Flumazenil in drug overdose: Randomized, placebo-controlled study to assess cost effectiveness

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Objective: To investigate cost effectiveness of administration of flumazenil to patients presenting with suspected acute drug overdose.

Design: Double-blind, prospective, placebo-controlled randomized study.

Setting: University teaching hospital.

Patients: Forty-three adults presenting with suspected drug overdose and having a Glasgow Coma Scale (GCS) score of <13. Patients with known benzodiazepine/tricyclic ingestion were excluded.

Interventions: Intravenous administration of flumazenil (up to 2 mg) or placebo.

Measurements and Main Results: Individual patient costs were assessed and data aggregated for each treatment group. Major diagnostic and therapeutic interventions were recorded and between group comparisons performed. Clinical response to study drug administration was assessed by obtaining pre- and post-drug GCS scores and observation of the patient for at least 180 mins for signs of resedation.

Aggregate cost or number of major diagnostic and therapeutic interventions were not different between groups. Patients randomized to the flumazenil group showed a marked increase in GCS score (7.4 to 11.8) compared with those in the placebo group (8.2 to 8.6).

Conclusion: Use of flumazenil in intentional drug overdose of unknown etiology is not cost effective. (Crit Care Med 1999; 27: 78–81)

KEY WORDS: overdose; flumazenil; coma; costs; cost effectiveness

Intentional drug overdose is a problem in most western societies that carries an enormous emotional and financial cost (1). Depending on the drug or drug combination that has been ingested, severe respiratory, metabolic, and cardiovascular derangement may be observed, making care of such patients extremely resource intensive both in the emergency room and in the intensive care unit (ICU). In 1990, an estimated 12 million Canadian dollars (1 Canadian dollar = 0.73 United States dollars) was spent in Alberta on the acute care of patients presenting to hospital with an intentional drug overdose (2).

In the majority of intentional overdoses, multiple drugs are ingested (3), usually limiting the value of the empirical therapeutic administration of specific drug antagonists, as exemplified by the poor complete response rate observed (3.4%) when naloxone is empirically administered to patients with acute alterations in mental status of unknown cause (4). Benzodiazepines, however, are the most common prescription drugs used by individuals attempting drug-assisted suicide (5) and empirical administration of flumazenil, a competitive benzodiazepine antagonist, has been found to be useful in the treatment of this patient population (6–9). The use of flumazenil in drug overdose patients is, however, very controversial (10, 11). A recent study (12) of flumazenil use in a tertiary care center found limited use in the emergency departments. Nevertheless, flumazenil is still occasionally administered to patients with suspected drug-induced coma in emergency departments, and the empiric administration of flumazenil has recently been advocated (13) in the management of drug overdose in children.

It has been suggested that the use of flumazenil in patients with an intentional drug overdose should result in a decrease in the number of diagnostic and therapeutic interventions (9, 14).

The purpose of this double-blind study was to determine whether emergency department and in-patient costs associated with acute care management of patients suffering from an intentional drug overdose presenting to a university-based emergency department would be reduced by treatment with flumazenil. A secondary objective was to determine if treatment with flumazenil would reduce the number of major diagnostic and therapeutic interventions required in management of drug overdose patients.

MATERIALS AND METHODS

This study was approved by the Investigational Review Board of the Faculty of Medicine at the University of Alberta. Informed consent was felt to be unnecessary as both therapies were considered to represent acceptable practice in treating suspected intentional drug overdose at the time the study was carried out.

All patients brought to the emergency department with a diagnosis of intentional drug overdose were

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Supported, in part, by a grant from Hoffman La Roche, Canada.

screened for eligibility to participate in the study. Patients qualified if suspected of taking an intentional drug overdose within 24 hrs of admission to the emergency department were between 16 and 64 yrs of age and had a Glasgow Coma Scale (GCS) score of <13 before study drug administration. Patients were excluded if they had historical and/or electrocardiographic (sinus tachycardia >130 beats/min; cQT interval ≥0.5 secs; QRS duration >0.1 secs) evidence of tricyclic antidepressant ingestion, known or suspected benzodiazepine overdose, or toxic alcohol ingestion (methanol or ethylene glycol). These decisions were made on the basis of evidence from emergency personnel of the medications found at the scene, presence of such medications on the person, or any other information suggesting that such medications had been ingested before admission. In addition, patients with a history or physical evidence of closed head injury, seizure disorder, known hypersensitivity to flumazenil or benzodiazepines, pregnancy, or those directly admitted to the ICU were excluded from participation in the study.

