Title: ADRENERGIC AND HEMODYNAMIC RESPONSE TO FLUMAZENIL (RO 15-1788) REVERSAL OF MIDAZOLAM SEDATION

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Introduction. Benzodiazepines are frequently used by anesthesiologists for anxiolysis, sedation, and amnesia. However, there is a marked variability in patient response and overdosage is not uncommon. Flumazenil (RO 15-1788) is a specific benzodiazepine antagonist acting on central nervous system receptor sites. Postsurgical benzodiazepine sedated patients have experienced intolerable anxiety immediately following reversal with flumazenil.[1] We therefore examined the adrenergic and hemodynamic effects of reversal of midazolam sedation by titration of flumazenil in pain free postoperative patients with regional anesthesia.

Methods. Twenty seven unpremidicated ASA class I - III male patients scheduled for elective surgery under regional anesthesia with intravenous sedation were randomized to one of two groups. None of the patients were taking benzodiazepine drugs or had a diagnosis of psychiatric illness. Each patient consented to this study, which was approved by our Institutional Review Board. The day before surgery all patients had a physical and psychomotor evaluation. Vital signs were also recorded. On the day of surgery 2 intravenous catheters were inserted, one for medication and one for blood samples. The first blood sample was drawn at this time. Following regional anesthesia all patients received midazolam sedation which was maintained until the end of surgery. On arrival in the recovery room patients deeply sedated and free of pain had a second blood sample drawn, vital signs, and psychomotor evaluations recorded. In a randomized double-blind fashion patients were then given either placebo or flumazenil in divided doses of 0.2 mg each at 60 second intervals until the patient's sedation was fully reversed or he had received five doses of test drug. The maximum dose of flumazenil was 1 mg over 5 minutes. The minimal dose was 0.4 mg. Five minutes after test drug was begun blood samples, vital signs, and psychomotor evaluations were repeated. All patients were observed and evaluated for 3 hours after the test drug was given. Serum catecholamines were determined by high pressure liquid chromatography. Statistical analysis was by paired t-test, with $p<0.05$ considered statistically significant.

Results. The two groups were demographically similar. Average intravenous midazolam dose was 18.5 ± 5.0 mg given during an average surgical time of 107 ± 7 minutes. The flumazenil group received an average of 0.7 ± 0.04 mg of I.V. flumazenil over 3 to 5 minutes. All patients in both groups had complete amnesia of the surgery. Five minutes after the test drug was begun all of the flumazenil group had recovered their premidazolam psychomotor abilities. None of the patients developed anxiety. There was no significant change in catecholamine levels from the preoperative control to the postoperative sedated state. Flumazenil antagonism of midazolam did not cause a significant change in catecholamine or hemodynamic measurements.

Discussion. Reversal of profound midazolam sedation and amnesia with a titrated dose of flumazenil was not associated with a significant change in serum catecholamines or hemodynamics. Furthermore, none of our patients experienced any anxiety subsequent to a titrated intravenous injection of flumazenil. The reported anxiety of surgical patients following reversal of midazolam with flumazenil[1] may be related to the dose (0.1 mg/kg) and method of administration. This fixed dose given over 30 seconds may be an overdose. When flumazenil is carefully titrated to the desired clinical effect at the rate of 0.2 mg/minute (in non-psychotic patients who are not taking benzodiazepines) there is no adrenergic or hemodynamic response to reversal of midazolam sedation.

References.

1. Louis M, Forster A, Suter PM, Gemperle M: Clinical and hemodynamic effects of a specific benzodiazepine antagonist (RO 15-1788) after open heart surgery. Anesthesiology 61:A61, 1984

Table 1: Flumazenil group sedated and reversed compared with placebo group

	NE	Epi	HR	MAP
Flum. Sed.	329±84	41±15	75±3	106±4
Flum. Rev.	456±108	49±16	73±4	110±3
Plac. Sed.	362±98	21±2	75±4	97±4
Plac. Rev.	468±158	19±0	69±4	100±6

$\bar{x}$ ± SEM, NE = norepinephrine, Epi = epinephrine, HR = heart rate, MAP = mean arterial pressure.

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