Title : CLINICAL AND HEMODYNAMIC EFFECTS OF A SPECIFIC BENZODIAZEPINE ANTAGONIST (RO 15-1788) AFTER OPEN HEART SURGERY

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Introduction. Because of their minimal cardiovascular effects, benzodiazepines (BZD) have been advocated for induction of anesthesia and sedation in intensive care in cardiac surgical patients.
Once the patients are extubated, the sedation induced by BZD may be undesirable because of the lack of collaboration and a prolonged immobilisation.
The purpose of this study was to evaluate, in open heart surgical patients, the potential beneficial effects of RO 15-1788 (RO) in antagonising the BZD induced sedation in the early postoperative (postop) period, and to assess its hemodynamic effects in a randomized and double blind fashion.

Methods. 20 patients (5 females, 15 males), undergoing open heart surgery under Fentanyl, N_2O, pancuronium anesthesia, consented to participate in the study, which was approved by the Committee of Ethics and Human Research of our Institution. Patients with history of chronic use or allergy to BZD were excluded. All the patients were equipped with a radial arterial catheter and a triple lumen pulmonary catheter, which allowed continuous recording of arterial and pulmonary pressures, measurements of central venous pressure (CVP) and pulmonary artery occluded pressure (PAOP), and determination of cardiac output (CO) using the thermodilution method. No other hypnotic drugs than BZD were administered for anesthesia and postop period. Induction was achieved with midazolam and postop sedation up to extubation with diazepam at a dose of 2.5 to 5 mg injected i.v., at least every three hours. Morphine sulfate was administered for postop analgesia, as clinically required.
Half an hour after extubation, while cardiorespiratory variables were satisfactory and stable, either RO at a dose of 0.1 mg/kg or Placebo (Plac) was injected i.v. over 30 secs in a randomized and double blind fashion. Clinical effects of the two drugs were assessed by evaluating alertness level, memory and orientation on a 0 to 2 scale before and 10 minutes after the injection. Measurements of vital capacity, at the same times, were performed to test the degree of collaboration. Hemodynamic variables were measured and calculated before and 1,3,5 and 10 minutes after the injection of RO or Plac.

Results. The major physical and clinical characteristics of the two groups (RO/Plac), constituted of ten patients each, were similar (table 1). There were also no differences in other variables such as temperature, biology, pre- and postop drugs regimens, duration of anesthesia and postop intubation. RO improved alertness level (p 0.001), memory (p 0.05) and collaboration (p 0.05) in significantly more patients than Plac did; orientation was comparable in the two groups (Chi square). Immediately after the injection, every patient of the RO-group manifested a feeling of discomfort associated in five patients with untolerable anxiety which required the administration of i.v. diazepam. None of these undesirable effects occured after Plac-injection.
Variations of heart rate (HR), mean systolic blood pressure (BP), and CO of the two groups are illustrated in figure 1. There were no significant differences when the two groups were compared at any time (unpaired t test), nor when comparison was made between pre- and post-injection data for either drug (analysis of variance). Systemic and pulmonary pressures and resistances, CVP, PAOP, stroke volume were also not influenced.
Discussion. This study confirms the efficacy of RO 15-1788 in antagonising BZD induced sedation, and demonstrates the absence of cardiovascular effects of this new compound, even when the patients became uncomfortable or very anxious after the injection. Since these untoward effects counteract the clinical benefit of RO on the level of consciousness, a routine administration of this drug to reverse the sedation induced by BZD in intensive care should not be advocated. However, when BZD intoxication is suspected, RO could be administered safely, as a diagnostic or therapeutic procedure, even in patients with impaired cardiovascular function.

Table 1 : Age, weight, left ventricular end-diastolic pressure (LVEDP), and postop dose of diazepam and morphine in the two groups ($\bar{x}$ ± SEM).

Group	Age (years)	Weight (kg)	LVEDP (mmHg)	Postop sedation Diazepam (mg)	Postop analgesia Morphine (mg)
Plac n=10	56 ± 3	77.7 ± 3.5	17.0 ± 2.2	21.6 ± 4.6	9.1 ± 1.8
RO n=10	58 ± 2	68.1 ± 4.3	14.0 ± 1.3	18.5 ± 1.9	10.5 ± 1.4

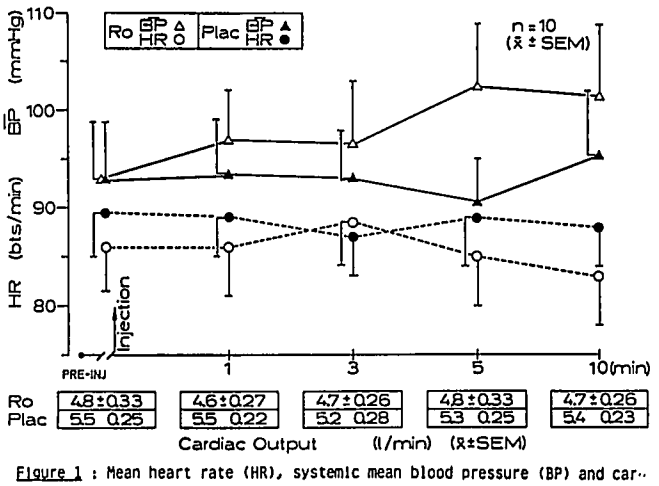

Figure 1 : Mean heart rate (HR), systemic mean blood pressure (BP) and cardiac output (CO) before and after administration of RO 15-1788 and Placebo.

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