Patients who qualified for the study were assigned in a restricted randomized double-blind fashion to receive flumazenil (2 mg in 20 mL) or placebo (20 mL of normal saline). The randomization sequence was generated by the pharmacy computer balanced in blocks of ten. Sealed envelopes, consecutively numbered, were stored in the emergency room. The study drugs were prepared by the pharmacy, which held the randomized treatment assignments. Evaluation of cost factors and data analysis was carried out by individuals blinded to group assignment until the study was completed.

An initial volume of 3 mL from the study syringe was administered over a period of 30 secs and repeated every 2 mins until the desired level of consciousness (GCS = 14) was attained, or a maximum of 20 mL had been given. Patients were then observed for a minimum of 3 hrs. If resedation occurred, the procedure was repeated and an infusion at 3 mL/hr (3 mg/hr) of study drug was commenced for 5 hrs. All other patient care was unaltered and patients were managed as per usual emergency room protocols. A blood sample (10 mL) and spot urine specimen (10 to 30 mL) was drawn for comprehensive drug screening purposes.

Study drugs were prepared in the hospital pharmacy and placed in vials which did not allow the emergency room staff to be aware of which drug was being injected. Evaluation of clinical and cost factors was done by an individual blinded to group assignment. All data analysis was also performed on a blinded basis to further reduce the potential for bias.

Withdrawal from the study occurred if there was seizure activity, new evidence of tricyclic overdose (corrected QT interval ≥0.5 secs, or QRS duration >0.1 secs), evidence suggesting that the source of overdose was a toxic alcohol (methanol or ethylene glycol), or development of focal neurologic signs.

Data collection included: age, gender, GCS score at baseline and at 5, 30, 60, 120, and 180 mins following drug administration, cost of and length of stay in emergency room, cost of and length of stay in ICU/hospital ward, physician associated cost, and cost of investigations, procedures, and interventions performed.

Costs were initially divided as labor, supply, and investigation. Labor costs were calculated using an acuity of illness weighted cost averaging system, currently in place for all patients admitted to the emergency room. Supply costs were determined by direct costing of supplies used for each procedure. Laboratory and radiological investigations were individually costed using data provided by the Departments of Laboratory Medicine/Pathology and Radiology.

Direct in-patient costs were calculated using the then current hospital costing model. This profile used acuity of illness weighted cost averaging to calculate nursing labor costs based on the Rush-Medicus patient classification system (15). It apportioned in a patient-specific manner the appropriate percentage of the aggregate costs incurred by the nursing unit in which the patient was located. We obtained direct costing of investigational costs incurred by the laboratory, radiology, and pharmaceutical departments. Supply costs were calculated using a severity of illness weighted costing model. Because of the large difference between ICU day costs and ward day costs, these costs were analyzed separately. Physician costs were calculated on patient billings actually paid by the Alberta Healthcare Insurance Plan. Study drug costs were calculated by costing out the amount of drug actually used during the treatment protocol.

Sample size estimates were determined based on a pilot project and literature review. The data was not obtained from a convenience sample or a consecutively enrolled patient series. Descriptive statistics and frequencies were determined for each group at each time period. The two groups were compared by Student's *t*-test and Fisher Exact test on demographic and clinical factors at baseline to determine if there was any difference between groups at the outset. If there were no differences between groups at baseline, then the outcome analyses were done by a test of proportions on death and side effects. Otherwise, if there was a significant difference between groups on one or more baseline factors, then those factors were used as covariates in the analysis. Comparisons were done by Student's *t*-tests on length of stay (emergency room, ICU, general ward), as well as on total costs incurred. The level of significance applied was .05.

