REUE | Original Article

Use of flumazenil in an Emergency Department: 1996 to 2019

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BACKGROUND AND OBJECTIVE. Flumazenil is a competitive benzodiazepine antagonist that is used to reverse the effects of a benzodiazepine overdose. Although considered safe. flumazenil's use in overdoses of unknown substances is controversial given that multiple drugs are often involved and benzodiazepines might be reversing the stimulant properties of some other agent a patient has taken. This study aimed to understand how flumazenil has been used in our hospital over a 24-year period and the adverse effects that arose after its use.

METHODS. Descriptive study of case records of patients with acute poisoning attended by Hospital Clínico Universitario Lozano Blesa in Tarragona from 1996 through 2019. Benzodiazepines were thought to be implicated in all the included cases.

RESULTS. We reviewed 4517 cases in which benzodiazepines were involved alone or in combination with other drugs or toxic substances. Flumazenil was administered in 1427 cases (31.6%). Adverse effects were observed in 13 patients (.9%). Two of the patients (.1%) had seizures.

CONCLUSIONS. Flumazenil has a wide margin of safety when used as an antidote for benzodiazepine poisoning. provided contraindications for use are borne in mind.

Keywords: Flumazenil. Benzodiazepines. Overdose. Adverse reactions.

Evolución en el uso de flumazenilo en un servicio de urgencias en el periodo 1996-2019

OBJETIVO. El uso del flumazenilo actúa como antagonista competitivo de las benzodiacepinas utilizándose como antídoto en intoxicaciones de etiología desconocida es controvertido. El objetivo de este trabajo es conocer la evolución de su uso en un servicio de urgencias hospitalarias y los efectos adversos derivados de su empleo.

MATERIAL Y MÉTODOS. Estudio descriptivo de los casos atendidos por intoxicación aguda en el Hospital Clínico Universitario Lozano Blesa de Zaragoza en un periodo de 24 años (1996-2019) en las cuales se sospechaba que estaban implicadas las benzodiacepinas.

RESULTADOS. Se registraron 4.517 casos en los que había intoxicación por benzodiacepinas. solas o asociadas a otros tóxicos o fármacos. Se administró flumazenilo en 1.427 (31.6%). Se registraron efectos secundarios en 13 pacientes (.9%). siendo en 2 (.1%) el evento secundario una crisis convulsiva.

CONCLUSIONES. El uso de flumazenilo como antídoto en la intoxicación por benzodiacepinas tiene un amplio margen de seguridad cuando se usa observando las contraindicaciones para su administración.

Palabras clave: Flumazenilo. Benzodiacepinas. Sobreingesta. Reacciones adversas.

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Introduction

Flumazenil is a water-soluble imidazobenzodiazepine with competitive inhibitory action on the ϒ-aminobutyric acid receptor, acting as a competitive antagonist of benzodiazepines (BZD). Synthesized in 1979 and marketed a few years later, its effect is due to the substitution of a phenyl group with a carbonyl group in the benzodiazepine molecule, which eliminates its sedative and hypnotic actions while maintaining its affinity for GABA receptors.[1,2]

According to the drug's Summary of Product Characteristics (SmPC), flumazenil is indicated for the total or partial reversal of the central sedative effects of BZD. Its indications include terminating the hypnotic-sedative effects in general anesthesia induced and/or maintained with BZD in hospitalized patients; reversing BZD-induced sedation in ambulatory and hospitalized patients undergoing brief diagnostic and therapeutic procedures; specific reversal of the central effects of BZD to allow recovery of spontaneous respiration; and the diagnosis and treatment of intoxications or overdoses caused solely or mainly by BZD.[3]

Therefore, it is used as an antidote to reverse the effects of BZD overdose, both in intoxications where BZD are the only substance involved and in those where they are associated with other agents.

Despite being considered a safe drug, over the years its use in patients with intoxication of unknown etiology has become controversial, since many intoxications involve multiple substances. In such cases, BZD may be antagonizing the stimulant or pro-convulsant properties of another co-ingested toxin.[4] In addition, flumazenil also has the potential to induce acute withdrawal symptoms in patients with chronic BZD use.[5] Its use is also contraindicated in patients with a history of seizure disorders, prolonged QRS interval, or suspicion of co-ingestion of convulsant agents such as tricyclic antidepressants, cocaine, or amphetamines, with seizures being one of the main complications described in relation to its administration.[6]

The objective of this study was to evaluate the evolution of flumazenil use in our center and the adverse effects related to its administration.

We conducted a retrospective descriptive study including cases treated for acute intoxication at *Hospital Clínico Universitario Lozano Blesa in Zaragoza* (Spain), in which BZD involvement was suspected, over a 24-year period (January 1st, 1996–December 31st, 2019). A case was defined as those in which the patient reported consumption of a dose higher than the therapeutic one according to the drug's technical sheet, or those in which intoxication was analytically confirmed.

