J Anesth (2002) 16:9–12

Journal of Anesthesia

Flumazenil reduces the hypnotic dose of propofol in male patients under spinal anesthesia

Yushi U. Adachi[1], Kazuhiko Watanabe[1], Hideyuki Higuchi[2], and Tetsuo Satoh[1]

[1]Department of Anesthesiology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan
[2]Department of Anesthesia, Japan Self-Defense Force Hanshin Hospital, 4-1-50 Kushiro, Kawanishi, Hyogo 666-0024, Japan

Abstract
Purpose. Flumazenil has been reported to produce a partial benzodiazepine-agonist-like effect in some psychopharmacological examinations. This study investigated the effect of flumazenil on the hypnotic activity of propofol in 60 men scheduled for minor surgical procedures done under spinal anesthesia.
Methods. After a steady state of spinal anesthesia had been reached, patients were pretreated with saline or flumazenil, 5 μg·kg^{-1}, followed by the administration of saline or midazolam, 10 μg·kg^{-1}. Then, 250 μg·kg^{-1}·min^{-1} of propofol was infused until hypnosis was achieved. Loss of response to a simple command with a slight stimulus, served as the endpoint for hypnosis. Immediately after achievement of the endpoint, propofol infusion was discontinued, and a 2-ml venous blood sample was obtained from the dorsal pedis vein to determine plasma propofol concentration.
Results. Flumazenil significantly decreased the dose of propofol required and the time required to achieve hypnosis compared with values in the control group (55 ± 10 [mean ± SD] *vs* 71 ± 14 mg and 212 ± 42 *vs* 268 ± 48 s, respectively; $P < 0.05$), whereas flumazenil attenuated the effect of midazolam in reducing the plasma concentration of propofol at hypnosis (2.9 ± 0.5 and 2.5 ± 0.6 μg·ml^{-1}, respectively; $P < 0.05$).
Conclusion. These results suggested that flumazenil may potentiate the hypnotic properties of propofol, despite flumazenil having an antagonistic effect on the enhanced hypnotic activity of propofol induced by the coadministration of midazolam.

Key words Flumazenil · Propofol · Hypnotic dose

Introduction

Flumazenil is the first highly specific benzodiazepine antagonist, and, since its introduction, there have been many reports and publications dealing with its properties [1,2]. Flumazenil has been reported to reverse the hypnotic or anesthetic effect of benzodiazepine derivatives, e.g., midazolam [2–4]; however, flumazenil was reported to have no effect in reversing propofol anesthesia [5–7]. In an experimental animal study, a high dose of flumazenil showed a benzodiazepine-like hypnotic effect [7]. Recently, there have been some reports demonstrating that a clinical dose of flumazenil had a partial benzodiazepine agonist-like effect in humans [8] and in experimental animals [9–13]. Because, from the viewpoint of psychopharmacology, the induction of anesthesia typically causes a change in or a loss of consciousness [11,12], we hypothesized that flumazenil administration might have a potentiating effect on anesthetics at induction. In the present study, we investigated the effect of flumazenil on the hypnosis induced by propofol in male patients who were scheduled for minor surgery under spinal anesthesia.

Subjects and methods

After obtaining approval from the Department Ethics Committee and obtaining written informed consent from the patients, we studied 60 patients scheduled for surgery. All participants were male; they were aged 45–85 years, of American Society of Anesthesiologists (ASA) physical status 1 or 2, and were undergoing minor surgery (mainly urological surgery) managed with spinal anesthesia. None of the patients had any psychological complications, and none were receiving medication. The participants were randomly assigned, using a computer-generated random-number sequence, to one of four treatment groups, of 15 patients each. From the beginning of anesthesia, heart rate, arterial blood pressure, and oxygen saturation were monitored noninvasively with a pulse oxymeter. None of the patients received premedication. Spinal anesthesia was per-

Address correspondence to: Y. Adachi
Received: January 11, 2001 / Accepted: July 25, 2001