RESULTS

One hundred and ninety eight patients were screened over a 17-wk period. Forty-five patients (22.7% of the screened subjects) met the criteria for entry and were randomized. Four patients who were randomized were excluded before study drug administration (one suffered a seizure; one diagnosed as an insulin overdose; one had a GCS score >15 following testing with ice; one patient later suspected of having ingested tricyclic-containing medications), consequently, forty-one patients were included in the analysis.

There was no significant difference between groups with respect to baseline and clinical demographic characteristics (Table 1). Eight patients in each group had a positive ethanol screen. The levels were quantitatively determined. The mean ethanol level was 65 ± 31 (SD) mmol/L in the flumazenil group and 54 ± 23 mmol/L in the placebo group. Opioids were qualitatively determined. Nine patients in the flumazenil group and 18 patients in the placebo group had a positive opioid screen. Following drug treatment, GCS score at 5 mins was significantly different from baseline in the flumazenil group (59%), whereas in the placebo group, the GCS score was almost unchanged (5%). There was

Table 1. Baseline demographic and clinical characteristics by group

Characteristic	Flumazenil	Placebo	*p* Value
Gender (F/M)	10/9	11/11	NS
Age[a] (yr)	36.9 ± 9.5	34.7 ± 10.7	NS
GCS Pre[a]	7.4 ± 2.8	8.2 ± 2.7	NS
GCS Post[a]	11.8 ± 4.1	8.6 ± 3.6	<.01
Drug Screen (+/–)			
Benzodiazepine	9/10	18/4	.05
Opioid	9/10	18/4	.05
Ethanol	8/11	9/13	NS

[a]Mean ± SD.

Table 2. Interventions by group

Intervention	Flumazenil	Placebo
CT scan of brain (Y/N)	2/17	3/19
Portable chest radiograph (Y/N)	7/12	10/12
Gastric lavage tube (+/–)	7/12	14/8
Endotracheal tube (+/–)	6/13	8/14
Mechanical ventilation (+/–)	3/16	1/21
ICU admission (+/–)	2/17	6/16

CT, computed tomography; ICU, intensive care unit.
All *p* values were nonsignificant.

Table 3. Time factors (min) by group (mean ± SD)

Factor	Flumazenil	Placebo	*p* Value
Time			
To discharge from ER	517 ± 263	505 ± 240	NS
To ward admission	144 ± 119	114 ± 83	NS
ICU length of stay	2700 ± 255	1454 ± 485	<.05
Ventilation	1230 ± 1506	1486 ± 605	NS

ER, emergency room; ICU, intensive care unit.

Table 4. Cost factors (dollars[a]) by group (mean ± SD)

Factor	Flumazenil	Placebo	*p* Value
Number	19	22	
Emergency room	244 ± 106	276 ± 111	NS
Nursing	140 ± 59	151 ± 51	NS
ER physician fee	93 ± 29	98 ± 33	NS
Drug	101 ± 57	5 ± 2	<.001
Inpatient	402 ± 1920	1258 ± 1100	NS
Medical consult	148 ± 77	109 ± 27	NS
ICU consult	400 ± 71	276 ± 63	NS
ICU	327 ± 2410	1245 ± 490	[b]
Total cost	1524 ± 2520	1432 ± 1420	NS

[a]Canadian dollar = 0.73 United States dollar; [b]sample size inadequate to compare costs.

a significant difference ($p < .05$) between the flumazenil and placebo groups in GCS at 5 mins in favor of flumazenil. Resedation was a significant problem occurring in five of nine patients who had a positive benzodiazepine screen and received flumazenil. Resedation occurred at 49 ± 31 mins, however, following a second bolus dose of flumazenil and the initiation of an infusion of flumazenil for a 5-hr period, as defined by the protocol, all patients were treated adequately and none were admitted to the ICU.

Major diagnostic and therapeutic interventions by group are shown in Table 2. There were no significant differences between treatments, although gastric lavage tubes were used in 37% of flumazenil and 77% of placebo cases. Time factors by group are presented in Table 3. Mean duration of stay per patient admitted to the ICU was significantly greater ($p < .05$) in the flumazenil group (impacted by a quadriplegic flumazenil case requiring a lengthy stay).

