

Title: ACTION OF A BENZODIAZEPINE ANTAGONIST DURING MIDAZOLAM INFUSION IN STEADY-STATE: QUANTITATIVE EEG STUDIES

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**Introduction.** Controllability of anesthesia esp. of the post operative period and critical care therapy with benzodiazepines could be enhanced by antagonizing their effect. This study was designed to evaluate the EEG effects of an i.v. bolus of a new benzodiazepine antagonist (Ro15-1788) during i.v. infusion of midazolam in steady-state.

**Methods.** The study contained 7 young healthy volunteers (3 females, 4 males). A loading dose of 6mg/min of midazolam (M) for 10 min and a maintenance dose of .275mg/min of M were instituted to reach steady-state plasma concentrations of 0.6 ug/ml within 45 min. 60 min after start of infusion a bolus of 10mg of Ro15-1788 (A) was given intravenously. Infusion of M was continued for 2.5 hours after administration of A. Anesthesia was defined as failure to respond to command of 52-55dB speech sound pressure level (SPL) after having set a stimulus of 82-87dB (SPL) ante concha. Four EEG traces ( $C_{-O_2}$ ,  $C_{-F_1}$ ;  $i=1,2$ ) were recorded for off-line analysis. The following parameters were calculated: median frequency (MF), mean amplitude (MA), percentage of activity in the bands: .5-2Hz, 2-5Hz, 5-8Hz, 8-12Hz and 12-32Hz. 10 min before midazolam infusion EEG recording was started and continued for at least 2 hours after the end ( $T_1$ ) of infusion. In parallel ECG, blood pressure, blood gases and respiratory rate were monitored.

Informed written consent and approval by the research committee were obtained.

**Results.** All volunteers displayed an alpha-type EEG. 2 min after start ( $T_0$ ) of infusion of M all volunteers had reached the above defined anesthetic level. Percentage of beta-activity as well as delta-activity increased in all cases. MF decreased to a minimum value of 1.3 Hz in 45 min. At that time percentage of EEG activity in the range of .5-2 Hz exceeded in all cases the 60% level. After the i.v. bolus of A all calculated EEG parameters returned to near normal values within 5 min. Except for the MA all parameters depicted in Tab.1 were indistinguishable (t-test) on a 5% level from the corresponding initial values. Within 120 min after administration of A all volunteers fell asleep but only 3 of them returned to the previously reached anesthetic state. At that time the EEG parameters esp. MF and percentage of delta and beta activity were much closer to the corresponding values at  $T +15'$  than to those at  $T +45'$  indicating the still persistent antagonistic action of A. 2 hours after cessation of infusion of M all volunteers were awake but power spectrum analysis (Fig.1) as well as calculated

parameters (Tab.1) showed marked differences from the initial values.

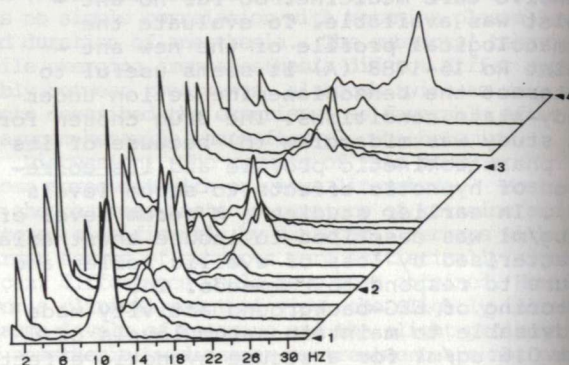


Fig.1: Power spectra for a typical case  
1: start of infusion; 2: i.v. bolus of A  
3: end of infusion; 4: awake

Time	MF (Hz)	MA (uV)	.5-5	8-12	12-32	State
	9.7	11.0	15.3	65.0	10.0	awake
10'	6.4	14.1	47.8	21.2	27.3	asleep
45'	1.3	15.7	77.1	11.7	12.3	asleep
5'	9.7	9.5	18.8	60.2	15.9	awake
30'	9.4	10.0	18.4	55.3	20.6	awake
60'	3.5 10.4	9.5 10.1	66.1 32.5	14.8 26.1	28.5 45.1	asleep awake
120'	6.6	11.2	59.9	13.3	31.9	asleep
60'	10.5 2.8	9.3 8.8	30.4 66.1	26.1 15.8	47.1 35.6	awake asleep
120'	11.2	8.1	29.9	24.5	45.2	awake

Tab1: Mean values (n=7) for MF, MA and percentage of activity in the indicated bands.  
1. line: initial values  
2. part: values after start of midazolam inf.  
3. part: values after cessation of midazolam infusion

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