Review: Flumazenil leads to clinical and electroencephalographic improvement in hepatic encephalopathy in patients with cirrhosis

Goulenok C, Bernard B, Cadranel JF, et al. **Flumazenil vs. placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis.** Aliment Pharmacol Ther. 2002;16:361-72.

QUESTION

In patients with cirrhosis, what is the effectiveness of flumazenil in treating hepatic encephalopathy?

DATA SOURCES

Studies were identified by searching MEDLINE and scanning *Current Contents* and bibliographies of relevant studies and contacting pharmaceutical companies.

STUDY SELECTION

Studies were selected if they were randomized controlled trials evaluating the efficacy of flumazenil in treating hepatic encephalopathy in patients with cirrhosis. Studies were excluded if insufficient data were reported.

DATA EXTRACTION

Data were extracted on study quality, patient characteristics, drug dose, treatment duration, and outcomes.

MAIN RESULTS

6 placebo-controlled studies involving 641 patients (326 assigned to flumazenil and 315 assigned to placebo) met the selection criteria. Treatment duration ranged from 5 minutes to 3 days. Combining data from 5 trials (317 patients assigned to flumazenil and 306 to placebo) showed that more patients who received flumazenil had clinical improvement than did those who received placebo (Table). Combining data from 3 trials (291 patients assigned to flumazenil and 286 to placebo) showed that more patients who received flumazenil had electroencephalographic improvement than did those who received placebo (Table). Adverse events were not reported in 4 trials. 1 trial reported adverse events in 4 patients assigned flumazenil (no mention was made of patients in the placebo group), and 1 trial showed no adverse effects in either group.

CONCLUSION

In patients with cirrhosis and acute hepatic encephalopathy, flumazenil leads to clinical and electroencephalographic improvement.

Source of funding: No external funding.

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Flumazenil vs placebo for acute hepatic encephalopathy in patients with cirrhosis*

Outcomes at 3 to 72 hr after injection	Weighted event rates		RBI (95% CI)	NNT (CI)
	Flumazenil	Placebo		
Clinical improvement	45%	3%	142% (111 to 168)	3 (2 to 4)
Electroencephalographic improvement	36%	6%	49% (39 to 56)	4 (3 to 5)

*Abbreviations defined in Glossary; RBI, NNT, and CI calculated based on reported Peto odds ratio and control event rate.

COMMENTARY

The mainstay of treatment for hepatic encephalopathy is lactulose or lactitol. Approximately 20 years ago, endo- or exogenous benzodiazepines were implicated in the pathogenesis of this disorder. In view of this hypothesis, several uncontrolled studies followed by 5 controlled trials evaluated the effectiveness of the benzodiazepine antagonist flumazenil in the treatment of hepatic encephalopathy. The latter trials were included in the meta-analysis by Goulenok and colleagues. Goulenok and colleagues actually included 6 trials but 1 of the 6 was a subset of a larger trial already included. This oversight does not affect the main conclusions of the meta-analysis because clinical and electroencephalographic improvement were reported separately in the 2 trials. The clinical effects were moderate or modest. Most authors suggest that flumazenil might be effective in a highly select subgroup of patients with encephalopathy; however, none of the studies was able to identify patients likely to respond.

What is the role of flumazenil in the treatment of this disorder? A trial of flumazenil in acute or chronic liver failure with encephalopathy is worthwhile because > 25% of patients are likely to respond according to this meta-analysis and the beneficial effect occurs much more rapidly—within minutes to hours—than with lactulose or lactitol.

Flumazenil is currently available only for parenteral administration, which precludes long-term use. An oral version might be useful, however, in view of an impressive case report by one of the pioneers of this form of treatment (1): A patient with debilitating hepatic encephalopathy despite maximal conventional treatment remained free of hepatic coma by using oral flumazenil on a liberalized diet for > 1 year. Thus, a trial of intravenous flumazenil should be considered in the management of acute disease and development of an oral form would be desirable for long-term use; the latter would require further trials, however.

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Reference

1. **Ferenci P, Grimm G, Meryn S, Gangl A.** Successful long-term treatment of portal-systemic encephalopathy by the benzodiazepine antagonist flumazenil. Gastroenterology. 1989;96:240-3.

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