Cost factors are presented in Table 4. There were no significant differences between groups in the total cost per patient, which was 1542 ± 2520 ($ Cdn) with flumazenil and 1432 ± 1420 ($ Cdn) with placebo ($ Cdn). Resedation occurred in five flumazenil treated patients. The cost per patient in this subpopulation was 717 ± 188 ($ Cdn). This relatively low cost of treatment reflects the discharge of all these patients from the emergency room without the need for ICU care. Two patients in the flumazenil group and six patients in the placebo group were admitted to the ICU. There were no differences between groups in specific cost areas such as the emergency room, nursing, emergency room physician fees, inpatient costs, or medical and ICU costs. As expected, drug costs were significantly more expensive in the flumazenil group relative to the placebo group, as there were only eight patients admitted to the ICU (two flumazenil and six placebo).

There were no major drug related complications observed in this study, and no patients died in either group.

DISCUSSION

This study suggests that the empirical administration of flumazenil to patients presenting with suspected intentional drug overdose is not associated with significant cost savings. A trend toward lower resource utilization and decreased ICU admission rates was apparent in the flumazenil group.

Every effort was made to ensure representative and random sampling of the population of intentional drug overdose patients. However, complexity of the pattern of drug ingestion by study participants and the limited sample size frustrated these efforts, since there were greater numbers of patients in the placebo group who had ingested opioids and benzodiazepines than in the flumazenil group. This discrepancy between groups is a limitation of the study that highlights the complexity of

drug ingestion in patients susceptible to taking an intentional drug overdose (3, 5), and underscores the futility of empirical administration of specific antagonists in this clinical condition (10). Although the GCS score significantly improved in the flumazenil group, this improvement did not translate into a decrease in time spent in the emergency room or a decrease in overall costs.

The main cost driver in the acute treatment of this patient population identified in this study was the need for, and time spent, in ICU care. The number of patients admitted to the ICU tended to be lower in the flumazenil group (two of 19 patients compared with six of 22 patients in the placebo group). Despite these numbers, the average cost for ICU care tended to be greater in the flumazenil group. This discrepancy between number of patients admitted and cost of ICU care was determined primarily by randomization to the flumazenil group of a quadriplegic who had ingested multiple drugs and suffered from pulmonary aspiration. The numbers of patients randomized were too small to factor out the major cost impact of this patient.

Surprisingly, there was no significant decrease in the number or complexity of diagnostic interventions. These data contrast with the findings of Hojer et al. (9), who found that several interventions assessed in this study were unnecessary following administration of 1 mg of flumazenil. This finding (9) reflects the disparate pattern of drug ingestion in our patient population, particularly the degree of ethanol and opioid ingestion. The combination of ethanol and benzodiazepines is not uncommon in multiple drug overdose patients (16) and is associated with a high mortality (17).

In this study, patients were excluded if they had historical evidence and/or clinical signs of tricyclic antidepressant ingestion. Our criteria were adequate in that no adverse events were reported. However, the number of patients fulfilling this criteria is limited, as this and other (11) studies demonstrate. The consequences of administering flumazenil to patients being treated with tricyclic antidepressants include grand mal seizure activity and death. Although some authors (18) suggest that flumazenil may be safely given to patients who have also ingested tricyclic antidepressants, this view is controversial (19, 20).

Blood and urine samples were obtained for comprehensive toxicology screening, but these data were available to the investigators subsequent to study drug administration. If this information had been available prior to the study, the disproportionate number of patients in the placebo group with a positive benzodiazepine drug screen could have been avoided by applying a stratification in the randomization. Post-stratification could not be carried out due to the limited sample size. Use of more rapid screening tools that could provide reliable qualitative assessment of the drugs ingested by intentional overdose patients would perhaps allow the cost-efficient and safe administration of specific antagonists. On site immunoassay screening tests that are easy to perform and provide diagnostic information within minutes have not been studied in this setting (21). Further cost effectiveness studies using such technology appear to be indicated.

