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[Intervention Review]

Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy

Ee Teng Goh[1], Mette L Andersen[2], Marsha Y Morgan[1], Lise Lotte Gluud[3]

[1]UCL Institute for Liver & Digestive Health, Division of Medicine, Royal Free Campus, University College London, London, UK. [2]Department of Hepatology, Rigshospitalet, Copenhagen, Denmark. [3]Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

Contact address: Lise Lotte Gluud, Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, Kettegaards Alle, Hvidovre, 2650, Denmark. liselottegluud@yahoo.dk.

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ABSTRACT

Background

Hepatic encephalopathy is a common complication of cirrhosis which results in poor brain functioning. The spectrum of changes associated with hepatic encephalopathy ranges from the clinically 'indiscernible' or minimal hepatic encephalopathy to the clinically 'obvious' or overt hepatic encephalopathy. Flumazenil is a synthetic benzodiazepine antagonist with high affinity for the central benzodiazepine recognition site. Flumazenil may benefit people with hepatic encephalopathy through an indirect negative allosteric modulatory effect on gamma-aminobutyric acid receptor function. The previous version of this review, which included 13 randomised clinical trials, found no effect of flumazenil on all-cause mortality, based on an analysis of 10 randomised clinical trials, but found a beneficial effect on hepatic encephalopathy, based on an analysis of eight randomised clinical trials.

Objectives

To evaluate the beneficial and harmful effects of flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy.

Search methods

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, and LILACS; meeting and conference proceedings; and bibliographies in May 2017.

Selection criteria

We included randomised clinical trials regardless of publication status, blinding, or language in the analyses of benefits and harms, and observational studies in the assessment of harms.

Data collection and analysis

Two review authors extracted data independently. We undertook meta-analyses and presented results using risk ratios (RR) with 95% confidence intervals (CI) and I^2 values as a marker of heterogeneity. We assessed bias control using the Cochrane Hepato-Biliary Group domains; determined the quality of the evidence using GRADE; evaluated the risk of small-study effects in regression analyses; and conducted trial sequential, subgroup, and sensitivity analyses.

Main results

We identified 14 eligible randomised clinical trials with 867 participants, the majority of whom had an acute episode of overt hepatic encephalopathy. In addition, we identified one ongoing randomised clinical trial. We were unable to gather outcome data from 2 randomised clinical trials with 25 participants. Thus, our analyses include 842 participants from 12 randomised clinical trials comparing flumazenil versus placebo. We classified one randomised clinical trial at low risk of bias in the overall assessment and the remaining randomised clinical trials at high risk of bias. The duration of follow-up ranged from a few minutes to two weeks, but it was less than one day in the majority of the trials.

In total, 32/433 (7.4%) participants allocated to flumazenil versus 38/409 (9.3%) participants allocated to placebo died (RR 0.75, 95% CI 0.48 to 1.16; 11 randomised clinical trials; low quality evidence). The Trial Sequential Analysis and the one randomised clinical trial assessed as low risk of bias (RR 0.76, 95% CI 0.37 to 1.53) found no beneficial or harmful effects of flumazenil on all-cause mortality. The methods used to evaluate hepatic encephalopathy included several different clinical scales, electrophysiological variables, and psychometric tests. Flumazenil was associated with a beneficial effect on hepatic encephalopathy when including all randomised clinical trials (RR 0.75, 95% CI 0.71 to 0.80; 824 participants; 9 randomised clinical trials; low quality evidence), or just the trial at low risk of bias (RR 0.78, 95% CI 0.72 to 0.84; 527 participants). The Trial Sequential Analysis supported a beneficial effect of flumazenil on hepatic encephalopathy. The randomised clinical trials included little information about causes of death and little information on non-fatal serious adverse events.

Authors' conclusions

We found low quality evidence suggesting a short-term beneficial effect of flumazenil on hepatic encephalopathy in people with cirrhosis, but no evidence of an effect on all-cause mortality. Additional evidence from large, high quality randomised clinical trials is needed to evaluate the potential benefits and harms of flumazenil in people with cirrhosis and hepatic encephalopathy.

PLAIN LANGUAGE SUMMARY

Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy

Background

What is hepatic encephalopathy?

Cirrhosis is a chronic disorder of the liver. People with cirrhosis may develop hepatic encephalopathy, a condition which results in poor brain functioning. In some people, there are obvious clinical features of disturbed brain functioning (overt hepatic encephalopathy); these changes may be short-lived or persist for long periods of time. In other people, there are no obvious clinical changes but some aspects of brain function, such as attention and the ability to perform complex tasks are impaired when tested (minimal hepatic encephalopathy). The reason people develop hepatic encephalopathy is complex but changes in brain neurotransmitters, which are the chemical messengers which allow nerve cells to communicate with one another, may play a role. The neurotransmitter gamma aminobutyric acid (GABA) is responsible for slowing or inhibiting brain activity and is thought to play a particularly important role.

What is flumazenil?

Flumazenil is a medicine that acts on one of the GABA receptors in the brain to modify its effects on these specialised cells and so may benefit people with hepatic encephalopathy. It has to be given into a vein (intravenous) and its effects do not last for more than a few hours.

Review question

We investigated the use of flumazenil for the treatment of hepatic encephalopathy in people with cirrhosis by reviewing clinical trials in which people were randomly allocated to treatment with flumazenil or an inactive dummy/placebo or no specific intervention.

Search date

We searched medical databases and conducted manual searches in May 2017.

Study funding sources

Five of the included randomised clinical trials received support from pharmaceutical companies.

Study characteristics

We included 14 randomised clinical trials with 867 participants. All randomised clinical trials compared intravenous infusion of flumazenil versus an inactive placebo (dummy infusion, e.g. a salt solution). The duration of treatment ranged from 10 minutes to 72 hours. Ten randomised clinical trials included participants with overt hepatic encephalopathy; three included participants with minimal hepatic encephalopathy; and one randomised clinical trial included participants with overt or minimal hepatic encephalopathy.

Key results

The analyses showed no effect of flumazenil on all-cause mortality (deaths of any cause) compared with placebo. People who received flumazenil were more likely to recover from their hepatic encephalopathy than people given a placebo. We found little information about serious side effects.

Quality of the evidence

Overall, the evidence for the effect of flumazenil on hepatic encephalopathy was of low quality; only one randomised clinical trial included had a low risk of bias.