Empiric Use of Flumazenil in Comatose Patients: Limited Applicability of Criteria to Define Low Risk

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Study objective: To develop clinical rules for the safe and effective use of flumazenil in suspected benzodiazepine overdose.

Methods: We assembled a retrospective series of 35 consecutive comatose patients admitted between October 1992 and July 1993 to a toxicologic ICU with the presumptive diagnosis of drug overdose. These patients were divided into two groups. Group A (low-risk) patients had a clinical picture compatible with uncomplicated benzodiazepine intoxication (calm, without abnormalities in pulse or blood pressure, lateralizing signs, hypertonia, hyperreflexia, or myoclonus) in the absence of predefined electrocardiographic or clinical signs of tricyclic antidepressant or other proconvulsant overdose, and absence of an available history of long-term benzodiazepine treatment or an underlying seizure disorder. Group B ("non–low risk") comprised all other patients. Efficacy of flumazenil was categorized as complete awakening (with normal level of alertness), partial awakening, or no change in alertness level. The safety of flumazenil was defined on the basis of the absence of seizures or death.

Results: In group A (n=4), flumazenil was associated with complete awakening in three patients and partial awakening in one. No seizures were observed. In group B (n=31), flumazenil was associated with complete awakening in 4 patients, partial awakening in 5, and no response in 22. In group B, five seizures occurred.

Conclusion: Comatose patients with clinical or ECG criteria thought to contraindicate the use of flumazenil have a reasonably high risk of seizures after administration of this drug. Low-risk patients may be able to receive flumazenil safely, but they may be only a small portion of comatose patients with suspected overdose.

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INTRODUCTION

Benzodiazepine intoxication is generally well tolerated, even in large doses, but can cause prolonged coma.[1] The efficacy and safety of flumazenil, the first specific benzodiazepine antagonist, in reversing coma due to isolated benzodiazepine overdose has been well proved.[2-7] Flumazenil can cause seizures, however, particularly in patients who have ingested tricyclic antidepressant drugs. Other factors that may increase the risk of seizures after flumazenil administration are chronic seizure disorder and long-term benzodiazepine use.[8-12] Flumazenil-associated seizures have occurred with and without acute benzodiazepine overdose. Thus caution must be exercised before flumazenil is used in cases of nonspecific coma associated with suspected self-poisoning, particularly because acute overdose in adults frequently involves multiple medications.

Our study hypothesis was that simple clinical rules can differentiate, among adult patients with coma and suspected drug overdose, between low-risk patients (defined below), in whom flumazenil would be effective and safe; and other patients, in whom flumazenil would be expected to be inefficacious and potentially dangerous.

MATERIALS AND METHODS

We included all patients given flumazenil in the setting of coma and suspected intoxication who were subsequently referred to our toxicology ICU. We had no exclusion criteria. Most of the study patients were given flumazenil by mobile prehospital provider units, each of which is staffed by a physician. We also included several patients who received flumazenil in our emergency department or in another ED before transfer to our ICU. At the time of the study, no strict criteria existed for the use of flumazenil, and both the decision to use this agent and the manner in which it was administered were at the discretion of individual clinicians.

Patients were grouped on the basis of their initial clinical presentation as being at low risk (group A) or not at low risk (group B). We defined low risk as the presence of a clinical picture compatible with uncomplicated benzodiazepine intoxication: the absence of findings suggestive of stimulant or antidepressant overdose and the absence of an available history of underlying seizure disorder or long-term use of benzodiazepines. The initial presentation was considered consistent with uncomplicated benzodiazepine intoxication if the patient had been described as calm, without localizing neurologic signs, myoclonus, hypertonia, or hyperreflexia; without documented abnormality in pupil size (less than 2 mm or 4 mm or greater), symmetry, or reactivity; with normal systolic blood pressure (greater than 90 mm Hg) and heart rate (50 to 100); and without prolongation of QRS complex (.10 second or less) or QT interval (QT observed, 110% or less of the expected value) on initial ECG. Stimulant or antidepressant overdose was suspected in the presence of agitated coma, anticholinergic syndrome, or sympathomimetic hyperactivity. Any patient who did not meet all criteria for low risk was classified in group B.

