



Digestive Endoscopy

Paradoxical reaction to midazolam in patients undergoing endoscopy under sedation: Incidence, risk factors and the effect of flumazenil



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ABSTRACT

Background: The incidence, risk factors and management strategy of paradoxical reaction to midazolam during endoscopy are yet to be clarified.

Methods: This single center prospective study included 4140 adult patients (2263 males, mean age of 57.7 ± 12.6) undergoing endoscopy under sedation with midazolam and pethidine between September 2011 and December 2011. The characteristics of patients with and without paradoxical reaction were compared. For patients who experienced paradoxical reaction and received flumazenil, their endoscopic images were reviewed to assess whether European Society of Gastrointestinal Endoscopy guidelines were met as quality indicator of endoscopy.

Results: The incidence of paradoxical reaction was 1.4%. In multivariate analyses, male gender, unsuccessful sedation in previous endoscopy, upper endoscopy, higher dose of midazolam, and lower dose of pethidine were identified as independent risk factors for paradoxical reaction. Despite paradoxical reaction, endoscopic procedures were successfully completed in 93.3% of cases when flumazenil was administered. The rates of meeting quality indicator of endoscopy were 92.3% in patients receiving flumazenil for paradoxical reaction and 97.6% in patients without paradoxical reaction.

Conclusions: For patients with risk factors for paradoxical reaction, active use of pethidine with a dose reduction of midazolam might be helpful to prevent the occurrence of paradoxical reaction. Administration of flumazenil might be positively considered in cases of paradoxical reaction.

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1. Introduction

Sedation is widely used for endoscopic procedures worldwide to reduce patients' anxiety and discomfort, consequently improving their tolerability and satisfaction for procedure. Endoscopic sedation also provides the endoscopist with the opportunity for a more thorough examination and improved outcomes of the procedure [1–4]. Benzodiazepines and propofol are two representative drugs for sedation during endoscopy. Although the use of propofol is increasing, benzodiazepines are still the most commonly used sedatives for endoscopic procedures. In the United States, sedation with a combination of a benzodiazepine and a narcotic is used

in approximately 75% of routine esophagogastroduodenoscopies (EGDs) and colonoscopies [5].

Among the various benzodiazepines, midazolam is distinguished by a more rapid onset of action, shorter duration of effect, and higher amnestic properties and therefore it is currently the most commonly used drug for endoscopic sedation [3,4]. However, it has been reported that paradoxical reactions or disinhibition reactions may occur with the use of benzodiazepines including midazolam [4,6]. Paradoxical reactions are characterized by increased talkativeness, emotional release, excitement, excessive movement, and even hostility and rage during and after procedures [4,6,7]. As their occurrence can severely impede or even prevent the performance of the procedure, paradoxical reactions are matters of great clinical significance to endoscopists. In previous studies, the incidence of paradoxical reaction following midazolam administration has varied from 1 to 24% [8–15]. In addition, several predisposing risk factors of paradoxical reaction have been suggested including young or advanced age, gender, history of alcohol abuse, genetic predisposition, and psychological background

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[6,10,16–18]. However, most previous reports on paradoxical reactions to benzodiazepines dealt with pediatric patients who have different demographic features from adults. Moreover, most risk factors suggested were based on anecdotal case reports and robust supporting evidence for these factors is still lacking. Therefore, the incidence and risk factors of paradoxical reaction to midazolam in adult patients are still unclear and yet to be clarified in a large prospective study.

Flumazenil is a benzodiazepine-specific antagonist that is widely used for reversing benzodiazepine-induced sedation and respiratory depression [4]. To date, however, the effects of flumazenil on paradoxical reactions during endoscopic procedure are not well described. Data are mainly from case reports or small studies of pediatric patients [11,12,19]. Because of this paucity in data, the role of flumazenil is not established in the management of paradoxical reactions during endoscopy.

In the present study, we aimed to elucidate the incidence and risk factors of paradoxical reaction to midazolam in adult patients undergoing endoscopy under sedation. We also evaluated the effect of flumazenil on paradoxical reactions which occurred during endoscopic procedures.

