Title : ABSENCE OF VENTILATORY AGONIST OR INVERSE AGONIST EFFECTS OF A OVERDOSE OF RO 15-1788, A SPECIFIC BENZODIAZEPINE ANTAGONIST

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Introduction. Ro 15-1788 is an imidazobenzodiazepine which has been proven to be an efficient specific benzodiazepine antagonist in humans (1). CNS agonist and inverse agonist effects of Ro 15-1788 have been reported in patients (2,3). Since besides their CNS properties (sedation, anxiolysis, anticonvulsive effects), classical benzodiazepines also depress respiration, we investigated whether a large dose of Ro 15-1788 has any agonist or inverse agonist effects on ventilation in human volunteers.

Materials and Methods. After informed consent, eight healthy young male volunteers participated to the study which was appoved by the ethical committee on human research of our institution. Each volunteer was studied on three different sessions during which each subject received two drugs intravenously at a 15-min interval: 1) placebo followed by midazolam (0.1 mg/kg over 1 min); 2) Ro 15-1788 (0.1 mg/kg over 5 min) followed by placebo; and 3) Ro 15-1788 followed by midazolam at the same dosages as on sessions 1 and 2. The effects of the first drug administered during the three sessions allowed to compare Ro 15-1788 to placebo. The administration of midazolam or placebo as second drug was to compare their effects after a pretreatment with Ro 15-1788 or placebo in order to document both the sensitivity of the measuring techniques as well as the efficacy of Ro 15-1788 as a benzodiazepine antagonist. The sequence of the three sessions was randomized and the drugs were administered in a double-blind fashion. The measurements were carried out up to 120 min after the first drug injection. Changes in ventilatory pattern were continuously assessed with a noninvasive monitoring technique already described (4), consisting of two air-filled bellows pneumographs attached circumferentially around the abdomen and the thorax. Calibration of the system was done before each experiment with the help of a pneumotachograph (Godart type 17212) using the least square method. The subjects were investigated in the supine position, and the pneumotachograph was disconnected from the subject after calibration. Tidal volume (V_T) and respiratory rate (f) were directly measured from the computerized calibrated pneumograph tracings, and minute ventilation ($\dot{V}_E$), mean inspiratory flow (V_T/T_i, an index of inspiratory drive) were calculated from the data stored in the computer. In addition, changes in psychomotricity were evaluated with a tracing test series with which the volunteers had previously been accustomed. Statistical comparison between the three groups was performed by means of an ANOVA for repeated measurements.

Results. The noninvasive respiratory monitoring was reliable since 95% of all pneumograph V_T values were within ±7% of simultaneous pneumotachograph data during the calibration procedure. As indicated in table 1, when compared with placebo, Ro 15-1788 produced no significant changes in any of the respiratory variables considered. In contrast, midazolam administered after placebo induced sleep in all subjects associated with a significant decrease in V_T, $\dot{V}_E$, and V_T/T_i, while when administered after Ro 15-1788, no significant effect was observed. Psychomotricity data showed similar results (table 2): the only significant changes in error counts, time out of trace, and the ratio of time out of trace over total time to perform the test were noted after the administration of midazolam following placebo, but not following Ro 15-1788.

Table 1. Baseline and peak effects of Ro 15-1788 (1-3 min) or midazolam (5-7 min) on ventilation measured during the three sessions ($\bar{x}$±SD; n=8; * $P<0.01$)

	V_T (ml)	f (/min)	$\dot{V}_E$ (l/min)	V_T/T_i (ml/sec)
Baseline	533±155	14±4	6.9±2.0	326±59
Placebo	519±143	14±4	6.7±1.20	324±60
Midazolam	304±39 *	17±2	5.1±0.9 *	238±49 *
Baseline	528±146	13±4	6.3±1.1	311±67
Ro 15-1788	510±113	14±5	6.9±2.0	338±57
Placebo	444±86	14±3	6.1±1.1	326±70
Baseline	540±150	14±3	6.8±1.2	330±67
Ro 15-1788	527±170	14±4	6.7±1.1	334±54
Midazolam	544±118	15±3	6.3±1.3	319±60

Table 2. Results of tracing test series during baseline, immediately before, and 15 min after the second drug ($\bar{x}$±SD; n=8; * $P<0.01$)

	Error count	Time out of trace (sec)	Time out of trace over total time (%)
Baseline	5±4	0.9±0.9	2±2
Placebo	4±4	0.7±0.8	2±3
Midazolam	29±1 *	11.5±7.3 *	22±11 *
Baseline	4±3	0.8±0.6	2±2
Ro 15-1788	6±6	1.0±1.0	3±2
Placebo	5±4	0.9±0.9	3±3
Baseline	5±4	0.9±0.9	2±2
Ro 15-1788	7±5	1.0±1.0	3±3
Midazolam	5±4	1.6±1.1	4±3

Discussion. The use of a noninvasive respiratory monitoring technique avoiding upper airway stimulation, increased resistance and dead space, is more sensitive to detect changes in breathing pattern than the use of a nose clip and mouth piece, which affect by themselves respiratory pattern and effects of drugs on ventilation. In spite of this approach, our study clearly demonstrates that Ro 15-1788 administered i.v. at ten times the recommended dose does not influence ventilation nor psychomotricity. Our results confirm the efficacy of Ro 15-1788 as an antagonist of the clinical effects of benzodiazepines; in addition, it is also very effective to antagonize the respiratory depressant effects of midazolam. Since Ro 15-1788 is administered in comatose patients to diagnose and/or treat benzodiazepine intoxication (5), further respiratory depression should not be feared in case the coma and respiratory depression are not due to a benzodiazepine intoxication.

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