Safety and Driving Ability following Low-Dose Propofol Sedation

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Key Words

Propofol · Sedation · Esophagogastroduodenoscopy · Driving ability · EGD

Abstract

Background and Aim: Automobile driving is prohibited after midazolam sedation because of the slow recovery of psychomotor function. This study prospectively assessed the safety of low-dose propofol sedation (study 1) and compared driving ability following propofol and midazolam sedation (study 2). **Methods:** Study 1: We prospectively investigated bolus injection of a low-dose of propofol (40–80 mg for <70 years and 30 mg for ≥70 years) for diagnostic esophagogastroduodenoscopy (EGD). Respiratory depression, time to full recovery, and overall patient satisfaction were evaluated and blood concentrations of propofol were measured. Study 2: A subset of subjects undergoing diagnostic EGD were randomized to receive 40 mg of propofol (n = 30), 4 mg of midazolam (n = 30) or no sedation controls (n = 20), and the residual effects of each drug were tested using a driving simulator. The primary outcome measure was driving ability. The second outcome measures were overall patient satisfaction and complications. **Results:** Study 1: Only 1.1% of 12,031 healthy subjects developed transient oxygen desaturation. Full recovery was present in 97.5% 30 min after the procedure; 99.8% were willing to repeat the same procedure. The blood levels of propofol (40–80 mg) at 60 min were <100 ng/ml. Study 2: Driving ability

recovered to the basal level within 60 min of propofol administration but not with 120 min with midazolam. There were no complications; overall patient satisfaction was similar between propofol and midazolam (8.9 vs. 8.5, p = 0.34). **Conclusion:** Low-dose propofol sedation was safe and recovery including driving ability was with 60 min.

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Introduction

Screening esophagogastroduodenoscopy (EGD) for the detection of early gastric cancer is widely practiced in Japan and many individuals undergo an annual diagnostic EGD. The desire for a comfortable EGD experience has resulted in an increasing prevalence of the intravenous sedation in Japan. Although many patients wish to drive soon after diagnostic EGD, driving is usually prohibited if intravenous sedation was administered. Propofol is a good candidate for the sedative agent in diagnostic EGD in that it is superior to benzodiazepines with regard to rapidity of induction of sedation and is associated with faster recovery. However, the possibility of respiratory depression has made many endoscopists reluctant to use propofol routinely [1–11].

Here we report a prospective investigation of nurse-administered bolus injections of low-dose of propofol (40–80 mg for those <70 years and 30 mg for those ≥70 years) for diagnostic EGD. We evaluated the results in

terms of complications, recovery rate, and overall patient satisfaction. The blood concentration of propofol (40 and 80 mg) was also measured. We used a driving simulator to compare the residual effects of propofol with those of midazolam on psychomotor function.

Patients and Methods

We prospectively evaluated low-dose propofol sedation administered by a nurse supervised by the endoscopist. Both the nurses and endoscopists had advanced cardiac life support (ACLS) certification. The study was done at the Showa Inan General Hospital and the study was conducted in accordance with the Helsinki Declaration and was approved by the ethics committee at the hospital. Verbal and written informed consent was obtained from all subjects. Subjects were excluded if they were less than 18 years old, pregnant, assigned to American Society of Anesthesiologists (ASA) class III and IV, overweight (body weight >100 kg), or allergic to the drugs used or its components (soybeans or eggs). Monitoring included continuous assessment of peripheral oxygen saturation (SpO₂) and heart rate. Clinical assessment of the patient, including measurement of respiratory effort by visual assessment and by palpation of the chest wall and abdominal excursion and/or palpation of exhaled breath, was performed routinely. When oxygen desaturation (SpO₂ <90%) continued more than 20 s, supplemental oxygen was given. The endoscopic team consisted of the nurse administering drugs and responsible for the patient, the endoscopist, and a second nurse to assist the endoscopist and the patient monitoring nurse.

Study 1

EGD was performed in the lateral decubitus position. Subjects received topical pharyngeal anesthesia with lidocaine. Propofol (Duprivan, AstraZeneca, Japan) was given by a bolus injection with a standard protocol of 40 mg for subjects <70 years old and 30 mg for subjects age 70 or over. Adequate sedation was generally achieved when the subject passed through the following sequence: eyes closing, one or two yawns, and cessation of body movements. The target level of sedation was moderate conscious sedation with subjects still being able to respond purposefully to verbal commands. When its target level was not obtained or the subjects were undersedated, an additional injection of 20 or 40 mg of propofol was given. However, in no instance was more than 80 mg given. A decline in SpO₂ to less than 90% was regarded as respiratory depression associated with the sedation. In addition to monitoring of vital signs, the subjects' condition was also assessed more globally by visual inspection. Monitoring and complications were recorded by a registered nurse.

