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# EFFICACY OF FLUMAZENIL IN THE MANAGEMENT OF BENZODIAZEPINE OVERDOSE

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**ABSTRACT**

Benzodiazepine overdose is the most commonly encountered drug overdose in Iran. It has been reported by many authors that flumazenil possesses highly specific antagonistic activity on central benzodiazepine receptors. We conducted a prospective study on 150 patients brought to the toxicology emergency ward in Loghman-Hakim hospital with benzodiazepine overdose to assess the efficacy of flumazenil to counteract benzodiazepine overdose. Upon arrival, patients were examined thoroughly and their Glasgow coma scale was recorded. Afterwards flumazenil was administered in sufficient dosage, between 0.25-0.50 mg. The most commonly consumed benzodiazepine was diazepam (50%). One hundred and thirty patients responded positively to flumazenil, characterized by improved response to painful stimuli, and decreased amnesia.

Twenty percent of the patients (26 cases) had an increased respiratory rate after flumazenil administration. In 86 patients, consciousness improved after 5 minutes, in 36 patients after 10 minutes and in 8 patients after 15 minutes. In 48 patients the psychomotor performance improved 5 minutes after antidote administration, while in 15 patients psychomotor performance improved after 30 minutes. Some patients developed resedation after flumazenil administration. In 25 patients resedation occurred after 15 minutes, in 59 patients after 30 minutes, and 34 patients showed this phenomenon after 45 minutes. Despite this last finding, we concluded that flumazenil effectively and rapidly antagonizes the central effects of benzodiazepines. It is also a valuable diagnostic agent with no serious side effects.

**Keywords:** Flumazenil, Benzodiazepine, Overdose.

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## INTRODUCTION

Flumazenil (Ro 15-1788) is a 1,4-imidazobenzodiazepine with highly specific and competitive antagonistic activity at the central benzodiazepine (BDZ) receptors.[17] It attenuates the cognitive, psychomotor, hypnogenetic, respiratory depressive and electroencephalographic (EEG) effects of BDZ agonists.[3] It is also reported that flumazenil (FLM) is valuable for the diagnosis of comatose patients with unknown overdose ingestions, unless tricyclic antidepressant ingestion is suspected.[4,5,10,11] BDZs are among the most widely used drugs in the society.[6] They are commonly prescribed for a broad spectrum of illnesses including anxiety disorders, stress, insomnia, seizures, muscular spasms and alcohol withdrawal; they are also used in patients undergoing general anesthesia and conscious sedation. Due to their availability, BDZs are frequently the cause of accidental and intentional overdoses.[12]

We designed the current analytical and observational study to evaluate FLM as a diagnostic and therapeutic agent.

## METHODS

This study was conducted prospectively and assessed the effect of FLM in reversing BDZ toxicity in overdosed patients brought to Loghman-Hakim Hospital affiliated to the Shahid Beheshti University of Medical Sciences, Tehran, between November 1994 and August 1995. Flumazenil was purchased from Roche, Switzerland.

All patients who were comatose, or had known or suspected BDZ overdose were included in this study and FLM administration was evaluated.

Upon arrival, patients were examined and their Glasgow coma scale (GCS) scores were calculated. Their GCS score was again calculated at 5 and 15 minute intervals after FLM administration.

Due to lack of objective criteria, parameters such as improvement in consciousness and psychomotor performance, increased response to pain stimuli, decreased level of amnesia and development of resedation were measured subjectively by managing physicians.

Other patient data gathered included gender, age, addiction history, type of agent involved in poisoning (except for 6 patients) and time of ingestion.

