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

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Introduction.Controllability of anesthesia espc. 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 1omin and a maintenance dose of .275mg/min of M were instituted to reach steady-state plasma concentrations of o.6 ug/ml within 45min.6omin after start of infusion a bolus of 1omg 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_z-O_i,C_z-F_i; 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.1o 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 commitee were obtained.

Results.All volunteers displayed an alpha-type EEG.2 min after start(T_o) of infusion of M all volunteers had reached the above defined anesthetic level.Percentage of beta-activity as well as delta-activity in creased 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 6o% 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 12o 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 espc. MF and percentage of delta and beta activity were much closer to the corresponding values at T_o+15' than to those at T_o+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.

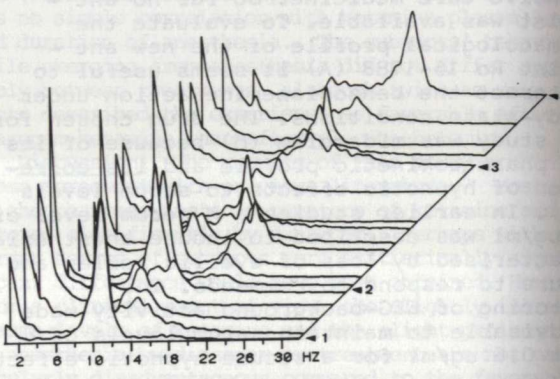

Fig.1: Power spectra for a typical case
1: start of infusion; 2:i.v.bolus ofA
3: end of infusion; 4: awake

Time	MF(Hz)	MA(uV)	.5-5	8-12	12-32	
	9.7	11.o	15.3	65.o	1o.o	awake
1o'	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	6o.2	15.9	awake
3o'	9.4	1o.o	18.4	55.3	2o.6	awake
60'	3.5	9.5	66.1	14.8	28.5	asleep
	1o.4	1o.1	32.5	26.1	45.1	awake
120'	6.6	11.2	59.9	13.3	31.9	asleep
60'	1o.5	9.3	3o.4	26.1	47.1	awake
	2.8	8.8	66.1	15.8	35.6	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
1.part:values after start of midazolam inf.
2.part:values after i.v. bolus of Ro15-1788
3.part:values after cessation of midazolam infusion