Title: STRESS RESPONSE FOLLOWING REVERSAL OF BENZODIAZEPINE-INDUCED SEDATION

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Introduction. Benzodiazepines are widely used during the perioperative period because of their anxiolytic, sedative and amnestic properties. Oversedation occurs frequently because of the marked variability in patient responses to benzodiazepines. With the availability of a benzodiazepine antagonist, flumazenil (Ro 15-1788), it is possible to rapidly reverse the residual sedative effects of benzodiazepines in the postoperative period.[1] However, previous reports have indicated potential problems with postoperative anxiety in patients who have received flumazenil.[2,3] We examined the effects of reversing benzodiazepine-induced sedation on patients' level of anxiety, memory function (recall), and stress hormone responses during the early postoperative period.

Methods. Nineteen consenting unpremedicated ASA I-III patients scheduled for elective surgery under local anesthesia with intravenous sedation were randomly assigned to one of two treatment groups. The study was approved by the local institutional review board. Preoperatively, patients completed sedation and anxiety analog scales. After insertion of the intravenous (iv) catheter, blood samples were obtained for determination of plasma catecholamines (norepinephrine and epinephrine), vasopressin, and β-endorphin levels using standard REA and RIA techniques. Following a 2 mg loading dose, midazolam was administered in 1-2 mg incremental doses during the operation. On arrival in the recovery room, the analog scales were repeated, patients were shown a picture, and blood samples were obtained for determination of plasma hormone levels. Patients were then administered either saline (control) or flumazenil (0.1 mg/ml) intravenously in a randomized double-blind fashion. At subsequent intervals of 5, 15, 30, 60 and 120 min, the analog scales, amnesia testing and blood sampling were repeated. Recall was assessed using a 24h follow-up questionnaire. The sedation analog scale was scored from 0 (wide awake) to 100 (asleep). Similarly, the anxiety analog scale was scored from 0 (relaxed) to 100 (very anxious). Continuous variables were analyzed using 2-way ANOVA with repeated measures, $p < 0.05$ was considered statistically significant (mean values ± SEM). Descriptive variables were analyzed using Chi-square analysis with Fisher's exact test.

Results. The two study groups were comparable with respect to demographic data. Average midazolam doses of 12-15 mg iv were administered over 45-90 min. The flumazenil group received 0.7±0.2 mg iv over 3-5 min. The sedation and anxiety analog scores as well as the incidence of amnesia are summarized in table 1. Sedation scores were significantly lower after flumazenil administration (vs. saline). In addition, patient recall in the early postoperative period was higher in the flumazenil group. While postoperative anxiety scores were lower in the flumazenil group, there was no significant change with reversal. Similarly, stress hormone levels were not changed following flumazenil reversal (table 2). β-endorphin concentrations were also unchanged from preoperative levels in both study groups.

Discussion. In contrast to earlier studies,[2,3] reversal of midazolam-induced sedation and amnesia was not associated with an increase in anxiety levels or stress hormone concentrations. This difference may be explained by the lower dose of flumazenil (0.01 mg/kg) used in our study compared to the doses used previously (0.1 mg/kg). Although flumazenil can safely and effectively reverse excessive sedation following administration of a benzodiazepine agonist, these studies emphasize the importance of carefully titrating the antagonist to produce the desired clinical effect. In summary, our data would indicate that it is possible to reverse midazolam-induced sedation and amnesia without provoking an undesirable stress response.

References.

1. Darragh A, et al: Lancet 2:1042, 1981
2. Louis M, et al. Anesthesiology 61:A61, 1984
3. Ricou B, et al. Br J Anaesth 58:1005, 1986

Table 1: Sedation, amnesia, and anxiety scores before surgery (B), before (0") and after reversal

	B	0"	5"	15"	30"	60"	120"
Sedation (mm)							
Control	12±2	82±3	69±5	53±8	48±9	45±9	36±9
Flumazenil	10±3	87±5	29±7*	17±4*	12±4*	15±4*	18±5
Amnesia (%)							
Control	0	87	62	50	62	25	-
Flumazenil	0	82	0*	9*	36	9	-
Anxiety (mm)							
Control	39±8	22±3	21±5	24±3	28±4	28±9	20±7
Flumazenil	54±9	14±4	15±5	14±3	13±7	16±6	16±9

*Significantly different from control, $p<0.05$

Table 2: Stress hormone levels (pg/ml) before surgery (B), and before (0") and after reversal

	B	0"	5"	15"	30"	60"	120"
Norepinephrine							
Control	435 (±87)	308 (±58)	252 (±49)	303 (±47)	319 (±44)	283 (±50)	474 (±69)
Flumazenil	332 (±36)	287 (±37)	288 (±38)	294 (±17)	313 (±23)	325 (±40)	427 (±72)
Epinephrine							
Control	55 (±10)	62 (±23)	63 (±26)	51 (±19)	51 (±14)	70 (±20)	131 (±36)
Flumazenil	23 (±10)	37 (±11)	48 (±10)	36 (±8)	24 (±7)	25 (±7)	41 (±9)
Vasopressin							
Control	5.6 (±1.7)	5.9 (±1.6)	5.8 (±1.4)	5.6 (±1.7)	5.4 (±1.3)	4.6 (±1.5)	3.2 (±1.4)
Flumazenil	6.2 (±1.1)	4.7 (±1.2)	5.7 (±1.3)	6.0 (±1.5)	5.6 (±1.4)	5.5 (±1.3)	3.4 (±1.1)