodynamic variables remained stable throughout the study, with the exception of a significant decrease in arterial pressure after midazolam, which was not relevant clinically.

The effects of placebo or RO on midazolam-induced sedation are summarized in figure 1 and table III. The preoperative degree of alertness and of sedation induced by administration of midazolam by mouth or i.v. was similar in both groups up to 15 min before the end of surgery. However, following the injection of the placebo or RO, the level of sedation was significantly less in the RO group when compared with the placebo

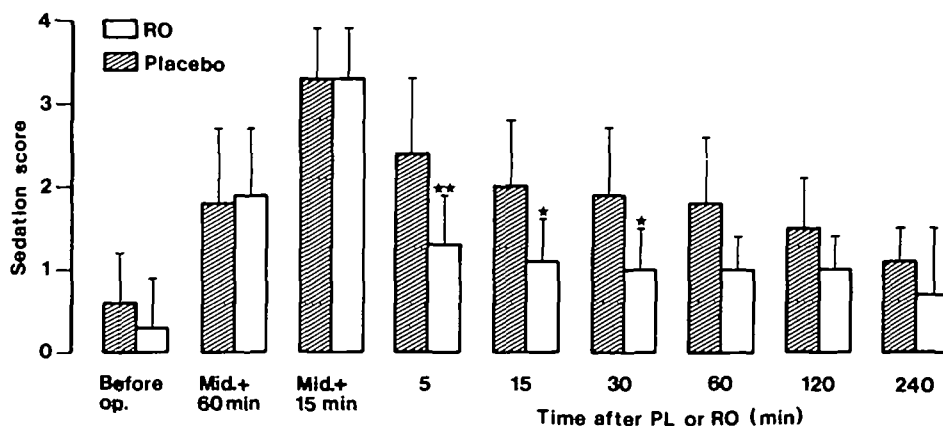


FIG. 1. Degree of sedation (mean score  $\pm$  SD) ( $n = 30$ ) determined before surgery, 60 min after oral (Mid. + 60 min) and after i.v. (Mid. + 15 min) midazolam, and for up to 240 min after the administration of RO or placebo (PL) i.v. \* $P < 0.05$ ; \*\* $P < 0.01$  (Wilcoxon rank sum test).

TABLE III. Number of patients whose scores of sedation were increased (Inc.) or decreased (Dec.) or whose sedation scores remained unchanged (Same) after the administration of placebo (PL) or RO, up to 240 min (n = 30). \*\*P < 0.01 Chi-square test

Score	5 min after		15 min after		30 min after		60 min after		120 min after		240 min after	
	PL	RO	PL	RO	PL	RO	PL	RO	PL	RO	PL	RO
Inc.	1	0	0	0	1	0	0	0	0	0	0	0
Same	9**	0	6	0	4	0	6	0	2	1	0	1
Dec.	20**	30	24	30	25	30	24	30	28	29	30	29

group, even though the degree of sedation after placebo did decrease spontaneously. This difference remained significant for 30 min, after which the degree of sedation was comparable in the two groups (fig. 1). When the comparison was made between the number of patients in whom sedation increased or decreased after the injection of PL or RO, the differences between the groups persisted for less than 15 min (table III).

Data concerning the comprehension and collaboration using the simple tests already described were difficult to interpret: there was only a significant decrease in aptitude in both groups after i.v. administration of midazolam. No difference was noted at any time when the two groups were compared. When collaboration was tested more objectively with the measures of vital capacity (table IV), both groups decreased their capacities after midazolam administered i.v. or by mouth. When compared with placebo, RO im-

proved the performance significantly for less than 15 min.

No difference in temporo-spatial orientation could be noted at any time between the groups: a similar degree of disorientation was observed after oral and i.v. midazolam. After PL or RO injection, equal number of patients in both groups were well orientated.

