Title : EFFECT OF RO 15-1788 (FLUMAZENIL) ON THE CO2 RESPONSIVENESS AFTER MIDAZOLAM-FENTANYL ANESTHESIA

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INTRODUCTION : Midazolam is a short acting water soluble benzodiazepine, widely used in anesthesia for patients undergoing various types of outpatient surgery procedures. Its anxiolytic, sedative and amnestic properties make it a particularly attractive choice. Previous studies have reported significant depression of the ventilatory response to carbon dioxide (CO2) after midazolam anesthesia (1). Recently, with the availability of a benzodiapezine antagonist (RO 15-1788-Flumazenil), it is possible to rapidly reverse the residual sedative effects of benzodiazepines in the post operative period (2). The purpose of the present study was to investigate the efficacy and safety of RO-15-1788 for reversal of respiratory depression following midazolam-fentanyl anesthesia in short outpatient surgery procedures.

METHODS : The study was performed in 20 healthy women, who were to undergo planned outpatient termination of pregnancy (8-12 weeks). None of them were on benzodiazepine medication. Informed consent was obtained and the Hospital Ethics Committee approved this protocol. Two hours before surgery, patients were premedicated with hydroxyzine (100mg) orally. Anesthesia was induced with midazolam (0.3mg/kg) intravenously, together with fentanyl (1µg/kg). A further dose of midazolam (0.1mg/kg) was administered if necessary. Anesthesia was maintened with 60 % N20 in 02 delivered by face mask. After termination of surgery, patients were randomly assigned to one of two groups. Patients in group 1 (n = 10) received 0.3mg RO 15-1788 (0.1mg/ml) intravenously. In group 2 (n = 10) placebo (normal saline) was injected according to the same regimen. Patient's ventilatory response to CO2 was assessed using Read rebreathing method : preoperatively (30min before induction of anesthesia), post operatively (just before the injection of RO 15-1788 or placebo, defined as TO) and at subsequent intervals of 10, 30, 60, 90 and 120 minutes. Linear regression equations were computed from minute ventilation (VE) and end tidal CO2 tension (PETCO2) for each challenge curve. All responses were linear with correlation coefficients ranging from 0.90 to 0.99. Data are expressed as mean values ± SD. Statistical analysis included Student's t test for paired and unpaired data, with P 0.05 considered statistically significant.

RESULTS : The two groups were comparable with respect to age, weight, total amount of midazolam (Gr 1 : 23.1 ± 2.3mg ; Gr 2 : 24 ± 3.5mg) and fentanyl (Gr 1 : 57 ± 10.3µg ; Gr 2 : 64 ± 24µg). The time elapsing between induction of anesthesia and TO was also comparable (Gr 1 : 26.8 ± 6.5 min ; Gr 2 : 28.1 ± 4min). The ventilatory effects observed are shown in table 1. Both groups had similar ventilatory scores expressed by the slope VE/PETCO2 prior (baseline) and immediately after anesthesia (TO), and these data showed a significant ventilatory depression (p 0.01). In group 2 (placebo) the depression of the slope VE/PETCO2 was observed throughout the study and still remained two hours after anesthesia. In group 1, flumazenil significantly reversed the ventilatory depression induced by midazolam- fentanyl, but at 120min the depression reappeared. When compared with group 2, the efficacy of flumazenil lasted only 60 minutes and there was no more significant difference between the two groups.

CONCLUSION : The results of the present study indicate that midozolam, when used with fentanyl in short outpatient surgery procedures, causes significant respiratory depression which lasted at least two hours. Flumazenil is an effective antagonist of high dose midazolam. However, its duration of action does not exceed 60min. Therefore the action of midazolam may outlast a single bolus injection of flumazenil. These results may warrant repeated boluses of flumazenil better than the increase of the dosage.

Table 1 : slope VE/RETCO2 (mean ± SD)

	Gr 1 (RO15-1788) n = 10		Gr 2 placebo n = 10
Baseline	2.13 (0.84)	NS	2.28 (0.89)
TO	1.33 (0.38)**	NS	1.12 (0.41)**
T10min	1.93 (1.23)	(*)	1.34 (0.49)**
T30min	1.83 (0.42)	(*)	1.42 (0.58)**
T60min	1.74 (0.58)	(*)	1.34 (0.29)**
T90min	1.71 (0.49)	NS	1.39 (0.57)**
T120min	1.45 (0.47)*	NS	1.48 (0.39)**

* $p < 0.05$ (*) $p < 0.05$ comparison between the two groups

** $p < 0.01$ compared to baseline in each groups

REFERENCES :
1/ Forster A., Gardaz J.P., Suter P., Gemperle M., Respiration depression by midazolam and diazepam. Anesthesiology 53 : 494-497, 1980
2/ Darragh A., Scully M., Lambe R. et al. : Investigation in man of the efficiency of a benzodiazepine antagonist RO15-1788 Lancet 2 : 8-10, 1981