We compared the two groups with regard to positive response to flumazenil and development of adverse effects. A positive response was defined as an improvement in the level of alertness immediately after administration of the drug. Complete, incomplete, or absent response was determined from the presence of specific chart notations affirming one of these responses or, if no such notation was available, by change in Glasgow Coma Scale (GCS) score. A postflumazenil GCS score of 15 was considered a complete response, whereas a posttreatment GCS score of 9 to 14 was considered an incomplete response. Adverse effects were defined as convulsions or death within 1 hour of the initial dose of flumazenil.

Initial history, physical examination, and ECG findings were routinely recorded for comatose patients. GCS score was also virtually always recorded. A trained research assistant blinded to the nature of the study and given only the initial history and physical examination notations (from the prehospital report or the ED record) abstracted data regarding initial findings. Abstracting was performed only after all references to flumazenil, and any charting of

Table 1.
Findings of qualitative toxicologic analyses.

Toxicologic Findings	Group A (N=4)	Group B (N=4)
Single benzodiazepine detection	2	3
Alcohol	1	1
Benzodiazepine + opioids	0	1
Phenothiazine	1	3
Carbamate tranquilizer	0	1
Antidepressant	0	11
Benzodiazepine + propoxyphene	0	1
Phenothiazine	0	1
Alcohol	0	0
Antidepressant + phenothiazine	0	6
Opioids	0	1
Chloralose	0	1
Others	0	1*

*β-Blocker and calcium-channel blocker (N=31).

events that occurred after the administration of flumazenil, were deleted from the document. The research assistant then recorded on a data form historical information available to medical personnel at the time of each patient's presentation, including history of convulsions and treatment with any medications, including benzodiazepines. Information recorded at a later time was not considered to present for the purpose of the study because it would have been unknown to providers at the time when they decided whether to use flumazenil. Physical signs abstracted from the initial medical record included vital signs, which were classified as normal or abnormal, and the presence or absence of agitation, focal neurologic signs, seizures, hypertonia, hyperreflexia, and myoclonus. Parameters not recorded on these charts were considered to be absent. The ECG was evaluated for heart rate and for width of QRS complexes and QT intervals.

A second trained research assistant, also blinded to the nature of the study, reviewed patient records to determine the response to flumazenil. This individual was also given only the initial record, but all notations regarding findings before the use of flumazenil, with the exception of initial GCS score, were deleted, leaving only that part of the record dealing with response to flumazenil.

All patients admitted to our unit underwent blood screening for benzodiazepines (ACA III enzyme-mediated immunoassay technique; Du Pont de Nemours) upon arrival at the hospital. For the purpose of this study we considered the result of a screen positive if any benzodiazepine was present at a level greater than the equivalent of .5 µg/mL diazepam. A more extensive toxicologic analysis was also performed in each case, including but not limited to a search for tricyclic antidepressants, barbiturates, and alcohol by enzymatic reaction in blood; and for phenothiazines by colorimetric reaction in urine. Other drug screening was performed at the request of the treating physician.

Table 2.
Response to flumazenil.

Type of Response	Group A (N=4)	Group B (N=31)
Complete awakening		
Positive	3	4
Negative	1	27
Complete or partial awakening		
Positive	4	9
Negative	0	22

Response to flumazenil, with regard to both efficacy and safety, was coded by patient group categorization. We calculated 95% confidence intervals (CIs) for the risk of adverse effects, as well as for the percentage of patients in the low-risk category. Numeric results are presented as mean values with ranges.

RESULTS

Thirty-five consecutive patients treated with flumazenil between October 1992 and July 1993 were included in the study. The mean age was 44 years (range, 17 to 90 years), and 25 were female. Flumazenil was administered before hospital arrival in 30 cases (86%) and in the ED in 5 cases (14%).

Only four patients (11%; 95% CI, 3% to 22%) met the criteria for group A. Benzodiazepines were detected in two of them. Group B comprised 31 patients. Toxicologic testing showed only three group B patients (10%) to have sustained isolated benzodiazepine overdose (Table 1).

In group A the mean loading dose of flumazenil was .5 mg (range, .4 to .8 mg). In patients with complete response this dose was followed by a continuous infusion, with doses ranging from .3 to .5 mg/hour, typically after admission to our ICU. The mean duration of treatment was 31 hours (range, 12 to 72 hours). In group B the mean loading dose was .75 mg (range, .3 to 2.0 mg). Continuous infusion was instituted in five cases, with doses ranging from .3 to .5 mg/hour; the mean duration of treatment was 16 hours (range, 6 to 36 hours).

