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

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The health technologies studied were flumazenil (2mg in 20 mL), a competitive benzodiazepine antagonist, and placebo (20 mL of normal saline).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adults (aged 16-64 years) presenting with a suspected, intentional drug overdose within 24 hours of admission to the emergency department and who had a Glasgow Coma Scale (GCS) score of less than 13 before study drug administration. There were a number of exclusion criteria, principally known benzodiazepine/tricyclic ingestion.

Setting
The setting was hospital. The economic study was carried out in Edmonton, Canada.

Dates to which data relate
No dates for effectiveness or cost data were reported.

Source of effectiveness data
Effectiveness data were taken from a single study.

Link between effectiveness and cost data
Effectiveness and cost data were collected prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
All patients (n=198) brought to the emergency department with a diagnosis of intentional drug overdose were screened for eligibility. Only 45 patients (22.7%) met the inclusion criteria and were randomised. Four of these patients were excluded before study drug administration and thus 41 were included in the analysis. There were 19 patients in the flumazenil group and 22 in the placebo group. The authors stated that sample size estimates were determined based on a pilot project and literature review. However, no power calculations were provided.
Study design
In terms of design, this was a double-blind, prospective, placebo-controlled randomised study carried out at a single centre in Canada. The randomisation sequence was generated by the pharmacy computer and was 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 randomised treatment assignments. Data analysis was carried out by individuals blinded to group assignment until the study was completed.

Analysis of effectiveness
The analysis was based on treatment completers only. The primary health outcomes used in the analysis were the Glasgow Coma Scale (GCS) score, major drug-related complications and mortality. There was no significant difference between groups with respect to baseline and clinical demographic characteristics i.e., age, gender and GCS score. However, the placebo group had significantly more patients admitted for benzodiazepine and opioid drug abuse compared with the flumazenil group. No adjustments were made for these confounding factors.

Effectiveness results
The number of major diagnostic and therapeutic interventions was not significantly different between groups, although gastric lavage tubes were used in 37% of flumazenil and 77% of placebo cases.

Patients in 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).

Five minutes after drug treatment, GCS score was significantly different from baseline in the flumazenil group (59%), whereas in the placebo group, the GCS score had only changed by 5% (p<0.05).

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

Clinical conclusions
Although there were no significant differences in the number of major diagnostic and therapeutic interventions between groups, GCS score after drug administration showed a marked increase in the flumazenil group compared with the placebo group.

Measure of benefits used in the economic analysis
No summary benefit measure was used, clinical outcomes being left disaggregated within a cost-consequences analysis.

Direct costs
Data collected included cost of and length of stay in emergency room, cost of and length of stay in intensive care unit (ICU)/hospital ward, physician associated cost, and cost of investigations, procedures, and interventions performed. Labour costs were calculated using acuity of illness weighted cost averaging system (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 relevant departments. Direct inpatient costs were calculated using the hospital-costing model, using acuity of illness weighted cost averaging to calculate nursing labour costs based on the Rush-Medicus patient classification system. Physician costs were calculated on patient billings 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. Discounting was not relevant due to the short time period of the study. Dates for prices and resources used were not reported.

Statistical analysis of costs
Costs were treated in a stochastic manner. Comparisons on length of stay and total costs incurred were carried out using
Student's t-tests. The 5% level of significance was applied, but it was not stated whether the study was powered to detect differences at this level of significance.

**Indirect Costs**
Indirect costs were not analysed, but this was probably due to the short-term nature of the study.

**Currency**
Canadian dollars (Can$)

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
No summary benefit measures were determined in the study and thus the reader is referred to the effectiveness results reported above.

**Cost results**
Mean duration of stay per patient admitted to the ICU was significantly greater in the flumazenil group compared with placebo (144 +/- 119 minutes versus 114 +/- 83 minutes; p<0.05). This was largely due to the impact of a quadriplegic flumazenil case requiring a lengthy stay.

There were no significant differences between the groups in terms of time to discharge from emergency room, time to ward admission, and ventilation time. There were no significant differences between the flumazenil and placebo groups in the total cost per patient (Can$1,524 +/- 2,520 versus Can$1,432 +/- 1,420, respectively).

There were no significant differences between groups in specific costs areas, other than drug costs, which, unsurprisingly, were significantly more expensive in the flumazenil group (Can$101 +/- 57 versus $5 +/- 2).

**Synthesis of costs and benefits**
A synthesis of costs and benefits was not undertaken by the authors despite the fact that flumazenil was more effective, but also more expensive.

**Authors' conclusions**
The authors concluded that the use of flumazenil in intentional drug overdose of unknown aetiology was not cost-effective.

**CRD COMMENTARY - Selection of comparators**
The reason for the choice of comparator was clear with placebo being used to test the relative effectiveness and cost of the intervention drug in a trial setting. The authors stated that informed consent was felt to be unnecessary as both therapies were considered to represent acceptable practice in treating suspected intentional drug overdose.

**Validity of estimate of measure of effectiveness**
Validity will have been enhanced by the use of a double-blind, randomised study design. However, results were presented for treatment completers only, rather than on an intention to treat basis. The authors also recognised that the sample size was limited (there were only 41 included in the final analysis, and no power calculations were provided to determine whether the sample size was sufficient to detect any clinically significant differences), and that results may
have been biased by the significantly greater proportion of patients in the placebo group who had ingested opioids and
benzodiazepines compared with the flumazenil group. The authors recognised that any attempt to overcome this
through post-stratification was prevented by the limited sample size.

Validity of estimate of measure of benefit
No summary measure of benefit was reported.

Validity of estimate of costs
Costs and resources included in the analysis were clearly reported, as well as the source of the cost/resource data. A
statistical analysis of costs was undertaken which should improve the generalisability of results. However, as with the
effectiveness results, no power calculations were presented so it is unclear whether the sample size was sufficient to
detect any economically significant differences between the two groups. As flumazenil was both more costly and more
effective than placebo, a synthesis of cost and effectiveness data should have been carried out.

Other issues
In the discussion, the authors did make some comparisons with other studies in terms of findings. They also recognised
some of the major limitations of the study, most of which were associated with the limited sample size. They did not
fully address the issue of generalisability, although this should be enhanced by the randomised study design and the
detail presented on cost/resource findings and sources of data.

Implications of the study
The implications of the study are that the empirical use of flumazenil in patients with intentional drug overdose is not
an optimal choice. The authors recommend that 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.

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Other publications of related interest

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