To accomplish this, the database of the hospital's Clinical Toxicology Unit was used. This unit performs daily review and recording of health records of patients treated for suspected toxic exposure in the emergency department and the hospital's intensive care unit. In addition to the implicated agent, data were collected regarding the circumstances of the intoxication, the patient's signs and symptoms, requested complementary tests and their results, treatment administered (both in prehospital and in-hospital care), case evolution, and final patient disposition. For the circumstances of intoxication, overdose was recorded when drug consumption occurred for recreational or hedonic purposes.

To assess whether flumazenil use adhered to recommended indications, reference was made to the indications included in the Clinical Toxicology Unit's protocols. These indications are the presence of respiratory depression, a Glasgow Coma Scale score < 8, and the differential diagnosis of coma. The protocol further emphasizes that flumazenil should not be used in most BZD intoxications presenting with mild symptoms.

Results are presented as mean and standard deviation (SD) for quantitative variables, and as total number and percentages for qualitative variables. Chi-square and Fisher's exact test were used to analyze associations between qualitative variables. Statistical significance was set at $P < .05$.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp.).

The study was approved by the management of Hospital Clínico Universitario Lozano Blesa in Zaragoza, as well as by the Research Ethics Committee of the Autonomous Community of Aragon (CEICA).

Results

During the study period, a total of 24,884 cases of acute poisoning were recorded in the Toxicology Unit, of which 4,517 (18.1%) involved BZD, either alone or in combination with other toxins or drugs. Figure 1 shows the annual trend of BZD-related emergency visits and flumazenil use. A gradual increase in BZD intoxications is observed, with a peak in 2008 and stabilization beginning in 2012.

Regarding the characteristics of patients with BZD intoxication, the mean age was 37.77 years (SD ± 15.04). With respect to sex distribution in the total number of acute BZD poisonings, 2,767 were women (61.2%).

Of all cases, 3,564 (79.4%) involved suicidal intent, 633 (14.1%) were due to overdose, 157 (3.5%) resulted from iatrogenesis, and 58 (1.3%) from domestic accidents. In 105 cases, the intent of the intoxication was not recorded.

A total of 1,265 patients (38.6%) had a prior history of medication overdose. In 3,126 cases (72.4%) there was a psychiatric history, and 977 patients (28.2%) had habitual consumption of drugs of abuse.

We observed concomitant alcohol use with BZD ingestion in 28.1% of cases, and concomitant opioid use in 3.3%. Approximately 11.5% (n = 520) reported concurrent use of selective serotonin reuptake inhibitors (SSRIs), 4.6% (n = 208) antipsychotics, and 2.2% (n = 98) tricyclic antidepressants.

Of the 4,517 cases involving BZD, flumazenil was administered in 1,427 (31.6%). Among this group, 160 patients (11.2%) received naloxone simultaneously.

Regarding flumazenil administration according to clinical status, it was given to 28.8% of cases with oxygen saturation (pulse oximetry) between 92–100% vs 41.8% of cas-

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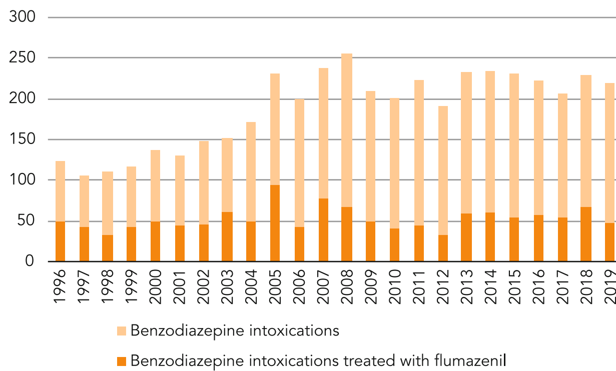

Figure 1. Distribution of benzodiazepine overdoses treated in the emergency department and flumazenil use throughout the 1996–2019 period.

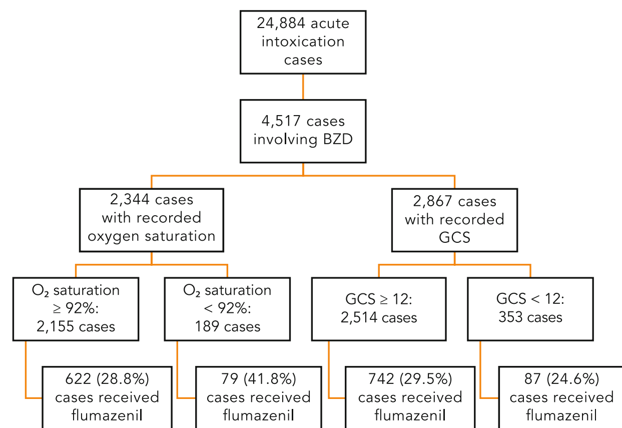

Figure 2. Use of flumazenil according to oxygen saturation and Glasgow Coma Scale score.
BZD: benzodiazepine; GCS: Glasgow Coma Scale.

es with saturation < 92%, a statistically significant difference ($P < .05$) (Figure 2).