Subjects were moved to the waiting room after they could stand by themselves and they were discharged after they were fully awake. Full recovery, including consciousness and psychomotor function was assessed using three criteria: (1) level of consciousness (fully awake and responding to questions from the recovery room nurse); (2) ability to stand on one-foot, and (3) ability to walk in a straight line for 5 meters without instability. These three criteria were assessed every 15 min starting 30 min after the procedure; full recovery was defined as meeting all three criteria. The nurses reconfirmed the absence of reemerging seda-

tive effects and finally permitted patients to leave the endoscopic unit. The subjects were asked about willingness to repeat the same procedure next time (yes/no) to assess their overall satisfaction for this procedure.

In a subset of subjects, the blood concentrations of propofol were measured before and 5, 30, 60 and 120 min after a bolus injection of 40 mg (n = 25) or 80 mg (n = 12) in order to evaluate the relation between the residual effects of propofol and their blood levels.

Study 2

Eighty healthy subjects undergoing diagnostic EGD were randomized to receive a bolus injection of 40 mg of propofol (n = 30), 4 mg of midazolam (n = 30), or no sedation (controls = 20). Patients were assigned randomly to the three groups using sealed opaque envelopes. Prior to the procedure driving ability was measured using a driving simulator and this was repeated before and 30, 60, and 120 min after drug administration. The control group did not receive any sedative drugs and also had driving ability evaluated using the same protocol. The primary outcome measure was the time when the driving ability was equivalent to that measured before the procedure. The second outcome measures were overall patient satisfaction and complications.

The levels of overall satisfaction were assessed by using a 10-cm visual analog scale (VAS), where 10 equaled excellent and 0 equaled poor [12]. The subjects were asked about their willingness to repeat the same procedure next year (yes/no). Within 48 h after the procedure, patients were contacted by telephone and asked about complications that might have developed after discharge.

Driving Simulation

Driving ability is a sensitive indicator of residual drug effects [13]. All subjects performed a 10-min divided attention driving simulation test (DADST) after a 5-min practice session using a commercially available simulator (DS-20, Mitsubishi Precision, Tokyo, Japan) that was located within the endoscopy unit. The subjects sat in front of a monitor and used a steering wheel, accelerator, and brakes to control the vehicle. The road scene display changed in accordance with the subject's actions. The object of the test was to steer an image of a car bonnet down the center of a winding road as accurately as possible (measuring the ability to track) using a steering wheel. During the test crossing pedestrians appeared randomly on the screen and often attempted to cross the road of the computer screen. To test vigilance and reaction time the subjects were required to properly identify and respond to the behavior of pedestrians. The results of the DADST were expressed as tracking error (standard deviation from the center of the road), accelerating reaction time (average time respond to pedestrians), and braking reaction time (average time respond to pedestrians).

Blood Concentrations of Propofol

The measurement of blood concentration of propofol was performed according to previously described methods [14, 15]. For the measurement of propofol, acetonitrile and internal standard added to a plasma sample and vortexed for 1 min. After centrifugation at 13,000 rpm for 5 min, 50-liter aliquots of the supernatant were directly injected into the HPLC system involving a C18 reverse-phase column. Propofol and the internal standard (thymol) were quantified using a coulometric electrochemical detection.

Fig. 1. Relation between blood concentrations of propofol after bolus injections of propofol (40 and 80 mg) and time course.

Statistical Analysis

Data are presented as means and SDs. Statistical tests to compare the measured results among the three groups were as follows: χ^2 test, with Yates' correction for continuity where appropriate, was used for comparison of categorical data; the Fisher exact test was used when the numbers were small. The Kruskal-Wallis test was used for ordinal variables of nonparametric data. For parametric data, analysis of variance was used when three and more means were compared and positive results were confirmed using Dunnett's procedure. $p < 0.05$ was regarded as significant. All statistical evaluation was performed by using SPSS version 12.0J software (SPSS Japan Inc., Tokyo, Japan).