FLM side effects, the performance of gastric lavage and administration of activated charcoal were also recorded. All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

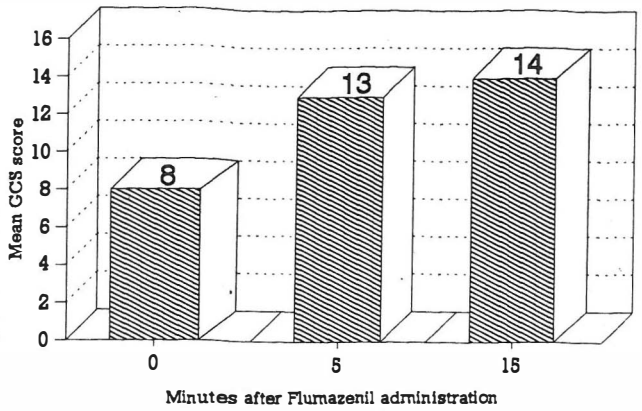


**Fig. 1.** Mean GCS score at 0, 5 and 15 minutes after flumazenil administration.

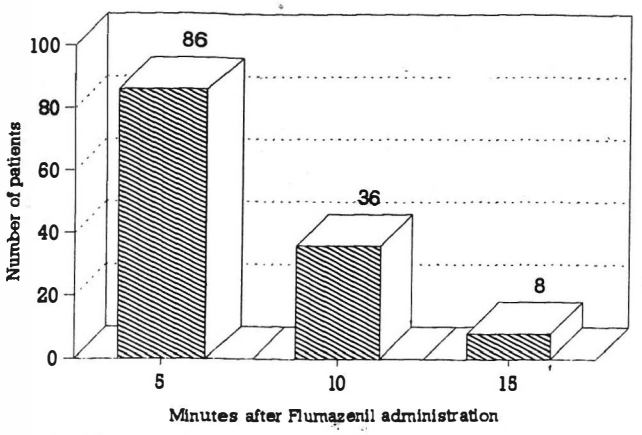


**Fig. 2.** Number of patients whose consciousness improved after flumazenil administration.

## RESULTS

One hundred and fifty-five patients, 84 females and 71 males were included in this study. Their age was between 15 and 84 years, averaging 49 years. There was no addiction history except to cigarettes in six male patients. The agents involved in poisoning are shown in Table I. As shown in this table diazepam was the most widely used agent (89 patients), followed by clonazepam (15 patients), chlordiazepoxide (11 patients), oxazepam (10 patients) and flurazepam (9 patients). The time elapsed between drug intake and hospital admission varied between 1 and 24 hours, averaging 10 hours. On admission 40 females and 47 male patients were in coma (GCS<9). The rest of the patients (44 females and 24 males) had a GCS≥9. FLM was administered with a dose of either 0.25 or 0.5 mg. In some patients the dose was repeated (Table II). Twenty-five patients (6 females and 19 males) did not

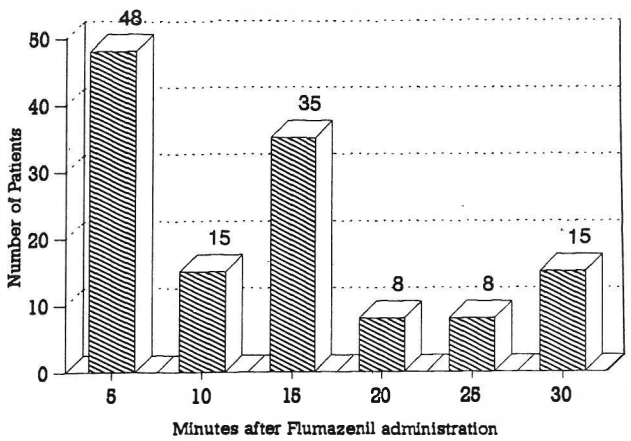


**Fig. 3.** Number of patients whose psychomotor performance improved after flumazenil administration.

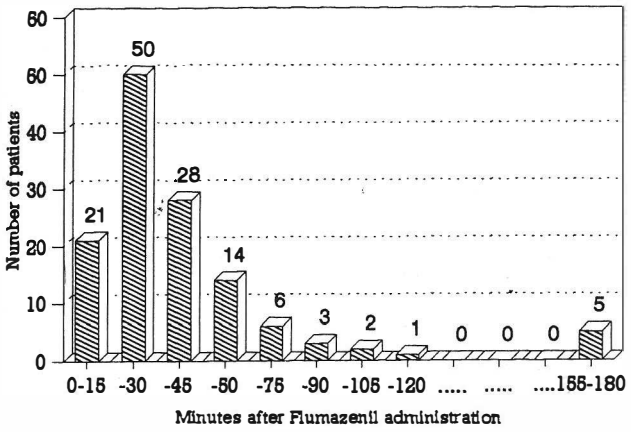


**Fig. 4.** Number of patients who developed resedation after flumazenil administration.

respond to FLM administration. In the remaining 130 patients who responded to FLM, GCS was recorded 5 and 15 minutes after its administration. Mean GCS levels show significant gradual improvement (Figure 1). All of this latter group showed an improved response to painful stimuli and decreased amnesia. 25 patients also showed increased respiratory rates.