In group A, flumazenil injection was followed immediately by complete awakening in three patients, and partial awakening in one (Table 2). No group A patient was intubated. In group B, flumazenil injection produced complete awakening in 4 patients (13%), partial awakening in 5 (16%), and no response in 22 (71%) (Table 2). Intubation was performed in 27 (87%).

Thus three of the seven patients who had complete awakening in response to flumazenil (43%) met criteria

Table 3.
Seizures after flumazenil administration.

Seizures	Group A (N=4)	Group B (N=31)
Yes	0	5
No	4	26

for low risk, whereas of 28 patients with less than complete awakening, 1 (4%) was in group A (Table 2). Similarly, when patients are categorized on the basis of response to flumazenil, 9 of the 13 patients overall who had at least partial awakening (69%) were in group B, whereas group A included none of the 22 patients with negative response (Table 2).

Three patients died, none during the hour after flumazenil administration. Seizures were the only adverse reaction noted. No group A patient seized during this period. Seizures in the five group B patients (16%; 95% CI, 5% to 34%) occurred a mean of 28 minutes (range, 15 to 60 minutes) after injection of flumazenil (Table 4); two of these patients had multiple seizures (three and five each).

All five patients with seizures had had neurologic or ECG abnormalities before flumazenil administration. One of these patients had presented with an anticholinergic syndrome, and one had a history of epilepsy. Although all five of these patients had been taking benzodiazepines for long periods, each failed to meet at least one other criterion for low risk, so a history of long-term benzodiazepine use was never the sole reason a patient was classified in group B. Toxicologic analysis of blood or urine was positive for proconvulsant drugs (tricyclic antidepressants, chloralose, phenothiazine, or dextropropoxyphene) in four of these patients (Table 4). Thus with regard to safety, categorization as low risk successfully excluded all five patients with adverse events associated with flumazenil.

DISCUSSION

Many patients with drug overdose present in coma, and it is often impossible to be certain whether this is due to overdose or to another factor. Empiric use of naloxone and hypertonic dextrose has been widely recommended in the past for both diagnostic and therapeutic purposes.[13,14] Such a strategy has been challenged, however, both because of concerns regarding possible adverse effects of their nonselective use and because of questions about their usefulness in diagnosis.[15,16] In today's climate of cost containment, there is good reason to avoid widespread and overbroad use of procedures that have not been shown to have specific utility. A therapeutic agent should treat a symptom that is otherwise dangerous and less than optimally responsive to other therapies. A diagnostic agent should provide information that is not otherwise available and that is additive in discriminating between possible causes of the presenting condition.

Flumazenil is a specific benzodiazepine antagonist at the central receptor site[17-19] with potential for use in reversing respiratory and central nervous system effects of pure benzodiazepine overdose and in identifying such patients from among the larger group who present in coma.[20-23] Its therapeutic value is likely limited, however, given the relatively low mortality of pure benzodiazepine overdose.[24] Furthermore, the therapeutic benefit must be balanced against adverse effects caused by flumazenil, which causes seizures in certain subgroups of patients.[7,8,12,22] These subgroups include patients who have overdosed

Table 4.
Clinical and laboratory characteristics of five patients with seizures after treatment with flumazenil.

Case	Sex/Age (Years)	Long-Term BZD Use	Long-Term Seizures	Prior Signs	ECG Findings	Time to Seizure (Minutes)	Toxicologic Analyses			
							BZDs	TCAs	PTZ	Others
1	M/54	Y	N	Hypertonia, hyperreflexia	Heart rate > 100	15	0	Amytriptyline, 2.75 µmol/L	+	Meprobamate 372 µmol/L
2	M/20	Y	Y	Mydriasis	Heart rate < 50	15	+	0	+	Opioids, codeine, acetylmorphine
3	F/20	Y	N	Mydriasis	Heart rate > 100	60	+	+ Dosulepine 9.5 µmol/ L	0	0
4	F/28	Y	N	Agitation, myoclonia	Normal	15	0	0	0	Chloralose
5	F/24	Y	N	Hypertonia, hyperreflexia, mydriasis	Heart rate > 100, QRS > .10 seconds, QTobs/QTth > 1.1	10	+	0	0	Propoxyphene, acetaminophen 1,350 µmol/L

BZD, benzodiazepine; **TCA**, tricyclic antidepressant; **PTZ**, phenothiazine.
BZD screening was positive if any BZD plasma level was greater than the equivalent of .5 µmol/mL diazepam.

