Flumazenil vs. placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis


Authors' objectives
To compare flumazenil and placebo in hepatic encephalopathy in patients with cirrhosis.

Searching
MEDLINE and Current Contents were searched, supplemented by a manual search. General reviews, references of published RCTs, and letters to pharmacological companies were also used. Only published articles or abstracts were sought.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), including crossover studies, were included. Uncontrolled trials and controlled trials without randomisation or with insufficient data were excluded. All of the included studies were double-blind.

Specific interventions included in the review
Flumazenil. All of the included studies were placebo-controlled. The doses of flumazenil used in the included studies were: 1 or 2 mg over 5 to 10 minutes; three sequential boluses (0.4, 0.8 and 1 mg) over 3 minutes, followed by intravenous infusion of flumazenil at 1 mg/hour for 3 hours; and 0.5 mg followed by 0.25 mg/hour for 3 days. The follow-up for the included studies ranged from 3 to 72 hours after drug injection.

Participants included in the review
Patients with cirrhosis and hepatic encephalopathy were included. The participants included in the review had hepatic encephalopathy ranging from grade I to grade IV (clinical grading).

Outcomes assessed in the review
Two events were chosen as end points to estimate clinical efficacy. These were clinical improvement, defined as a decrease in both clinical and electroencephalographic (EEG) hepatic encephalopathy grade, and EEG improvement. Survival was also chosen as an end point, but none of the included trials investigated this outcome. The methods used to evaluate clinical improvement included the modified Glasgow coma scale, clinical grading, and clinical portosystemic encephalopathy grading. The methods used to evaluate EEG improvement included Fisher's classification, EEG conventional grading, and EEG grading.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The methodological quality of each RCT was assessed using a validated questionnaire (see Other Publications of Related Interest no.1) that included 14 items: one about the aim of the study; four concerning a description of the studied population; three concerning the blindness of the study; five concerning the statistical methods; and one concerning the results. The scores could range from -2 to 26. Two observers assessed the methodological quality of each RCT independently.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following items were provided for each included study: the number of patients excluded after randomisation or lost to follow-up; age; gender; cause of cirrhosis, Child-Pugh score (see Other Publications of Related
Interest no.2); the mean duration of follow-up; the stage of hepatic encephalopathy; inclusion criteria for the participants; duration and dosage of flumazenil; washout period between the two treatment periods; end points; evaluation criteria; use of placebo; and blindness of the study.

**Methods of synthesis**

How were the studies combined?

A meta-analysis was performed according to a predetermined protocol based on the recommendations of Sacks et al. (see Other Publications of Related Interest no.3). All analyses were performed according to the intention-to-treat method.

For each end point, treatment efficacy was assessed by the Peto method (fixed-effect model; see Other Publications of Related Interest no.4) and the DerSimonian and Laird method (random-effects model; see Other Publications of Related Interest no.5). For crossover RCTs, the meta-analysis was performed using first-phase data, and a sensitivity analysis was carried out including the two treatment periods.

The pooled odds ratios (ORs; Peto method) and mean rate differences (DerSimonian and Laird method) were estimated for each study, along with the 95% confidence intervals (CIs).

**Results of the review**

Six RCTs (2 parallel and 4 crossover) and a total of 641 participants were included in the meta-analysis.

The total scores for methodological quality ranged from 19 to 26.

**Clinical improvement.**

First-phase data only (5 RCTs, n=623): the mean percentages of patients with clinical improvement were 27% in the treated groups and 3% in the placebo groups. Both methods showed the difference to be significant in favour of flumazenil: the OR was 6.15 (95% CI: 4.0, 9.5, p<0.001) when using Peto's method, while the mean rate difference was 28.6% (95% CI: 16.7, 40.5, p<0.001) without significant heterogeneity when using DerSimonian and Laird's method. Sensitivity analysis including second period of crossover studies (6 RCTs, n=1,205): the mean percentages of patients with clinical improvement were 19% in the treated groups and 2% in the placebo groups. Both methods showed the difference to be significant in favour of flumazenil: the OR was 5.50 (95% CI: 3.8, 7.9, p<0.001) when using Peto's method, while the mean rate difference was 30.9% (95% CI: 14.3, 47.5, p<0.001) without significant heterogeneity when using DerSimonian and Laird's method.

**EEG improvement.**

First-phase data only (3 RCTs, n=577): the mean percentages of patients with EEG improvement were 35% in the treated groups and 6% in the placebo groups. The Peto method showed the difference to be significant in favour of flumazenil (OR 5.8, 95% CI: 3.4, 9.7, p<0.001), whereas the DerSimonian and Laird method did not. Sensitivity analysis including second period of crossover studies (5 RCTs, n=1,180): the mean percentages of patients with EEG improvement were 25% in the treated groups and 4% in the placebo groups. Both methods showed the difference to be significant in favour of flumazenil: the OR was 5.2 (95% CI: 3.7, 7.1, p<0.001) when using Peto's method, while the mean rate difference was 21.8% (95% CI: 5.2, 38.4, p<0.01) when using DerSimonian and Laird's method.

**Authors’ conclusions**

This meta-analysis showed that flumazenil induces clinical and EEG improvement of hepatic encephalopathy in patients with cirrhosis.
CRD commentary
The review question was clearly stated and was well supported by pre-specified inclusion and exclusion criteria. The literature search was adequate, although the search dates and terms were not reported. In addition, there was no attempt to search for unpublished studies and it was not reported whether non-English language articles were sought. Hence, relevant studies may have been missed. Publication bias was not assessed. The data were appropriately pooled in a quantitative synthesis, and heterogeneity was investigated. Details of the review process (i.e. how many reviewers were involved, whether decisions were made independently, and how disagreements were resolved) were not reported for the validity assessment and data extraction. The authors’ conclusions appear to follow on from the findings, but should be interpreted in light of the limitations mentioned.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that further studies are needed to define the role of flumazenil in the treatment of severe hepatic encephalopathy, both in terms of its beneficial effect in clinical complications (e.g. pulmonary infection) of this condition and in reducing mortality.

Bibliographic details

PubMedID
11876688

Other publications of related interest

This additional published commentary may also be of interest. Reichen J. Review: flumazenil leads to clinical and electroencephalographic improvement in hepatic encephalopathy in patients with cirrhosis. ACP J Club 2003;138:15.

Indexing Status
Subject indexing assigned by NLM

MeSH
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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.