The results concerning anterograde amnesia are summarized in table V. Whereas no patient had any impaired recall on the day before operation, two-thirds of the patients, in both groups, suffered from anterograde amnesia after midazolam by mouth. After i.v. midazolam, amnesia was present in 29 patients in group PL and in 30 in group RO. RO reversed the amnesia in all the patients for at least 15 min, while at that time, in the PL group, 60% of the subjects still had problems with recollection. Sixty minutes after the injection of RO or PL, an increasing

TABLE IV. Vital capacity (litre min<sup>-1</sup>) (mean values ± SD). PL = placebo group; RO = 15-1788 group. \*P < 0.05 unpaired t test

	Before op.	60 min after midazolam by mouth	15 min after i.v. midazolam	Time after PL or RO (min)					
				5	15	30	60	120	240
PL	2.7 ± 0.8	2.1 ± 1	1.2 ± 1.2	1.8 ± 0.9	2.2 ± 0.8	2.2 ± 0.8	2.3 ± 0.8	2.4 ± 0.8	2.5 ± 0.7
RO	2.7 ± 0.8	2.3 ± 0.9	1.1 ± 1.2	2.3 ± 0.8	2.3 ± 0.8	2.4 ± 0.7	2.5 ± 0.8	2.5 ± 0.7	2.5 ± 0.7

TABLE V. Number of patients with anterograde amnesia (n = 30). PL = placebo group; RO = RO group. \*\*\*P < 0.001 (Chi-square test)

	Before op.	60 min after midazolam by mouth	15 min after i.v. midazolam	Time after PL or RO (min)			
				5	15	60	120
PL	0	20	29	18	17	22	8
RO	0	21	30	0	2	7	8

TABLE VI. Number of patients presenting side effects after injection of placebo (PL) or RO 15-1788 (RO) ( $n = 30$ ). †Subjective side effects = anxiety, sensation of impending death. \* $P = 0.052$  (Chi-square)

	Subjective side effects†	Nausea	Brady-cardia	Local intolerance
PL	0 *	3	1	3
RO	5	2	4	3

number of patients suffered from amnesia again, but significantly more after PL than after RO. There was no difference between the two groups, 120 min after the administration of RO or PL.

The side effects are indicated in table VI: there was no statistical difference between the two groups, although 17% of patients described feeling anxious after the injection of RO compared with none after placebo ( $P = 0.052$ ).

Two patients had to be excluded after the administration of midazolam by mouth because they became confused, disorientated and aggressive; these reactions to BZD were completely and quickly reversed by the injection of RO 0.1 mg kg<sup>-1</sup>.

#### DISCUSSION

This study confirms the efficacy, usefulness and safety of a BZD for pre- and peroperative sedation under regional anaesthesia in elderly and fragile patients, although an unexpected reaction occurred in two out of the 62 patients (3.2%) studied.

It also corroborates the efficacy of RO 15-1788 as a specific BZD antagonist, since the amnesia and sedation induced by midazolam were promptly reversed by this drug. The absence of effect of RO on tempo-spatial orientation and on the subjective evaluation of collaboration in both groups reflects more the absence of accuracy of these two tests than the inefficiency of the BZD antagonist since, when collaboration was measured objectively by asking patients to perform the vital capacity, it improved significantly after the injection of RO.

#### Duration

The duration of action of RO varies according to which variable is being considered—as described previously (Lauven et al., 1985). In the present study, the efficacy of RO lasted for less than 15 min when the incidence of improvement or deterioration in collaboration and sedation were

considered; it lasted less than 60 min when the effect on the incidence of amnesia and when scores of sedation were taken into account. The duration varied also according to the half-life of the BZD administered and of the study design (O'Boyle et al., 1983; Klotz et al., 1985). For example, when midazolam is infused continuously after injection of RO (Lauven et al., 1985), the duration of action cannot be compared with our data.

As the half-life of midazolam is estimated to be between 1.5 and 3.5 h (Dundee et al., 1984), the drug was partially eliminated at the time of RO injection; this explains why, 5 min after PL, 12 of the 30 patients were no longer amnesic.