Table 1. Demographic characteristics of the patients

Groups	Placebo-Placebo	Flumazenil-Placebo	Flumazenil-Midazolam	Placebo-Midazolam
n	15	15	15	15
Age (years)	65 (8)	69 (8)	67 (6)	68 (8)
Weight (kg)	63 (8)	61 (11)	65 (8)	62 (9)
Height (cm)	163 (6)	163 (6)	165 (6)	161 (7)
ASA physical status 1/2 (*n*)	10/5	11/4	11/4	9/6

Values are means (SD). There were no significant differences among groups
ASA, American Society of Anesthesiologists

formed with the patients in the lateral position, at L3/4 with 2.0–2.3 ml of 0.3% dibucaine solution. Then the patients were returned to the supine position, and after confirmation that the level of anesthesia was below the dermatome of Th6-8, 3 l·min^{-1} of oxygen was administered, using a face mask.

After blood pressure, heart rate, and depth of anesthesia had reached a steady state, the 15 patients in each of the four groups were pretreated with: placebo and placebo (PP), flumazenil and placebo (FP), flumazenil and midazolam (FM), or placebo and midazolam (PM). The PP and PM groups received 2 ml of saline intravenously administered, followed by saline or midazolam 10 μg·kg^{-1}, at a 2-min interval. The FP and FM groups received flumazenil 5 μg·kg^{-1}, followed by saline or midazolam 10 μg·kg^{-1}, also at a 2-min interval. Propofol infusion to the patient was started through an antecubital venous line, at the rate of 250 μg·kg^{-1}·min^{-1}, using an infusion pump (Terufusion; Terumo, Tokyo, Japan), with a maintenance dose of acetate Ringer solution, at about 2 ml·min^{-1}. Loss of response to a simple command ("open your eyes"; "breathe slowly"), with a slight stimulus (shaking the patient's shoulder) was defined as the end-point for hypnosis. Responses to verbal commands were evaluated by a blinded anesthesiologist at 10-s intervals [14]. Immediately after the end-point was achieved propofol infusion was discontinued, and a 2-ml venous blood sample was obtained from the dorsal pedis vein. The dose of propofol and the time required for establishment of hypnosis were recorded. All procedures were finished before the beginning of surgery. Blood samples were centrifuged for 15 min at 3500 rpm, and separated plasma was frozen until assayed.

Plasma concentrations of propofol were determined within a month, using high-performance liquid chromatography with fluorescence detection at 310 nm and after excitation at 276 nm (RF550; Shimadzu, Kyoto, Japan). The areas under the chromatographic peaks were calculated with an integrator (PowerChrom; ADInstrument, Tokyo, Japan). Propofol concentrations were estimated based on the peak-area ratio of propofol and the internal standard, thymol. Linear relationships were obtained between propofol and the internal standard peak-area ratios. The correlation coefficient was in excess of 0.997 in the range of 50 ng·ml^{-1} to 10 μg·ml^{-1} (seven points of concentration). The detection limit of propofol by this assay was 10 ng·ml^{-1}.

Analysis of variance was used to evaluate differences in results among groups. Determination of significant difference ($P < 0.05$) was followed by Fisher's least significant difference multiple comparison post-hoc test. All calculations were performed using a statistical software package (NCSS 2000; Number Crunchers, Kaysville, UT, USA).

Results

There were no significant differences in the background characteristics (age, weight, and height) among the four treatment groups (Table 1). There were no complaints of adverse effects of the administration of flumazenil or midazolam. No patient showed detectable signs or symptoms related to the pretreatment drugs. All patients emerged from anesthesia and were re-sedated before the surgery; however, after the surgery, none of them could recall this episode.

In the PP group, the values for mean dose and time to achieve the end-point of hypnosis were significantly higher than those in the FP, FM, or PM groups (Table 2). The plasma concentrations of propofol at hypnosis were significantly lower in the FP, FM, and PM groups than in the PP group, and there were significant differences between the FP or FM and PM groups.

The blood pressure and heart rate showed no significant differences among the four groups at any measuring points (Table 3).