2. Methods

2.1. Patients

Subjects of this prospective study were adult patients (age ≥ 20) who underwent endoscopy under sedation in Samsung Medical Center between September 2011 and December 2011. Only patients undergoing diagnostic EGD, colonoscopy with or without polypectomy, or diagnostic upper gastrointestinal (GI) endoscopic ultrasonography were included in the study population. Patients who underwent therapeutic procedure such as endoscopic submucosal dissection, percutaneous endoscopic gastrostomy, endoscopic hemostasis, endoscopic variceal ligation, or stenting were excluded. These therapeutic procedures are invasive and patients can be stimulated by pain or discomfort associated with these procedure, which can be confused with paradoxical

reaction. During the above period, a total of 5389 patients met the inclusion criteria and were asked to participate in the study and to answer a self-administered questionnaire before the endoscopy. A total of 4140 patients (76.8%) agreed to answer the questionnaire and were finally enrolled in this prospective study. All patients provided written informed consent according to our institutional guidelines. The institutional review board at Samsung Medical Center approved the study protocol.

2.2. Questionnaire for assessing risk factors for paradoxical reactions

The questionnaire included the questions about demographic data, previous experience of endoscopy with or without sedation, current medication, and medical history including comorbidity and psychiatric disorder (Table 1). Patients' current status of alcohol drinking, smoking, and medication use were assessed. Heavy drinking was defined as the alcohol consumption of at least 40 g/day for men or at least 20 g/day for women [20]. Attending nurses or endoscopists checked the completeness of questionnaire before starting the procedure and asked patients to complete the questionnaire if patients missed questions. All participating endoscopists in the present study had more than 500 cases of EGD experience and received education about the definition of paradoxical reaction used in the present study before the initiation of the study.

2.3. Protocol for sedation and procedure

All enrolled patients received a combination of midazolam and pethidine for sedation after topical pharyngeal anesthesia with lidocaine. The protocol used for sedation was modified from American Gastroenterological Association recommendation [4]. The initial intravenous dose of midazolam was 1 mg for patients older than 70 or weighing < 60 kg and 2 mg for patients ≤ 70 years of age and ≥ 60 kg. An additional dose of 0.5–1 mg of midazolam was administered at 2-min intervals until adequate sedation was achieved. The induction dose of pethidine was 25 mg for patients older than 70 or weighing < 60 kg and 50 mg for patients ≤ 70 years

Table 1
Baseline characteristics of patients according to the presence of paradoxical reactions.

	No paradoxical reaction (n = 4081)	Paradoxical reaction (n = 59)	P-value
Age (years)			0.574
Mean \pm SD	57.7 \pm 12.5	56.6 \pm 15.0	
Median (range)	57.9 (21–95)	60.9 (25–87)	
Male gender (%)	2222 (54.4)	41 (69.5)	0.021
Body mass index (kg/m ²) ^a	23.0 \pm 3.1	22.9 \pm 2.9	0.799
Endoscopy experience (%)			<0.001
Endoscopy under unsuccessful sedation	187 (4.6)	8 (13.6)	
Endoscopy under successful sedation	3305 (81.0)	41 (69.5)	
Endoscopy without sedation	338 (8.3)	1 (1.7)	
No previous experience of endoscopy	251 (6.2)	9 (15.3)	
Heavy drinking ^b (%)	1036 (25.4)	22 (37.3)	0.037
Smoking (%)	477 (11.7)	14 (23.7)	0.005
Somniloquy (%)	543 (13.3)	12 (20.3)	0.115
Comorbidity except psychiatric disorder (%)	1529 (37.5)	21 (35.6)	0.768
Benzodiazepine use (%)	106 (2.6)	1 (1.7)	1.000
Opioid or centrally acting analgesics use (%)	51 (1.2)	1 (1.7)	0.528
History of psychiatric disorder (%)	165 (4.0)	3 (5.1)	0.517
Type of endoscopy (%)			0.001
Lower	836 (20.5)	2 (3.4)	
Upper	3245 (79.5)	57 (96.6)	
Level of sedation (%)			0.996
Moderate	2558 (62.7)	37 (62.7)	
Deep	1523 (37.3)	22 (37.3)	
Midazolam dose (mg) ^a	3.27 \pm 1.04	3.71 \pm 1.21	0.001
Pethidine dose (mg) ^a	42.8 \pm 11.4	40.3 \pm 12.3	0.121

^a Mean \pm SD.

^b Alcohol consumption of at least 40 g/day for men or at least 20 g/day for women.

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