Results

Study 1

Between January, 2003 and December, 2006, diagnostic EGD was performed in 12,031 healthy subjects using the low-dose propofol sedation (30–80 mg) (table 1). The subjects' age ranged from 18 to 84 years. Propofol (60–80 mg) was required in 4% ($n = 482$), all of whom were less than 70 years of age. 6,188 subjects (51%) underwent EGD for cancer screening. A biopsy was taken in 991 subjects (8.2%). The procedure time of EGD in almost all subjects was 5 to 8 min. Oxygen desaturation requiring supplemental oxygen occurred in 1.1%; mask ventilation or endotracheal intubation were not required in any case. In no case did prolonged apnea or laryngospasm occur. Full recovery 30 min after the procedure was present in 97.5%, 100% of the subjects completely recovered 60 min

Table 1. Demographic and clinical data for 12,031 healthy subjects who underwent diagnostic EGD using low-dose propofol sedation

Male	7,827 (65)
Mean age, years (range)	57.7 (18–87)
Body weight, kg (range)	32–95
Propofol sedation (30–40 mg)	11,549 (96)
SpO ₂ <90%	234 (1.9)
Oxygen administered	129 (1.1)
Prolonged apnea	0 (0)
Full recovery rate 30 min after the procedure	11,931 (97.5)
Full recovery rate 60 min after the procedure	12,031 (100)
Willingness to repeat the same procedure	12,001 (99.8)

Values represent numbers (%), unless indicated otherwise. EGD = Esophagogastroduodenoscopy.

after the procedure, and 99.8% of the subjects agreed to repeat the same sedation for their next screening examination.

The relation between the blood concentrations of propofol after a bolus injection of propofol (40 or 80 mg) and the time course is shown in figure 1. The population, which was analyzed for blood level metabolism of propofol, was comparable to the population presented in table 1.

Blood propofol concentrations at 60 min after injection of propofol (40 or 80 mg) were less than 100 ng/ml.

Study 2

Table 2 shows demographic and clinical profiles of subjects participating in the comparative study of propofol, midazolam, or neither (controls). There were no complications and overall patient satisfaction on a 10-point VAS was similar between propofol and midazolam (8.9 vs. 8.5, $p = 0.34$). Driving skills (tracking errors, accelerating reaction time, and braking reaction time) recovered to the basal levels in all subjects receiving propofol within 60 min of administration. On the other hand, the midazolam group had significantly more tracking errors ($57 \pm 6\%$ vs. $86 \pm 8\%$) and slower reaction times (0.52 ± 0.3 s vs. 0.89 ± 0.5 s) at 120 min (table 3).

Discussion

The advantages of propofol in comparison with benzodiazepines as a drug for endoscopic conscious sedation include almost immediate onset of action and fast recovery

Table 2. Comparison between healthy subjects who received propofol versus those who received midazolam

	Propofol (n = 30)	Midazolam (n = 30)	Control (n = 20)	p value
Age, years	56 ± 17	52 ± 14	55 ± 11	0.67
Male	21	19	11	0.56
Mean body weight, kg	62 ± 11	59 ± 12	61 ± 9	0.71
EGD indication				
Screening	24	22	17	0.60
GI symptoms	6	8	3	0.30
EGD duration, min	6.2 ± 0.7	6.5 ± 1.2	6.1 ± 0.9	0.74
SpO ₂ <90%	0	1	0	
Oxygen administered	0	1	0	
Heart rate <50 beats/min	0	0	0	
Complication within 48 h after procedure	0	0	0	
Overall satisfaction*	8.9 ± 1.0	8.5 ± 1.2	6.6 ± 1.8	0.0017
Willingness to repeat the same procedure, %	100	93	85%	0.0013

EGD = Esophagogastroduodenoscopy.

Values represent mean ± SD. * Scale 0–10, where 10 is excellent and 0 is poor. Overall satisfaction between propofol and midazolam; 8.9 ± 1.0 vs. 8.5 ± 1.2, *p* = 0.34.

ery. This report describes our experience in terms of safety and overall satisfaction with nurse-administered low-dose propofol given to 12,031 healthy subjects undergoing diagnostic EGD. Previous reports have involved propofol dosages ranging from 30 to 300 mg for endoscopic sedation [1–11]. The protocol adopted in our study strongly focused on the safety and the initial dose of 30 or 40 mg of propofol was designed to minimize hypoxemia during the EGD. Significant respiratory compromise (SpO₂ <90%) was rare compared with previous reports [16, 17] and no subject required mechanical ventilation during the procedures via either endotracheal intubation or a mask.