#### Safety and side effects

No major undesirable effect of RO was observed: local tolerance was excellent. A light burning sensation without any subsequent phlebitis at the site of injection occurred in 10% of patients in each group, suggesting that this side effect was attributable to the solvent (glycolic acid, 40% NaOH, lecithin, HCl, H<sub>2</sub>O) and not to the active drug.

Although the incidence of anxiety and sensation of impending death was not statistically significant ( $P = 0.052$ ), it occurred after the injection of RO only. In spite of the fact that this kind of emotional reaction was not described in most previous investigations in man, it was observed in 100% of the patients and considered as a severe complication by Louis and colleagues (1984). However, this side effect occurred in less than 20% of our patients and could be easily treated by reassurance without the necessity to administer any sedative drug. This state could be attributed to the specific effect of the drug, influenced by the dose and rate of administration or by the preoperative emotional state which depends on environment, age and severity of disease, or both. Since no anxiety was observed when RO was administered alone (Darragh et al., 1983) or to reverse previously induced BZD sedation in many studies (Forster, Rouiller et al. 1983), a specific effect of the drug can be ruled out. The difference in incidence and severity of anxiety where RO was administered after the same dose of BDZ suggests that this psychological side effect is most probably related to the difference in emotional state between patients (Editorial, 1975). Indeed, in the study by Louis and colleagues, the subjects were stressed because of a more severe disease (coronary disease, undergoing aorto-coronary bypass sur-

gery) and a more hostile environment (intensive care unit) than our patients. The age of the patients could also be an important factor, since it is believed that elderly patients react differently to stress.

The hypothesis which suggests that a stressful situation enhances the production of endogenous ligands (Lippa et al., 1978; Braestrup et al., 1983) could explain the mechanism of the increased incidence of anxiety after the administration of RO in distressed patients. This theory is also substantiated by the fact that RO can produce a withdrawal syndrome (Lukas and Griffiths, 1982), which includes anxiety in patients chronically treated with BZD (Hallstrom and Lader, 1981).

### Indications

The therapeutic value of this new compound has yet to be determined. RO could be administered to allow a differential diagnosis of a confused state as, for example, during a transurethral surgery, to differentiate water intoxication from BZD-induced disorientation.

RO could be useful also when it is necessary to awaken a patient in the perioperative period (Harrington nodes, electrocoagulation of trigeminal nerve, etc.) or in intensive care unit to allow neurological evaluation of sedated patients.

Although caution should be taken in its current use, as mentioned by Ashton (1985), it has been documented that RO could be useful in drug intoxication in order either to treat a life-threatening situation, or to prove or exclude involvement of BZD (Scollo-Lavizzari, 1983; Hofer and Scollo-Lavizzari, 1985). It has obviated the need for mechanical ventilation in severe BZD intoxication (Geller et al., 1984).

A paradoxical reaction is a serious side effect of BZD, although it is rare and as yet not fully understood (Greenblatt and Shader, 1974). The subjects become confused and aggressive and can harm themselves. In this study, two patients presented such a reaction to midazolam; the administration of RO was very effective in treating and calming these patients, thus ensuring satisfactory operating conditions.

When a short acting BZD is administered, RO is probably unnecessary since, as shown in the study, most of its clinical effectiveness was no longer evident after 15 min. However, with longer-acting BZD such as diazepam or flunitrazepam, RO could be more useful, but should be

administered under close supervision—as when naloxone is administered after morphine (Johnstone et al., 1974), since its duration of action is shorter than that of such BZD.

For this reason, the authors suggest that RO should not be administered at the end of outpatient anaesthesia, since it could provide a transient improvement of alertness during which the patients could be released from the hospital.

Since evidence of a withdrawal syndrome has been reported in man as soon as after 6 weeks of BZD treatment (Murphy, Owen and Tyrer, 1984), RO should be administered with caution when patients have received BZD for a long period.

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