

## EFFICACY OF FLUMAZENIL IN THE MANAGEMENT OF BENZODIAZEPINE OVERDOSE

MOHAMMAD ABDOLLAHI, \*Pharm.D., Ph.D., NASER JALALI, \*\*  
M.D., RAMESH GHAFARI, \*\*\*M.S., Pharm.D., MOHAMMAD  
SHARIATPANAHI, † Ph.D., AND BEHROOZ JANAT, ‡ Pharm.D.

*From the Department of Pharmacology and Toxicology, Tehran University of Medical Sciences, and the  
Toxicology Ward of Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran,  
Islamic Republic of Iran.*

### 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 re sedation after flumazenil administration. In 25 patients re sedation 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.

*MJIRI, Vol. 11, No. 2, 99-102, 1997.*

---

**Corresponding author and address:** Dr. Mohammad Abdollahi,  
Department of Toxicology & Pharmacology, Faculty of Pharmacy,  
Tehran University of Medical Sciences, Tehran, P.O. Box 14155-  
6451, Fax: 6461178, Islamic Republic of Iran.

\* Assistant professor of pharmacology & toxicology, Tehran  
University of Medical Sciences.

---

\*\* Associate professor of clinical toxicology and anesthesiology,  
Shahid Beheshti University of Medical Sciences.

\*\*\* Yale University, USA, and Tehran University of Medical  
Sciences.

† Professor of Toxicology, Tehran University of Medical Sciences.

‡ Resident of Ph.D, Tehran University of Medical Sciences.

## INTRODUCTION

Flumazenil (Ro 15-1788) is a 1,4-imidazobenzodiazepine with highly specific and competitive antagonistic activity at the central benzodiazepine (BDZ) receptors.<sup>17</sup> It attenuates the cognitive, psychomotor, hypnogenetic, respiratory depressive and electroencephalographic (EEG) effects of BDZ agonists.<sup>3</sup> 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.<sup>4,5,10,11</sup> BDZs are among the most widely used drugs in the society.<sup>6</sup> 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.<sup>12</sup>

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 re-sedation 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

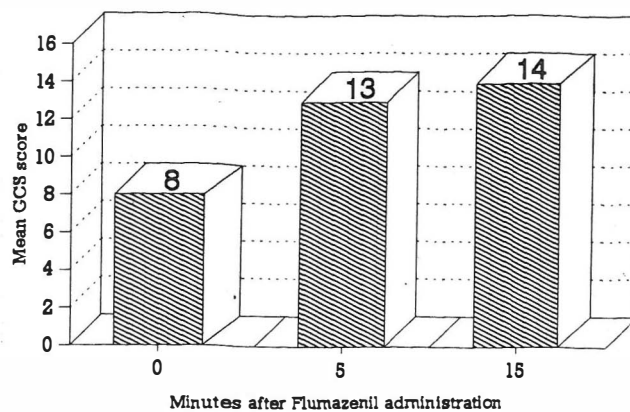


Fig. 1. Mean GCS score at 0, 5 and 15 minutes after flumazenil administration.

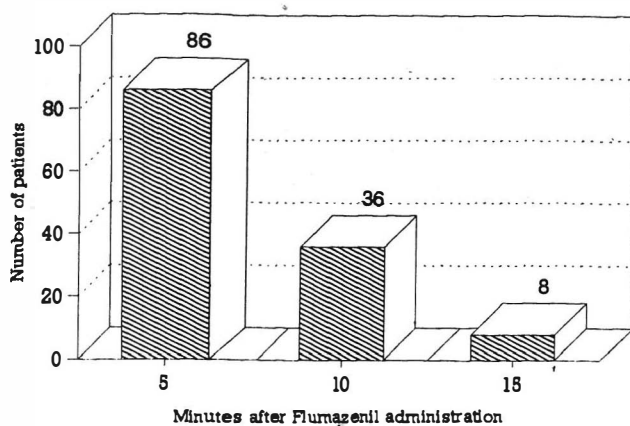


Fig. 2. Number of patients whose consciousness improved after flumazenil administration.

committee on human experimentation.

## 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



## Flumazenil in Benzodiazepine Overdose

after the initial dose, serious re sedation at a later time is unlikely.<sup>14</sup>

Although FLM improved the consciousness of patients recovering from BDZ overdose, the need for adequate monitoring during the re sedation 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<sup>9</sup> 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.

### REFERENCES

1. Aarseth HP, Bredesen JE, Grynne B: Benzodiazepine-receptor antagonist, a clinical double-blind study. *Clin Toxicol* 26: 283-292, 1988.
2. Bodenham AR: Death after flumazenil. *Br Med J* 299 (5): 457, 1989.
3. Brogden RN, Goa-Karen L: Flumazenil, a reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 42: 1061-1089, 1991.
4. Burkhart KK, Kulig KW: The diagnostic utility of flumazenil (a benzodiazepine antagonist) in coma of unknown etiology. *Ann Emerg Med* 19: 319-321, 1990.
5. Burkhart KK, Kulig KW, Rumak BH: The diagnostic utility of flumazenil (a benzodiazepine antagonist) in coma of unknown origin. *Vet Hum Toxicol* 31: 376, 1989.
6. Coates W, Evans TC, Gehle D: Flumazenil for the reversal of refractory benzodiazepine-induced shock. *J Toxicol Clin Toxicol* 29: 537-542, 1991.
7. Danton AN, Schwam E, Pitman V: Flumazenil: US clinical pharmacology studies. *Eur J Anaesthesiol Suppl* 2: 81-95, 1988.
8. Geller E, Crome P, Schaller MD: Risks and benefits of therapy with flumazenil (Anexate (R)) in mixed drug intoxications. *Eur Neurol* 31: 241-250, 1991.
9. Herd B, Clarke F: Complete heart block after flumazenil. *Hum Exp Toxicol* 10: 289, 1991.
10. Hodgkinson DW, Driscoll P: Diagnostic utility of flumazenil in coma with suspected poisoning (letter). *Br Med J* 302: 238, 1991.
11. Hojer J, Baehrendtz S: The effects of flumazenil (Ro 15-1788) in the management of self-induced benzodiazepine poisoning. *Acta Med Scand* 224: 357-365, 1988.
12. Hojer J, Baehrendtz S, Matell G: Diagnostic utility of flumazenil in coma with suspected poisoning; a double-blind, randomised controlled study. *Br Med J* 301: 1308-1311, 1990.
13. Lim AG: Death after flumazenil (letter). *Br Med J* 299: 858-859, 1989.
14. Product information, Mazicon (R), flumazenil, Roche Laboratories, Nutley, New Jersey, 1991.
15. Ritz R, Zuber M, Elsasser S: Use of flumazenil in intoxicated patients with coma; a double-blind placebo controlled study in ICU. *Intens Care Med* 16: 242-247, 1990.
16. Skielboe M, Andersen PM, Weber M: Reversal of benzodiazepine intoxication by flumazenil. *Resuscitation* 22: 245-252, 1991.
17. Weinbroum A, Halpern P, Geller E: The use of flumazenil in the management of acute drug poisoning (a review). *Intens Care Med* 17: 532-538, 1991.
18. Winkler E, Almog S, Krieger-D: Use of flumazenil in the diagnosis and treatment of patients with coma of unknown etiology. *Crit Care Med* 21: 538-542, 1993.