Based on the Glasgow Coma Scale (GCS), an antidote was administered in 742 cases (29.5%) with a GCS ≥ 12. In 87 patients (24.6%) who received an antidote, the GCS was < 12, with no statistically significant difference observed ($P > .05$) (Figure 2).

In 513 cases (35.9%) in which flumazenil was administered, BZD were associated with the use of other medications, whereas in 346 cases (24.2%) BZD were combined with illegal drugs.

Regarding adverse effects associated with flumazenil use, 13 patients (0.9%) developed significant clinical reactions after administration. Of these, 9 patients (0.6%) exhibited agitation following flumazenil administration; in 2 cases (0.1%), the event was a seizure after flumazenil administration; and 2 patients (0.1%) experienced vomiting.

Of the 9 cases presenting agitation, 6 involved concurrent use of a drug of abuse (4 with alcohol, 1 with opioids, and 1 with cocaine).

In the 2 seizure cases following flumazenil administration, one involved concomitant ingestion of alcohol and an SSRI (paroxetine), and the other involved a mood stabilizer (lithium).

Discussion

As reported in other publications from our setting, there is a predominance of female sex among acute BZD intoxications, with a high percentage of cases involving self-harm intent.[7-10]

Traditionally, flumazenil has been considered a safe antidote without intrinsic activity, recommended not only to reverse coma due to BZD overdose but also as a diagnostic tool in comatose patients in emergency departments and prehospital emergency systems.[11] This explains why, in our series, flumazenil and naloxone were co-administered in 67 cases (4.7%), including 8 cases with TCA co-ingestion. This is particularly relevant because flumazenil administration in such patients may increase the risk of seizures, QRS prolongation on ECG, or arrhythmias derived from TCA toxicity—effects that may have been mitigated by the presence of BZD.[5,12]

The number of cases with recorded oxygen saturation may appear low; however, it must be considered that routine use of pulse oximetry was progressively implemented in the emergency department. This variable was not added to the toxicology data sheet until 2005.

BZD rarely cause respiratory depression—unlike barbiturates—because their action as GABA agonists produces diffuse CNS depression (sedative–hypnotic–anxiolytic), but with a wide therapeutic margin and minimal respiratory or cardiovascular depression. Therefore, deaths from isolated BZD ingestion are extremely rare. Most deaths involve co-ingestion of alcohol, opioids, antidepressants, or antipsychotics.[13]

Our results show extensive use of flumazenil as an antidote in patients attending the emergency department for BZD overuse or suspected intoxication, regardless of consciousness level, respiratory status, or co-ingested substances. Despite this, the complication rate was very low, indicating high safety when protocols are followed. Mathieu-Nolf *et al.* reported a 9% complication rate (1 case among 478 patients receiving flumazenil), with contraindicated use in 39% and inappropriate use in 96% of the sample.[14]

As previously noted, seizures are a well-known serious adverse effect, especially in patients with prior convulsive disorders. Seizures are not considered a direct toxic effect of flumazenil but result from reversal of the anticonvulsant effects of BZD in the presence of pro-convulsant drugs or other predispositions. Several studies highlight this contraindication, including Veriaiah *et al.*,[15] citing UK National Institute for Health and Care Excellence guidelines advising avoidance of flumazenil in TCA co-ingestion, and the work of Mizuno[16-21] describing the elevated seizure risk.

However, in our study, only two post-flumazenil seizures were reported. This is consistent with findings from Penninga *et al.*,[17] where seizures were rare, and from Nguyen *et al.*, who reported no seizures among 23 flumazenil-treated patients, despite 35% reporting co-ingestion of pro-convulsant drugs.[17,21]

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Agitation and vomiting were also noted as secondary effects, which may partially mimic withdrawal symptoms, as described by Osés *et al.* and Martínez *et al.*[12,18-23]

This study has the limitations inherent to a retrospective descriptive design. The most significant limitation stems from the quality of medical records, where many relevant variables—especially oxygen saturation and level of consciousness—were frequently absent. Systematic documentation of these parameters began only after 2005.

In conclusion, our study shows that patients with BZD intoxication in our center have a low rate of complications associated with flumazenil use.

Given the high frequency of these intoxications, it is essential to adhere to protocols and treatment indications to ensure proper antidote use.

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