TITLE: PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF THE INTERACTION BETWEEN FLUMAZENIL AND MIDAZOLAM WITH APERIODIC EEG ANALYSIS, IN VOLUNTEERS

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We developed a pharmacokinetic-pharmacodynamic interaction model for midazolam (M) and flumazenil (F), a benzodiazepine antagonist. CNS effects were quantified with TNW_{12-30} (total number of waves between 12-30 Hz)[1], a parameter derived from the EEG with an aperiodic analysis technique. F has no intrinsic effect on this parameter.[2]

After obtaining institutional approval and informed consent 8 male volunteers participated in the study, which consisted of 3 experimental sessions, separated by one week. During investigations, the subjects were in the supine position with eyes closed. After a 15-min baseline EEG recording between Fp_1-M_1 and Fp_2-M_2, an infusion of placebo or F was started. The infusion scheme was designed to attain 'steady state' plasma F concentrations of 0, 10 or 20 ng/ml from 30 to 120 min. At 30 min M, 15 mg (with F 0 ng/ml) 30 mg (with F 10 ng/ml) or 60 mg (with F 20 ng/ml) was given i.v. over 5 min. The EEG was recorded until the subjects awoke. Venous blood samples were taken for 7.5 h. Plasma drug concentrations were measured by HPLC. Noncompartmental and compartmental approaches were used to determine the pharmacokinetics of F and M respectively. $T_{\frac{1}{2}}k_{e0}$, the half-time for plasma concentration and effect equilibration for M was estimated with a nonparametric method.[2] The obtained plasma concentrations of M in the effect compartment were related to TNW_{12-30} with a sigmoid maximum effect model. Statistical analysis was done with linear regression, repeated measures ANOVA and paired t-tests.

The subjects fell 'asleep' 2-5 min after the start of the M infusion and awoke after 30-100 min. One subject was excluded from the study because he felt dizzy during F infusion. Mean total plasma clearance, steady state volume of distribution and elimination half-life were 344 ± 31 (mean ± SD) ml/min, 55 ± 5 l and 133 ± 22 min for M, and 960 ± 78 ml min, 87 ± 14 l and 72 ± 8 min for F. Mean pharmacodynamic data are given in Table 1. In one subject E_{max} of M could not be estimated with confidence. In the other subjects E_{max} and were not affected by F, whereas the EC_{50} of M increased linearly with increasing concentration of F. F concentrations resulting in a twofold increase in EC_{50} of M varied from 5.0-8.3 ng/ml. The results are consistent with the competitive nature of the antagonism.

Table 1. Pharmacodynamics of midazolam, in the absence (A) of and with 10 ng/ml (B) or 20 ng/ml flumazenil

	Dose of M (mg)	$t_{\frac{1}{2}}k_{e0}$ (min)	E_0	E_{max} (waves/s)	EC_{50} (ng/ml)	
A	15	2.2±1.2	0.6±0.3	8.3±0.9	276± 64	3.9±1.7
B	30	3.3±3.3	0.7±0.4	8.2±1.4	624±187	3.5±1.0
C	60	2.9±1.2	0.6±0.4	7.6±0.6	1086±379	3.7±1.4

* Data are mean ± SD

References
1. Anesthesiology 71:A119, 1989
2. Anesthesiology 71:A120, 1989

INTERACTION OF NICARDIPINE (Nic) AND HYPOCAPNIC ALKALOSIS (HA) ON CEREBRAL VASOMOTRICITY AND INTRACRANIAL PRESSURE.

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The effect of hypocapnic alkalosis (3.5 kPa) on nicardipine induced (1µg.Kg-1 in internal carotid[1]) cerebral vasodilatation was studied by measuring cerebral artery diameter in 16 different locations on a carotid arteriogram (lateral incidence). Intracranial pressure (ICP) was recorded by an intraventricular catheter. 12 patients were divided in two randomized groups undergoing general anesthesia (methohexital, fentanyl, pancuronium bromide and mechanical ventilation with oxygen-enriched air (FiO2 = 0.30) were studied. On **T°** both groups had an arteriogram in normocapnia (**NA**). The first group (**G1**) was studied first in hypocapnia (**T1**) then following injection of **Nic** (**T2**) ; the second group (**G2**) was studied first after injection of **Nic** (**T1**) then in hypocapnia (**T2**). This study protocol received approval by our hospital ethical commitee.

The results were analysed using Wilcoxon's T and W tests. Both groups were statistically similar for age, blood pressure, heart rate and PaO2 at the three steps of the study. **HA** caused a 9.6 % decrease in arterial diameter (AD) (**G1 T1**, $p < 0.05$) compared with baseline, and a 14.9 % decrease when preceded by an injection of **Nic** (**G2.T2**, $p < 0.05$). However in the later case the decrease was 3 % in comparison with baseline (NS).

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Nic increased **AD** by 18.5 % when preceded by **HA** (**G1.T2**, $p < 0.05$), while the increase was 7.3 % in comparison with baselines values (p = NS). **HA** decreased ICP by 46 % (**G1.T1**, $p < 0.05$) and by 42 % after **Nic** (G2.T2, $p < 0.05$).

	T°	T1	T2
G1(n = 6)	**NA**	**HA**	**Nic**
AD mm	1.37 ± 0.05	1.24 ± 0.12	1.47 ± 0.13
ICP cm H2O	16 ± 6	9 ± 5	9 ± 5
G2 (n = 6)	**NA**	**Nic**	**HA**
AD mm	1.32 ± 0.08	1.51 ± 0.10	1.28 ± 0.12
ICP cm H2O	15 ± 7	16 ± 10	8 ± 4

The effect of **HA** on ICP was maintained after **Nic** infusion. **Nic** did not cause an increase in ICP[2]. **Nic** and **HA** mutually cancel their vasomotor effects as shown previously by Harris in the baboon using Nimodipine[3].

1 Int. J. Clin. Pharmacol. Biopharm., 1979, 17 : 1-11.
2 Br. J. Clin. Pharmacol. 1985,20 : 67S-74S
3 Stroke 1982, 13 : 759-766.