All propofol sedated patients regained normal neuropsychological function within 30 min after the procedure [11, 16]. In previous reports, the average time until full recovery was 15–20 min and the average time to discharge was 60 min. Sanou et al. [18] conducted five cognitive tests designed to assess short-term memory, delayed memory, the ability to plan complex tasks, attention, and language comprehension following propofol-sedation and reported that cognitive functions were still depressed after 3 h. Riphaut et al. [19] recommended that patients remain in a supervised environment for at least

Table 3. Driving ability before and at 30, 60 and 120 min after injection of each drug

	Driving ability		
	tracking error	accelerating RT	braking RT
<i>Propofol group (n = 30)</i>			
Before	32 ± 2.7%	0.56 ± 0.21	0.66 ± 0.34
30 min after injection	74 ± 3.2%*	0.88 ± 0.34*	0.56 ± 0.54
60 min	45 ± 2.3%	0.43 ± 0.32	0.49 ± 0.28
120 min	37 ± 1.9%	0.34 ± 0.17	0.32 ± 0.31
<i>Midazolam group (n = 30)</i>			
Before	57 ± 5.7%	0.52 ± 0.26	0.45 ± 0.21
30 min after injection	Not tested	Not tested	Not tested
60 min	156 ± 16.7%**	1.06 ± 0.51**	0.88 ± 0.34*
120 min	86 ± 7.7%*	0.89 ± 0.49*	0.56 ± 0.41
<i>Control group (n = 20)</i>			
Before	32 ± 2.7%	0.56 ± 0.31	0.76 ± 0.41
30 min	46 ± 3.1%	0.46 ± 0.28	0.55 ± 0.27
60 min	39 ± 2.9%	0.66 ± 0.43	0.46 ± 0.52
120 min	31 ± 1.7%	0.57 ± 0.34	0.54 ± 0.33

RT = Reaction time (second). * *p* < 0.05, ** *p* < 0.01 Significantly different from before (baseline level) in each group.

3 h after propofol sedation and that patients refrain from driving and unescorted use of public transport for 24 h after sedation. However, these recommendations followed studies where the propofol dosages were 105 ± 60 mg, which is significantly more than the 30–40 mg dosage used here.

Generally, propofol is given by bolus titration with an initial dose of 30–50 mg followed by doses of 10–20 mg beginning 30–60 s later with the appropriateness of additional bolus doses being determined by the level of sedation and the respiratory effect. This approach requires the use of highly skilled personnel. In contrast, we used a defined protocol where, depending on the patient age, either 30 or 40 mg was given by bolus injection. As shown in table 2, the average weight of the healthy Japanese subjects was about 60 kg such that the dosage used averaged 0.67 mg/kg. Using this dosage we showed driving ability returned to baseline within 60 min after completion of the EGD and 98% of the 12,031 subjects fully recovered to the basal level 30 min after the procedure. This differs remarkably from the effects of midazolam where impaired driving was still present at 2 h after the procedure (table 3).

A previous study examined the relationship between blood alcohol concentration and psychomotor effects and attempted to provide a standard based on the maximum permitted blood alcohol levels for driving in three European countries (20, 50 and 80 mg/100 ml) as the reference points [13]. The impairment in driving skill with a blood propofol concentration of 200 ng/ml was less than that observed with a 50 mg/100 ml of alcohol and not greater than that observed with 20 mg/100 ml of alcohol [13]. These results are consistent with our findings that driving levels recovered to the baseline level when the blood levels of propofol (40 and 80 mg) at 60 min were less than 100 ng/ml (fig. 1; table 3).

Screening EGD for early gastric cancer is a health initiative that is more relevant to the Japanese population. On the other hand, colonoscopy is more relevant in the Western population where the median body weight is likely to be much higher than 60 kg. The results of this report are applicable to a patient population comprising healthy outpatients undergoing diagnostic EGD. For patients undergoing colonoscopy or therapeutic endoscopic procedures, additional doses of propofol and combination of other drugs may be required.

In conclusion, low-dose propofol sedation for diagnostic EGD was safe and clinical recovery and recovery in driving ability was rapid.

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