A comparison of midazolam and diazepam in premedication for upper gastrointestinal endoscopy

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ÖZET: **Gastrointestinal sistem endoskopisi için premedikasyonda diazepam ve midazolam'ın karşılaştırılması**

Üst gastrointestinal sistem endoskopisi için premedikasyonda diazepam ve midazolam'ın sedatif etkileri karşılaştırılmış ve flumazenil'in diazepam ile midazolam'ın sedatif etkilerini geri çevirmedeki etkinliği araştırılmıştır. Midazolam yeterli sedasyon sağlamada daha etkili görülmüş ve midazolamla sağlanan sedasyon süresi diazepam ile karşılaştırıldığında daha kısa bulunmuştur. Flumazenil, diazepam ve midazolamın sedatif etkilerini geri çevirmede eşit oranda etkili bulunmuştur.

Anahtar kelimeler: **Endoskopi, diazepam, midazolam, flumazenil**

SUMMARY

Sedative effects of diazepam and midazolam in premedication for upper gastrointestinal endoscopy were compared and efficiency of flumazenil in reversing the sedative effects of diazepam and midazolam was evaluated. Midazolam appereared to be more efficient at providing adequate sedation and duration of sedation provided with midazolam was shorter compared to diazepam. Flumazenil was equally effective at reversing the sedative effects of diazepam and midazolam.

Key words: **Endoscopy, diazepam, midazolam, flumazenil**

PREMEDICATION with benzodiazepines is a common practice in upper gastrointestinal endoscopy (1). Diazepam has been the most commonly used benzodiazepine used in upper gastrointestinal endoscopy (2). Although it can provide full relaxation and cooperation over 75% of patients (3), its sedative effect may be prolonged up to 10 hours due to its conversion to active metabolites.

Midazolam, a water soluble benzodiazepine derivative is an alternative to diazepam. Its half life is 2-3 hours and its reported to cause adequate sedation over 90% of patients in different series (3).

In this study we compared the sedative effects of diazepam and midazolam in patients undergoing upper gastrointestinal endoscopy. Also efficiency of flumazenil at reversing the sedative effects of diazepam and midazolam were compared.

PATIENTS AND METHODS

91 patients (46 female and 45 male) were included in the study. Demographic features of the patients are shown in the Table 1. 41 patients received iv diazepam 0.15-0.25 mg/kg, 50 patients received iv midazolam 0.07-0.15 mg/kg, until full sedation was achieved. Following endoscopy patients were randomized as to receive iv flumazenil 2 ml (20 patients who received diazepam, 25 patients who received midazolam). Then patients were evaluated for endoscopic tolerance (Table 2). and duration of endoscopy during the procedure (Table 3). and for sedation, cooperation and orientation at minutes 0, 10,30,60 and 120 following the procedure with the system proposed by Birkenfeld et al (4) (Table 4).

Table 1. *Characteristics of patients*

Study Group	No of Patients	Sex (F/M)	Mean Age
Diazepam (0.15-0.25 mg/kg iv) (9-26 mg)	21	9/12	34.6 (24-53)
Diazepam (0.15-0.25 mg/kg iv) (8-28 mg) + Flumazenil (0.2 mg iv)	20	10/10	33.7 (22-49)
Midazolam (0.07-0.15 mg/kg) (4.5-9 mg)	25	14/11	36 (22-59)
Midazolam (0.07-0.15 mg/kg) (4.5-9 mg) + Flumazenil (0.2 mg iv)	25	13/12	31 (18-49)

Geliş tarihi: 15.12.1994, Kabul tarihi: 2.1.1995

Table 2. *Evaluation of endoscopic tolerance*

Patient relaxed, no gagging, not interrupting endoscopy, endoscopy succesful.	Good
Patient not relaxed, gagging, not interrupting endoscopy, endoscopy succesful.	Moderate
Patient not relaxed, gagging, trying to pull endoscope, endoscopy succesful/unsuccesful.	Poor

RESULTS

Endoscopic tolerance was good in 81% (17/21) of patients who received diazepam and in 80% of patients (16/20) who received midazolam and 100% of patients who received midazolam and 100% of patients who received midazolam and flumazenil. Endoscopic tolerance of patients who received midazolam and midazolam plus flumazenil was better than patients receiving diazepam and diazepam plus flumazenil (Table 5). ($p<0.05$).