Discussion

The results of the present investigation suggested that flumazenil may have a potentiating effect on propofol anesthesia. Differences in the required dose of propofol

Table 2. Dose, time to end-point of hypnosis, and plasma concentration of propofol required to achieve hypnosis

Groups	Placebo-Placebo	Flumazenil-Placebo	Flumazenil-Midazolam	Placebo-Midazolam
Dose of propofol (mg)	71 (14)	55 (10)*	55 (14)*	48 (16)*
Time (s)	268 (48)	212 (42)*	194 (44)*	180 (47)*
Concentration ($\mu g \cdot ml^{-1}$)	3.4 (0.7)	3.0 (0.5)*:**	2.9 (0.5)*:**	2.5 (0.6)*

Values are means (SD)
* $P < 0.05$ *vs* placebo-placebo group; ** $P < 0.05$ *vs* placebo-midazolam group

Table 3. Changes in blood pressure and heart rate during the investigation

	Placebo-Placebo		Flumazenil-Placebo		Flumazenil-Midazolam		Placebo-Midazolam	
Groups	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)
Control	106 (12)	62 (9)	110 (9)	63 (11)	107 (11)	65 (10)	108 (11)	63 (12)
After spinal anesthesia	88 (11)	57 (9)	90 (9)	55 (10)	91 (10)	55 (12)	88 (9)	57 (11)
At start of propofol infusion	87 (10)	58 (11)	88 (11)	56 (9)	89 (9)	57 (11)	89 (10)	56 (13)
Hypnotic end-point	86 (15)	59 (9)	85 (16)	57 (10)	88 (8)	55 (13)	87 (10)	55 (15)
At emergence	81 (9)	62 (11)	79 (8)	60 (11)	79 (11)	58 (14)	78 (10)	59 (13)

Values are means (SD). There were no significant differences among groups at any point
MAP, Mean arterial pressure; HR, heart rate

and time to achieve hypnosis were found at the induction of anesthesia. The decreased plasma concentration of propofol observed with flumazenil administration also supported the enhancing effect of flumazenil on the hypnotic activity of propofol. The synergistic interaction of propofol and midazolam is well known [15,16]. Flumazenil may attenuate the interaction between midazolam and propofol, despite its potentiating effect on propofol. The results of the present study, in the clinical setting, were well consistent with those of our previous animal experiments in mice [11,12]. Because of ethical limitations, we could not demonstrate whether the effect of flumazenil on the hypnotic activity of propofol was dose-dependent. However, the administration of $5 \mu g \cdot kg^{-1}$ flumazenil clearly showed a potentiating effect on the hypnotic activity of propofol. The dose we studied is acceptable and is recommended for reversing the effect of benzodiazepine derivatives in operating rooms.

We have no clear explanation for the lack of consistency between the results of present study and those of prior investigations [5–7]. There are numerous studies of the interaction between propofol and flumazenil. These investigations, however, focused on clarifying the reversal, or antagonistic effect, of flumazenil on the hypnotic activity of anesthetics. In these investigations [5,6], flumazenil was administered after a hypnotic or anesthetic state was reached. In such settings, it might be difficult to detect an interaction between flumazenil and propofol. Recently, Maranets and Kain [17] reported that preoperative anxiety increased the dose of propofol required at induction and during anesthesia. Thus, if the administration of flumazenil had a benzodiazepine agonist-like effect (this effect was reported by Smith and Bickel [8]), it would be acceptable that flumazenil reduced the hypnotic dose of propofol required at the induction of anesthesia in the present investigation.

The limitations of the design in the present investigation should be addressed. In this study, we studied patients under spinal anesthesia. However, it is possible that local anesthetics may affect hypnosis [18,19]. Another limitation of the present study was that the participants consisted of only relatively elderly men. Gan and coworkers [20] reported that women emerged from general anesthesia faster than men. The population in the present investigation, however, may have been more sensitive to the effect of anesthetics than another population consisting of both sexes. Further investigation is needed, including investigations of the effects in different population, e.g., in young individuals, or women. Our investigation did not assess the dose-dependency of each drug interaction [21]. Further pharmacological approaches may be required.

In conclusion, in male patients under spinal anesthesia, flumazenil attenuated midazolam's potentiation of the hypnotic effect of propofol, whereas flumazenil itself showed a potentiating effect on the hypnotic activity of propofol.