In conclusion, this study indicated that the empirical use of flumazenil in patients with intentional drug overdose is not cost effective. Future studies in this area should be directed to identifying those patients who would most benefit from specific drug antagonist treatment, since this information may improve the cost effectiveness of such therapy.

REFERENCES

1. D'Mello DA, Finkbeiner DS, Kocher KN: The cost of antidepressant overdose. *Gen Hosp Psychiatry* 1995; 17:454–455
2. Rapoport J, Teres D, Barnett R, et al: A comparison of intensive care unit utilization in Alberta and western Massachusetts. *Crit Care Med* 1995; 23: 1336–1346
3. Michel K, Waeber V, Valach L, et al: A comparison of the drugs taken in fatal and nonfatal self-poisoning. *Acta Psychiatr Scand* 1994; 90:184–189
4. Hoffman JR, Schriger DL, Luo JS: The empiric use of naloxone in patients with altered mental status: A reappraisal. *Ann Emerg Med* 1991; 20:246–252
5. Stein MD, Bonanno J, O'Sullivan PS, et al: Changes in the pattern of drug overdoses. *J Gen Intern Med* 1993; 8:179–184
6. Ritz R, Zuber M, Elsasser S, et al: Use of flumazenil in intoxicated patients with coma. A double-blind placebo-controlled study in ICU. *Intensive Care Med* 1990; 16:242–247
7. Winkler E, Almog S, Kriger D, et al: Use of flumazenil in the diagnosis and treatment of patients with coma of unknown etiology. *Crit Care Med* 1993; 21:538–542
8. Burkhart KK, Kulig KW: The diagnostic utility of flumazenil (a benzodiazepine antagonist) in coma of unknown etiology. *Ann Emerg Med* 1990; 19: 319–321
9. Hojer J, Baehrendtz S, Matell G, et al: Diagnostic utility of flumazenil in coma with suspected poisoning: A double blind, randomised controlled study. *BMJ* 1990; 301:1308–1311
10. Hoffman RS, Goldfrank LR: The poisoned patient with altered consciousness. Controversies in the use of a 'coma cocktail'. *JAMA* 1995; 274:562–569
11. Gueye PN, Hoffman JR, Taboulet P, et al: Empiric use of flumazenil in comatose patients: Limited applicability of criteria to define low risk. *Ann Emerg Med* 1996; 27:730–735
12. Visconti JA, Anderson HG Jr, Dasta JF: Pharmacoepidemiologic study of flumazenil use in a University Teaching Hospital. *Hospital Pharmacy* 1996; 31:959–964
13. Perry HE, Shannon MW: Diagnosis and management of opioid- and benzodiazepine-induced comatose overdose in children. *Curr Opin Pediatr* 1996; 8:243–247
14. Votey SR, Bosse GM, Bayer MJ, et al: A new benzodiazepine antagonist. *Ann Emerg Med* 1991; 20:181–188
15. Halloran EJ: Nursing workload, medical diagnosis related groups, and nursing diagnoses. *Res Nurs Health* 1985; 8:421–433
16. Kaa E, Teige B: Drug-related deaths during the 1980s. A comparative study of drug addict deaths examined at the institutes of forensic medicine in Aarhus, Denmark and Oslo, Norway. *Int J Legal Med* 1993; 106:5–9
17. Serfaty M, Masterton G: Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br J Psychiatry* 1993; 163:386–393
18. Weinbroum A, Rudick V, Sorkine P, et al: Use of flumazenil in the treatment of drug overdose: A double-blind and open clinical study in 110 patients. *Crit Care Med* 1996; 24:199–206
19. McDuffee AT, Tobias JD: Seizure after flumazenil administration in a pediatric patient. *Pediatr Emerg Care* 1995; 11:186–187
20. Longmire AW, Seger DL: Topics in clinical pharmacology: Flumazenil, a benzodiazepine antagonist. *Am J Med Sci* 1993; 306:49–52
21. Buechler KF, Moi S, Noar B, et al: Simultaneous detection of seven drugs of abuse by the Triage panel for drugs of abuse. *Clin Chem* 1992; 38: 1678–1684