Title: EFFICACY OF RO 15-1788, A BENDZODIAZEPINE ANTAGONIST, VS PHYSOSTIGMINE AFTER MIDAZOLAM-ALFENTANIL ANESTHESIA IN MAN


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Introduction: Midazolam (M) is frequently used for premedication and for intravenous sedation and/or hypnosis. A disadvantage of the use of M can be a prolonged postoperative sedation or hypnosis. Recently, a specific antagonist, RO 15-1788 (RO) has been developed, which reverses sedation by competition with benzodiazepines at the receptor level. In this study we compared the efficacy of RO and physostigmine (PH), a non-specific antagonist, after M-alfentanil anesthesia in man.

Methods: After approval of the local Ethics Committee and obtaining informed consent, 32 healthy patients, 18 to 44 years, who were to undergo surgery lasting between 0.5-2.5 h, were studied. The patients were not on benzodiazepine medication. They were premedicated with M 0.1 mg/kg 1h. 30 min before surgery. Anesthesia was induced with an i.v. bolus of alfentanil 0.150 mg/kg followed by infusion of 0.125-0.150 mg/kg/h, and vecuronium. After endotracheal intubation, M, 0.2 mg/kg, was given as an i.v. bolus followed by infusion of 0.06-0.36 mg/kg/h. All patients were ventilated with 30% N2O in O2 and supplemental doses of vecuronium were given if necessary. The alfentanil infusion was stopped 15 min before and the M infusion at skin closure. Residual neuromuscular blockade was antagonized with neostigmine and atropine. Ventilatory depression caused by alfentanil was antagonized with naloxone. After extubation, patients were transported to the recovery room where they were randomly allocated to receive either RO or PH. Injection was from a 30 ml syringe containing either 1 mg RO or 2 mg PH; 2 ml was given in the first min and 1 ml every next min until 10 ml was given. The time from the start of administration until awakening was noted. Heart rate, blood pressure and respiration rate were monitored throughout the study.

To determine the efficacy of RO vs PH, the patients were asked to perform two psychomotoric tests: the blocks- and deletion-of-P's test. Assessments were made the evening before, immediately before, and 5, 30, 60 and 120 min after injection. At the same times, the degrees of sedation (O=awake and tense, 1=awake and relaxed, 2=drowsy, 3=asleep but arousable, 4=asleep not arousable), orientation in time and space and local and general tolerance were noted. Statistical analysis was performed by the Mann-Whitney U-test, for comparison between the groups. Differences were considered significant at a P<0.05. Results are presented as mean ± SD.

Results: The RO (n=17) and PH (n=15) groups were comparable with respect to age, body weight, total amount of M (66.5 ± 10.6 mg in the RO group and 81 ± 24.4 mg in the PH group) and alfentanil (3.1 ± 17 mg in the RO group and 14.6 ± 12.4 mg in the PH group) administered. They had similar test scores on the evening before surgery. In the recovery room, before injection of RO or PH, all patients were heavily sedated and unable to perform tests or answer questions. After RO all patients were fully awake within 6-7 min, i.e. after 0.7-0.8 mg, but sedation recurred 10-20 min later in all but one patient. After PH, all but 2 patients remained sedated until 120 min, although to a lesser degree than before injection. Comparison of the efficacies of RO and PH showed that the degree of sedation was less, and test performance and orientation were better at 5 and 30 min after RO (fig). Heart rate, blood pressure and respiration rate did not change in the RO group. In the PH group heart rate increased to more than 140 beats/min in 7 patients and in 3 other patients the blood pressure decreased. Thermoblotchies from the site of injection were not observed. During the injection of RO 2 patients vomited. Between 30 and 120 min after PH 2 patients complained of nausea.

Discussion: The results demonstrate that RO is a more effective antagonist of high dose midazolam than PH with less hemodynamic side-effects. The onset of action of RO is short (<5 min). The duration of action of RO, 1 mg, is also short, as shown by the increase in the degree of sedation and the decreased test performances after 30 min. This is probably related to its pharmacokinetics: the elimination half-life of RO is 1 h, as compared to 1.5-2.5 h for M. Therefore the action of M may outlast a single bolus injection of RO.

References:

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