REPORT FROM THE TROPICS

The Use of Flumazenil in Reversing the Midazolam and Diazepam Sedation in Outpatients Undergoing Gastroscopy

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ABSTRACT

A prospective double blind randomized study was conducted to assess the efficacy and safety of flumazenil in patients for upper gastrointestinal endoscopy, sedated with midazolam or diazepam. Flumazenil significantly reduced the degree of sedation in both treatment groups without significant intergroup differences. There was no evidence of rebound sedation during the observation period of 4 hours. Anterograde amnesia was effectively antagonized in both groups. Flumazenil was a well tolerated safe and effective benzodiazepine antagonist. The combination of benzodiazepine with flumazenil makes it possible to reduce the recovery period and may be useful in outpatients undergoing endoscopy.

Introduction

Benzodiazepines have profound and specific effects on memory. Most notably, the drugs greatly impair ability to learn new information i.e., they produce anterograde amnesia[1]. They also have anxiolytic, sedative and hypnotic activities and thus the benzodiazepines, midazolam and diazepam are often used for sedation of outpatients undergoing gastroscopy[2,3].

Midazolam and diazepam differ in their plasma half-life and active metabolites both of which can influence recovery after sedation.

Flumazenil (Ro-15-1788) is an imidazobenzodiazepine which blocks the central effects of benzodiazepines[4]. It has a short elimination half-life of 54 minutes which is closer to that of midazolam but considerably shorter than that of diazepam which is 43 hours[5,6]. Partial reversal of neurological depression has been noted after its use as an antagonist[5].

The aim of this study was to evaluate any difference in the efficacy of flumezanil in reversing the central effects of the relatively short lasting midazolam and the slowly eliminated diazepam as well as to assess the safety of flumazenil and possible rebound sedation.

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Patients and Methods

This study was carried out in the Gastrointestinal Endoscopy Unit at King Fahd University Hospital, Al-Khobar, Saudi Arabia. Sixty consecutive patients of both sexes, ASA grades 1 and 2 with age ranging between 18-75 years who were subjected to upper gastrointestinal endoscopy, were enrolled, in a double blind randomized study. A complete clinical examination, including physical examination was carried out on all patients. Patients were excluded if they had severe pulmonary disease, clinically significant arrhythmias, hepatic or renal diseases, pregnancy, and patients with severe psychiatric disorders treated over a long period with psychotropic drugs including benzodiazepines. The study was carried out in accordance with the second Helsinki Declaration. Informed consent was obtained from participating patients.

Patients were randomly allocated to receive either midazolam (Dormicum) 0.07-0.15 mg/kg body weight (b.w.) or diazepam (Valium) 0.15-0.20 mg/kg b.w. intravenously.

Soon after the endoscopy, 0.6 mg flumazenil was injected intravenously. The dose was increased to a maximum of 1.0 mg in some patients. The intravenous injection was given by a senior medical resident who was unaware of the type of sedation given. The patients were assessed by the investigator who was also not aware of the type of sedation given. Before and at 5, 15, 30, 60, 120 and 240 minutes after injection of flumazenil, blood pressure, heart rate and respiratory rate were recorded. The degree of sedation at these times was assessed according to a scoring-system (Table 1); patients who scored a total of 7 were considered as awake and alert. Statistical analysis was performed using the paired and unpaired student's 't'-test ($p < 0.05$ was considered to be significant), Fisher's exact test and Yate's test.

Results

The two groups of patients were comparable with regard to sex, age weight and duration of endoscopy (Table 2). There was no intergroup difference regarding respiratory rate, heart rate and blood pressure. Flumazenil significantly ($p < 0.05$) reduced the degree of sedation in both groups but there were no significant intergroup differences. Five minutes after injection of flumazenil the patients in both groups were awake and remained so during the entire observation period of 4 hours.

In both treated groups, the benzodiazepines produced anterograde amnesia. This was more so with midazolam which caused anterograde amnesia in 90% of patients as compared to 80% in the diazepam treated group. Flumazenil reversed the anterograde amnesia in all the midazolam and 93% of diazepam treated patients (Table 3). No side effects were encountered.

TABLE—1. Scoring System used to assess degree of Sedation

Assessment of alertness	*Score*
Patient sedated, not arousable	0
Patient sedated, but arousable	1
Patient drowsy	2
Patient awake	3
Orientation for time & space	
Not evaluable	0
Partially oriented	1
Fully oriented	2
Cooperation + Collaboration	
Not evaluable	0
Execution by imitation	1
Execution of verbal orders	2
Patients with a total score of 7 were considered awake and alert.	

TABLE 2. Demographic Data

Group	*No.*	*Male/ Female*	*Age (Years)* median range	*Weight (Kg)* median range
Midazolam	30	17/13	50 (18—72)	69 (51—99)
Diazepam	30	15/15	53 (19—75)	66 (43—97)

Duration of endoscopy 5 (3—10) minutes [(median (range)]

TABLE 3. Anterograde amnesia judged at 120, 240 minutes and 24 hours after injection of Flumezanil

	Midazolam			*Diazepam*		
	120 min Y/N (%)	240 min Y/N (%)	24 hr Y/N (%)	120 min Y/N (%)	240 min Y/N (%)	24 hr Y/N (%)
Do you remember injection of benzodiazepine?	28/2 (93)	28/2 (93)	27/3 (90)	27/3 (90)	26/4 (87)	25/5 (83)
Do you remember at all the Gastroscopy	3/27 (10)	2/28 (7)	1/29 (3.4)	6/24 (20)	7/23 (23)	7/23 (23)
Do you remember your stay in the recovery room?	—	—	30/0 (100)	—	—	28/2 (93)

Discussion

Outpatient endoscopic investigations using intravenous sedation are being preformed with increasing frequency in patients belonging to different ages. Since the recovery facilities in many units are not ideal, early recovery of neurological function is desirable. Diazepam and midazolam are the most popular benzodiazepines used in gastrointestinal endoscopy. The imidazobenzodiazepine, flumazenil, possesses a high affinity for the benzodiazepine receptors and functions as a competitive antagonist of benzodiazepines and thus reverses the action of the benzodiazepines[7,8].

The observations in the present study showed that flumazenil effectively reversed the sedation and eliminated the anterograde amnesia of midazolam and diazepam. This was sumilar to that reported by other authors[9,10,11]. The action was fast and not associated with any side effects. Despite the relatively short elimination half-life of flumazenil, and contrary to the observations of Gupta et al[12], no resedation was observed in the present study during the post administration period of four hours. This was irrespective of whether the relatively shorter acting midazolam or the slowly eliminated diazepam was used. The absence of significant difference in the effect of flumezanil in patients sedated with either midazolam or diazepam despite differences in the pharmacokinetics of the latter two drugs needs further evaluation.

It was concluded from the observations in the present study that flumazenil was effective in reversing the sedation and eliminating the anterograde amnesia in benzodiazepine sedated patients. There were no adverse effects and in the dosage used in this study flumezanil was found to be safe for use in outpatients.

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