The elapsed time between FLM administration and onset of improvement of consciousness and psychomotor performances are depicted in Figures 2 and 3 respectively. 86 patients had improved consciousness 5 minutes after FLM, 36 patients improved after 10 minutes and 8 patients after 15 minutes.

Some of the patients who initially responded developed resedation later. The elapsed time between FLM intake and onset of resedation is illustrated in Figure 4. Mental confusion (50 cases), nausea and vomiting (13 cases), agitation (3 cases) and cardiac arrhythmias (2 cases) were the mild adverse reactions encountered in the course of this study.

**Table I. Patients intoxicated with benzodiazepines.**

| Agents involved in poisoning | Number of patients |
|---|---|
| Diazepam | 89 |
| Clonazepam | 15 |
| Flurazepam | 9 |
| Oxazepam | 10 |
| Chlordiazepoxide | 11 |
| Diazepam + Imipramine | 6 |
| Diazepam + Amitriptyline | 2 |
| Diazepam + Trifluperazine | 3 |
| Diazepam + Phenobarbital | 4 |
| Unknown | 6 |
| Total | 155 |

**Table II. Flumazenil dosage.**

| Dose administered (mg) | Times post-ingestion | Number of patients |
|---|---|---|
| 0.25 | 1 | 10 |
| 0.25 | 2 | 108 |
| 0.25 | 3 | 8 |
| 0.25 | 4 | 20 |
| 0.50 | 1 | 9 |

## DISCUSSION

FLM can have great diagnostic importance in comatose patients or in intoxicated patients who are unable to provide information concerning type and amount of toxic agent consumed.[15,16,18] In our study 26 patients did not respond to FLM. This questions their BDZ intoxication, despite their claims. FLM improves consciousness within a short period of time, and gives the clinician an opportunity to communicate with the patient in order to acquire relevant and useful information.[4,8,12]

Improvement of consciousness and resumed protective airway reflexes make gastric lavage a safe procedure without risking pulmonary aspiration.[17] Nonetheless it does not replace proper primary care.[8] FLM also improves psychomotor performance within a short period of time (5-30 minutes) and also decreases amnesia. Aarseth et al.[1] administered FLM in 18 patients suspected to be intoxicated by BDZs and reported its significant effect on consciousness; all patients awakened within minutes. They also report no adverse effect except deterioration of clinical condition 1 to 2 hours after FLM was given. Resedation recurred up to 3 hours after FLM administration.[1] In general, if a patient shows no signs of resedation within 2 hours

after the initial dose, serious resedation at a later time is unlikely.[14]

Although FLM improved the consciousness of patients recovering from BDZ overdose, the need for adequate monitoring during the resedation period must be emphasized. FLM is usually given up to 1 mg as a single dose. The dose may be repeated every 20 minutes, not to exceed 3 mg per hour. The maximum dose used in our study was 0.5 mg. Similar to what Herd and Clarke[9] reported, cardiac arrhythmias and agitation were the worst side effects we encountered. Fortunately, these are not common.

## CONCLUSION

When confronting a drug-intoxicated comatose patient, the first step is diagnosis, and the second is treatment. Diagnosis includes type, amount and time of drug intake; according to these parameters, treatment should be instituted.

Considering the great number of people who use BDZs in the society, and knowing that BDZs cause a decrease in consciousness, it is very important to increase the patient's consciousness in order to gain information concerning the ingested drugs and thus improve the patient's overall condition. FLM effectively and rapidly antagonizes BDZs central effects, and is a great diagnostic agent with no serious adverse reactions.

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