on a proconvulsant drug (especially a tricyclic antidepressant) in addition to a benzodiazepine, as well as patients with underlying seizure disorder. It is unclear whether risk is also increased in patients who have taken benzodiazepines on a long-term basis in the absence of these other characteristics.[9,22,25]

The fact that benzodiazepine overdose typically produces a nonspecific coma state without pathognomonic characteristics increases the possible benefit of its use as a diagnostic agent. Patients with a complete response might conceivably avoid an extensive diagnostic workup. On the other hand, the nonspecific characteristic of benzodiazepine overdose makes the pretreatment classification of patients with and without pure benzodiazepine overdose difficult.

We hypothesized, however, that even if comatose patients with pure benzodiazepine overdose cannot be distinguished on clinical grounds from other comatose patients (such as other sedative-hypnotic overdoses), they could be distinguished from cases of overdose involving common proconvulsant agents, in whom flumazenil is probably most dangerous. Tricyclic antidepressant overdoses, in particular, are thought to be recognizable because of their associated anticholinergic signs and ECG abnormalities[26], although these features are not uniformly present in all such overdoses.[27] In addition, we excluded other patients at potential risk from flumazenil because of an underlying seizure disorder. We created criteria to identify patients who should not receive flumazenil and attempted to determine whether exclusion of such patients would yield a low-risk group in whom this agent could be used safely and effectively.

Despite the limited number of patients, our study yields several conclusions. First, a substantial risk of seizures exists after the use of flumazenil in patients who present in coma with suspected drug overdose. Our five patients with seizures represent 16% of the non–low-risk patients (95% CI, 3% to 30%). Four of them proved to have overdosed on proconvulsant drugs (as well as benzodiazepines), and in such cases seizures (with their generation of significant lactic acidosis) should be considered significantly dangerous.[27] None of these five patients met criteria for low risk.

We identified only four patients who met our definition of low risk. Although adverse effects did not occur in these patients, this fact does not exclude the possibility that a larger sample would not experience complications from flumazenil. Thus we cannot say that giving flumazenil to patients with these characteristics has been proved safe. Administration of flumazenil only to such low-risk patients cannot be expected to have a major effect because this group represents such a small percentage of comatose patients (11%; 95% CI, 3% to 22%).

It is of course possible that more liberal criteria could increase the proportion of patients to whom flumazenil could be given. We considered eliminating the history of prior benzodiazepine use as a determinant of non–low-risk status because it is not certain that this factor alone increases risk of seizures after flumazenil administration. We also recalculated our results in its absence and found that this would have resulted in three additional patients being classified as being at low risk. None of these patients had an adverse reaction to flumazenil. Although this would safely expand the low-risk group, most patients (80%; 95% CI, 63% to 92%) would still not qualify.

We conclude that flumazenil should not be given empirically to all patients with coma and that it is potentially dangerous in patients who do not meet criteria for low risk. Furthermore, classification of patients into low-risk and non–low-risk categories would limit the number of candidates for flumazenil. We cannot speculate as to whether a different or expanded set of criteria could be created to allow a larger proportion of patients to receive flumazenil without incurring significant risk of adverse effects. On the basis of our experience, however, and that reported in the literature, it seems unlikely that any other set of criteria for low risk could be developed that would be both safe and more than minimally inclusive.

Our study has several limitations. First, our ICU receives selected patients, most with complicated medical problems. We generally do not receive patients with simple benzodiazepine overdose. The small percentage of flumazenil responders may not be representative of all patients with nonspecific coma. On the other hand, overdose with benzodiazepines is typically part of a mixed drug overdose, so it is unlikely that many patients would benefit from flumazenil.

Second, our patient group was small. It seems clear, however, that at least those patients who fail to meet criteria for low risk are at substantial risk of seizure after administration of flumazenil. Thus we feel we are justified in concluding that empiric use of flumazenil in comatose patients is of extremely limited value.

Among patients who present with coma and suspected drug overdose, the risk of seizure after administration of the benzodiazepine antidote flumazenil is significant. We recommend that flumazenil not be given to all such patients. Use of clinical criteria for low risk can identify a small group of patients in whom this agent may be both safe and effective. In light of the very small number of

patients in this group, however, its overall clinical utility, in patients presenting with coma and suspected drug overdose, remains limited.

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