Title : DOUBLE BLIND RANDOMIZED STUDY EVALUATING THE EFFECTS OF A SPECIFIC BENZODIAZEPINE ANTAGONIST ON CEREBRAL BLOOD FLOW

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Introduction. RO 15-1788 (RO) is a specific benzodiazepine antagonist with a similar chemical structure but no objectively demonstrable agonistic or inverse agonistic property. The purpose of this study was to evaluate the effects of this agent on cerebral blood flow (CBF) when administered alone or in association with midazolam (Mid), and to compare them with the influence of Mid injected alone, and placebo (Plac).

Methods. Seven healthy males, mean age 35.6 ± 5 ($\bar{x} \pm SD$), weighing 73 ± 9 kg, volunteered, after informed consent, for the study which was approved by the Committee of Ethics and Human Research of our institution. Each subject was investigated during four different sessions which were randomized and separated by at least 3 days. The different sessions were as follows :

1. Plac-Plac
2. Mid-Plac
3. RO-Plac
4. Mid-RO

During each session EKG and end-tidal CO_2 were continuously monitored, blood pressure (BP) was measured each minute using a non-invasive automatic device (Dinamap®). CBF was measured with the ^{133}Xenon inhalation techniques using 12 detectors on each hemisphere.

The subjects were installed in the supine position with an i.v. canula on each hand (Butterfly#23®), two infusions of NaCl 0.9 % running at the rate of 100 ml/hr, with a face mask allowing for the inhalation of ^{133}Xenon and the monitoring of end tidal CO_2 ($FECO_2$). After a resting period of 10 minutes in a semi-dark quiet room, two of the three studied drugs were injected i.v. one in each hand, over a 15 second period in a double-blind fashion : either Mid 0.15 mg/kg diluted up to 10 cc with NaCl 0.9 %, or RO (0.1 mg/kg) diluted up to 10 cc with NaCl 0.9 %, or Plac (10 cc of NaCl 0.9 %). Two minutes after the beginning of the injection, 4-5 mCi of ^{133}Xenon was inhaled during a 1 minute uptake period, and CBF was then calculated during a 10 minutes washout period from the head curves and the end tidal sampling of ^{133}Xenon. The average of F1 which represents the fast compartment flow and the average of ISI_2 (initial slope index of Risberg) which represents a combination of the fast and slow flow compartments were calculated from the values obtained with the 24 head detectors.

All the data are expressed as the mean ± SD. The differences in CBF between the Plac-Plac and the three other sessions were compared using a one-way analysis of variance, differences being detected with a Scheffé-test, $p < 0.05$ being considered significant.

Results. During the Mid-Plac session all the subjects were asleep and became arousable between 10 and 15 minutes after the injection; amnesia was observed in all the subjects and lasted for 53 ± 15 minutes. After injection of the other drug combinations no amnesia was noted and none of the subject fell asleep. After the RO-Mid and the RO-Plac session, however, all of them expressed a feeling of anxiety. The biggest changes in hemodynamics and $FECO_2$ were measured in the Mid-Plac session 4 min after the injection. Mean BP decreased from 89 ± 8 to 79 ± 7 mmHg ($p < 0.05$), heart rate and $FECO_2$ increased from 66 ± 7 to 73 ± 6 beats/min (non significant (NS)) and from 39 ± 5 to 43 ± 5 mmHg (NS) respectively. During the other 3 sessions the changes measured were smaller and never significant.

The CBF results are indicated in table 1. The differences measured between the Mid-Plac session and the others were statistically different ($p<0.01$), the administration of Mid alone producing a significant decrease in CBF, while the value after administration of RO alone or in association with Mid were similar to the values measured after Plac alone.

TABLE 1 : Individual and mean values of CBF (F1 and ISI_2) after administration of placebo (PLAC), midazolam (MID)(0.15 mg/kg), RO 15-1788 (RO)(0.1 mg/kg) or an association of midazolam and RO 15-1788.

	PLAC - PLAC		MID - PLAC		RO - PLAC		MID - RO	
Subjects	F1#	ISI_2	F1#	ISI_2	F1#	ISI_2	F1#	ISI_2
1	49.0	36.0	25.5	22.5	56.0	43.0	45.0	33.0
2	60.0	46.0	29.0	25.0	45.5	40.0	73.0	51.5
3	43.5	36.5	----	30.0	55.0	44.5	50.5	42.0
4	55.0	41.0	45.5	40.0	51.0	38.0	----	----
5	74.0	53.0	----	45.0	75.0	53.0	73.5	57.0
6	59.0	42.5	42.0	37.0	65.5	43.0	69.0	45.0
7	73.0	54.0	54.5	40.5	----	----	67.0	55.0
Mean ± SD	59.1 ± 11.4	44.1 ± 7.3	39.3 ± 12.0**	34.3 ± 8.5**	58.0 ± 10.6	43.6 ± 5.2	63.0 ± 12.2	47.3 ± 9.0
n	7	7	5	7	6	6	6	6

ml/100 g . min-1
** statistically different ($p<0.01$) from other groups

Discussion. The study demonstrates the absence of effects of RO 15-1788 on CBF and the efficiency of this new drug in antagonising the depressive effect of midazolam on CBF. The absence of changes in CBF after RO alone confirms the lack of objectivable agonistic or inverse agonistic activity of this new compound, even though all the subjects became anxious after receiving RO alone or in association with Mid.