Acknowledgments. We would like to express our sincere thanks to Dr. Attila Kofalvi for the informative comments on this paper.

References

1. Amrein R, Hetzel W (1990) Pharmacology of Dormicum® (midazolam) and Anexate® (flumazenil). Acta Anaesthesiol Scand 92:6–15
2. Whitwam JG (1995) Flumazenil and midazolam in anaesthesia. Acta Anaesthesiol Scand (Suppl) 108:15–22
3. Ghouri AF, Ruiz MAR, White PF (1994) Effect of flumazenil on recovery after midazolam and propofol sedation. Anesthesiology 81:333–339
4. Wilson E, David A, Mackenzie N, Grant IS (1990) Sedation during spinal anaesthesia: comparison of propofol and midazolam. Br J Anaesth 64:48–52
5. Fan SZ, Liu CC, Chao CC, Lin SM (1995) Lack of effect of flumazenil on the reversal of propofol anaesthesia. Acta Anaesthesiol Scand 39:299–301
6. Fassoulaki A, Sarantopoulos C, Papilas K (1993) Flumazenil reduces the duration of thiopentone but not of propofol anaesthesia in humans. Can J Anaesth 40:10–12
7. Murayama T, Shingu K, Ogawa T, Tomoda K, Shindo K, Tamai S, Mori K (1992) Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats. Br J Anaesth 69:61–64
8. Smith BJ, Bickel WK (1999) Flumazenil discrimination by humans under a two-response and a novel-response procedure. J Pharmacol Exp Ther 291:1257–1268
9. Izumi T, Inoue T, Tsuchiya K, Hashimoto S, Ohmori T, Koyama T (1999) Effects of the benzodiazepine antagonist flumazenil on conditioned fear stress in rats. Prog Neuropsychopharmacol Biol Psychiatry 23:1247–1258
10. Belzung C, LeGuisquet AM, Crestani F (2000) Flumazenil induces benzodiazepine partial agonist-like effects in BALB/c but not C57BL/6 mice. Psychopharmacology 148:24–32
11. Adachi Y, Watanabe K, Uchihashi Y, Higuchi H, Satoh T (2001) The effect of flumazenil on the hypnotic dose of propofol in ddY mice. Masui (Jpn J Anesthesiol) 50:164–167
12. Adachi YU, Watanabe K, Higuchi H, Satoh T (2001) High-dose flumazenil potentiates the hypnotic activity of propofol, but not that of thiopental, in ddY mice. Acta Anaesthesiol Scand 45:848–852
13. Schulze-Bonhage A, Elger CE (2000) Induction of partial epileptic seizures by flumazenil. Epilepsia 41:186–192
14. Adachi YU, Uchihashi Y, Watanabe K, Satoh T (2000) Small dose midazolam or droperidol reduces the hypnotic dose of propofol at the induction of anaesthesia. Eur J Anaesthesiol 17:126–131
15. Short TG, Plummer JL, Chui PT (1992) Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. Br J Anaesth 69:162–167
16. Teh J, Short TG, Wong J, Tan P (1994) Pharmacokinetic interactions between midazolam and propofol: an infusion study. Br J Anesth 72:62–65
17. Maranets I, Kain ZN (1999) Preoperative anxiety and intraoperative anesthetic requirements. Anesth Analg 89:1346–1351
18. Tverskoy M, Fleyshman G, Bachrak L, Ben-Shlomo I (1996) Effect of bupivacaine-induced spinal block on the hypnotic requirement of propofol. Anaesthesia 51:652–653
19. Ben-Shlomo I, Tverskoy M, Fleyshman G, Cherniavsky G (1997) Hypnotic effect of i.v. propofol is enhanced by i.m. administration of either lignocaine or bupivacaine. Br J Anaesth 78:375–377
20. Gan TJ, Glass PS, Sigl J, Sebel P, Payne F, Rosow C, Embree P (1999) Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. Anesthesiology 90:1283–1287
21. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL (2000) Response surface model for anesthetic drug interactions. Anesthesiology 92:1603–1616