

**Title:** APPLICATION OF A BENZODIAZEPINE ANTAGONIST (RO 15-1788) UNDER STEADY-STATE CONDITIONS OF MIDAZOLAM

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**Introduction.** Benzodiazepines are widely used in anesthetic practice and intensive care medicine. So far no antagonist was available. To evaluate the pharmacological profile of the new antagonist Ro 15-1788 (A) it seems useful to counteract the benzodiazepine action under steady-state conditions. The drug chosen for this study was midazolam (M) because of its fast pharmacokinetic profile and its correlation of hypnotic effects to serum levels (2,3). In earlier studies a M serum level of 0.5 ug/ml was described to induce anesthesia characterised by loss of eye lid reflex and failure to respond to commands. The monitoring of EEG-background activity made it advisable to maintain serum levels of about 0.6 ug/ml for a secure hypnotic effect.

**Methods.** 7 healthy young volunteers participated in the study (with informed written consent and approval by the research committee). ECG and heart rate, blood pressure (by oscillotometry) and respiratory rate were monitored and blood gases were frequently checked. Clinical laboratory parameters were controlled prior to and 24 h and 7 d after the study. Multiple blood samples were taken for determining M serum concentrations by gas chromatography (1). Furthermore, an EEG was recorded continuously (4).

M steady-state conditions were achieved by a dosage regimen based on pharmacokinetic analysis of an open two compartment model. An initial fast infusion rate of 6.0 mg/min lasting 10 min was followed by a steady-state infusion of 0.275 mg/min to a total infusion period of 210 min and a total dose of 115 mg. 60 min after the start of the M infusion A was intravenously injected as a bolus dose of 10 mg.

Anesthetic state was defined as failure to respond to commands of 52-55 dB speech sound pressure level (SPL) after an acoustic stimulus of 82-87 dB SPL ante concha. The vigilance of the test persons was measured by performing psychomotor tasks at predetermined times. The test results were interpreted by the time-error-product (TEP).

**Results.** M serum concentrations reached and exceeded the desired value within 2 min and after initial overshooting remained near 0.6 ug/ml for the whole infusion period. After cessation of the infusion M serum levels declined according to a half-life of 2.5 h and a total plasma clearance of about 450 ml/min. 2 min after the start of the infusion all

test persons fell asleep. The above defined anesthetic state was maintained until the administration of A 60 min later. 30-50 s after A dosage all participants were awake and within 2 min fully orientated. About 30 min later they developed an anterograde amnesia lasting 180 min (median; range 75 - 240 min) after cessation of the M infusion. All test persons performed the first psychomotor task 15 min after administration of A. The last test after dosage of A was possible 90 min later. The first Test possible after cessation of the M infusion was performed in a median time of 45 min (range 15-180 min). At the end of the observation period (6 h after cessation) the TEP of the psychomotor tasks was increased by a factor of 1.75 compared to the TEP performed before the study.

All laboratory parameters remained within normal during the total observation period of one week. Neither severe cardiovascular nor any respiratory depression could be observed.

**Discussion.** It could be demonstrated that M administered as described is able to induce and maintain anesthesia. Despite the high dose infused serum half-life and total plasma clearance remained unchanged. These data again underline M to be the benzodiazepine of best controllability. Often it is desirable to antagonize the benzodiazepine action. This is possible with a substance like Ro 15-1788. After i.v.-administration the antagonizing effects can promptly be observed. This study additionally demonstrates that neither M up to a total dose of 115 mg nor Ro 15-1788 up to a dose of 10 mg induce changes in laboratory parameters of healthy young volunteers during an observation period of one week.

#### References.

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