Among 25 patients who received midazolam 3 (12%) were fully alert and oriented at 10th minute, 10 patients (40%) at 30 th minute, 9 patients (36%) at 60 th minute and 3 patients (12%) were fully alert and oriented and cooperated at 120th minute (Table 6).

Of 21 patients who received diazepam, 4(19%) were fully alert and oriented at 10th minute, 3 patients (14%) at 30th minute, 12 patients at 60th minute and 2 patients were alert and oriented at 120th minute (Table 6).

All the patients (100%) who received flumazenil either following diazepam or midazolam were fully oriented and cooperated at 10th minute of injection (Table 6).

DISCUSSION

Neuropharmacological effects of Benzodiazepines

Table 4. *Scoring system used to assess degree of sedation*

Assessment of Alertness	Score
* Patient sedated, not arousable	0
* Patient sedated, but arousable	1
* Patientdrowsy	2
* Patientawake	3
Orientation for time and place	
* Not evaulable	0
* Partially oriented	1
* Fully oriented	2
Cooperation and Collaberation	
* Not evaulable	0
* Execution by imitation	1
* Execution by verbal order	2

* *Patients with a total score of 7 were considered awake and alert*

Table 3. *Duration of endoscopy*

Study Group	No of Patients	Duration of Endoscopy
Diazepam	21	15 ± 3
Diazepam + Flumazenil	20	14 ± 2
Midazolam	25	14.5 ± 2
Midazolam+Flumazenil	25	15 ± 1

are thought to stimulate the inhibitory mechanisms in the central nervous system (5). Benzodiazepines are bound to specific receptors in pre and post synaptic plates where gamma aminobutyric acid is inhibitory transmitter (6). The affinity of benzodiazepines to the synaptic plate are correlated with the pharmacological effects of these drugs (6).

Diazepam has been the most popular benzodiazepine used for sedation in upper gastrointestinal endoscopy. In various series, it has been reported to cause sedation and retrograde amnesia over 75% at patients when used in doses between 0.15-0.3 mg/kg iv (7).

However because of conversion of the drug to active metabolites, its sedative effect may be prolonged up to 10 hours (3).

Midazolam is a water soluble benzodiazepine which is gaining popularity. Its half life 2-3 hours and has been reported to provide amnesia earlier and sedative effect to last shorter compared to diazepam. In various series, when used in doses between 0.036-0.107 mg/kg its reported to cause sedation and amnesia over 90% of patient.

In our study, midazolam was superior to diazepam at providing full sedation. Its sedative effect was significantly shorter compared to diazepam. These findings are consistent with the findings in the literature. The efficiency of flumazenil at reversing the sedative effects of diazepam and midazolam was not significantly different.

We conclude that midazolam is at least as succesful as diazepam at providing full sedation and relaxation in patients undergoing upper gastrointestinal endoscopy and duration of sedative effect is significantly shorter compared to that of diazepam.

Table 5. *Endoscopic tolerance*

Study Group	Tolerance		
	Good	Moderate	Poor
Diazepam	17 (81%)	4(19%)	-
Diazepam+Flumazenil	16 (80%)	4(20%)	-
Midazolam	25 (100%)	-	-
Midazolam+Flumazenil	25 (100%)	-	-

Table 6. *Efficiency of flumazenil in reversing the sedative effect of diazepam and midazolam*

Time(min.)	Score	Diaz.	Diaz.+Flu.	Mid.	Mid. + Flu.
0	7	0	0	0	0
	<7	21	20	25	25
10	7	4 (19%)	20 (100%)	3 (12%)	25 (100%)
	<7	17	0	22	0
30	7	3 (14%)	20 (100%)	10 (40%)	25 (100%)
	<7	14	0	12	0
60	7	12 (58%)	20 (100%)	9 (36%)	25 (100%)
	<7	2	0	3	0
120	7	2 (9%)	20 (100%)	3 (12%)	25 (100%)
	<7	0	0	0	0

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