Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is flumazenil an alternative for the treatment of hepatic encephalopathy?

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Abstract

INTRODUCTION
Flumazenil is an antagonist of the GABA/benzodiazepines receptor complex that might play a role in the treatment of hepatic encephalopathy. However, its efficacy and safety are a matter of debate.

METHODS
To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

RESULTS AND CONCLUSIONS
We identified two systematic reviews including fourteen randomized trials. We concluded flumazenil does not reduce mortality in patients with hepatic encephalopathy and it is not clear whether it leads to any clinical improvement because the certainty of the evidence is very low.

Problem

Hepatic encephalopathy is one of the most frequent complications of chronic liver disease [1]. Among multiple mechanisms to explain its causes, the role of sensorineural pathways involving GABA receptors has been proposed. For this reason, the use of an antagonist of the GABA/benzodiazepine receptor complex, flumazenil, has been posed as an alternative for this complication. However, some gastrointestinal, cardiac and neurological adverse effects have been described with the use of this intervention and it is not clear what is its real efficacy and safety in the management of hepatic encephalopathy.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- The use of flumazenil does not reduce mortality in patients with hepatic encephalopathy, and it is not clear whether it improves the resolution of encephalopathy or any clinical outcome, because the certainty of the evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematics reviews [2],[3] including fourteen primary studies reported in 25 references [4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28], all of them corresponding to randomized controlled trials.
What types of patients were included*	All of the trials included patients with liver cirrhosis [4],[8],[11],[14],[17],[19],[21],[22],[23],[24],[25],[26],[27],[28]. Two trials also included patients with acute liver failure [8],[28]. Six trials evaluated patients with acute hepatic encephalopathy [11],[17],[21],[24],[27],[28]and in two trials patients with chronic hepatic encephalopathy [4],[22]. In the rest of the trials [8],[14],[19],[23],[25],[26] the timing of hepatic encephalopathy was not specified. In relation to the severity of hepatic encephalopathy, four trials included patients with minimal hepatic encephalopathy [14],[19],[23],[25], two with grade I hepatic encephalopathy [4],[25], four with grade II [4],[11],[25],[26], nine with grade III [4],[11],[17],[22],[24],[25],[26],[27],[28] and six with grade IV [11],[17],[21],[24],[26],[28]. In addition, patients with abnormal trunk evoked potentials were included in one trial [14], impaired visual evoked potentials in one trial [19], abnormal electroencephalography in two trials [8],[27], abnormal Number Connection Test in two trials [14],[19], abnormal Digit Symbol Substitution Test in one trial [23] and ammonium levels over 30 µmol/L in one trial [8].
What types of interventions were included*	Flumazenil was used intravenously in all of the trials. In two [17],[21] it was used with 20 cc of saline solution, in one [24] with 50 cc of saline solution and in one [26] with 19 cc of saline solution. Regarding dosification, the most frequent was 1 mg single dose in five trials [11],[17],[19],[22],[26] and 2 mg single dose in three trials [4],[21],[24]. The rest of the trials used 6.5 mg per day for three days and 1 mg in a fourth day, with a total of 20.5 mg in a first part and 1 mg in 10 minutes in a second part [8], 1 mg/hour for five hours with a total of 5 mg [25], 0.2 mg once [23], 0.2 mg/kg once [27], 0.5 mg and subsequently 1 mg in 30 minutes [28] and 1 mg of loading together with 0.5 mg every 30 minutes until completing 3 mg [14]. Continuous intravenous infusion was used in four trials [4],[8],[25],[28]. In three trials [4],[8],[28] intravenous loading doses were used. One of them [8], used 0.5 mg in the first part and 1 mg in the second part of the intervention. Another trial [4], used three sequential boluses of 0.4, 0.8 and 1 mg in one minute, each prior to the use of continuous infusion. The last trial [28] used an intravenous bolus of 0.5 mg. In the remaining ten trials [11],[14],[17],[19],[21],[22],[23],[24],[26],[27] intravenous infusion was used in bolus. All the trials compared against placebo.
What types of outcomes were measured	The main outcomes according to the systematics reviews were: • Complete resolution of encephalopathy • Clinical improvement • Mortality • Quality of life • Severe and non-severe adverse effects • Electroencephalographic improvement.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information on the effects of flumazenil in hepatic encephalopathy is based on eleven randomized trials [4],[8],[11],[17],[21],[22],[23],[24],[25],[26],[28] including 872 patients. The rest of the trials did not report the outcomes of interest, or none of the identified reviews could extract the data so they could be incorporated into a meta-analysis.
Nine trials measured the outcome hepatic encephalopathy [4],[8],[11],[17],[21],[24],[25],[26],[28] and eleven trials reported mortality [4],[8],[11],[17],[21],[22],[23],[24],[25],[26],[28].
The summary of findings is the following:

- It is not clear whether flumazenil improves hepatic encephalopathy, because the certainty of the evidence is very low.
- Flumazenil does not reduce mortality in patients with hepatic encephalopathy. The certainty of the evidence is high.

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Flumazenil in hepatic encephalopathy				
Patients	Patients with hepatic encephalopathy			
Intervention	Flumazenil			
Comparison	Placebo			
Outcome	Absolute effect*		Relative effect (95% IC)	Certainty of evidence (GRADE)
	WITHOUT flumazenil	**WITH flumazenil**		
	Difference: patients per 1000			
Hepatic encephalopathy	933 per 1000	700 per 1000	RR 0.75 (0.70 to 0.80)	⨁◯◯◯[1,2] Very low
	Difference: 233 patients less (Margin of error: 187 to 280 less)			
Mortality	94 per 1000	71 per 1000	RR 0,75 (0,48 to 1,16)	⨁⨁⨁⨁ High
	Difference: 23 patients less per 1000 (Margin of error: 49 less to 15 more)			
Quality of life	The trials did not report this outcome		--	--

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT flumazenil** is based on the risk in the control group of the trials. The risk **WITH flumazenil** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded in two levels due to high inconsistency of the results.
[2] The certainty of the evidence was downgrade due to publication bias, which was estimated from the funnel plot.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to patients with chronic liver disease and hepatic encephalopathy in its various degrees. The studies reflect the spectrum of severity of hepatic encephalopathy.
- It is not advisable to apply this evidence to patients with minimal hepatic encephalopathy, because only two trials is specified included this population [23],[25].

About the outcomes included in this summary

- We selected the outcomes resolution of encephalopathy, mortality and quality of life as critical for decision-making according to the opinion of the authors of this summary. They generally coincide with the outcomes selected in the systematic reviews identified [2],[3] and the main guidelines [1].
- Even though quality of life was considered as a relevant outcome, it was not reported by the primary studies identified [3].

Balance between benefits and risks, and certainty of the evidence

- It is an intervention with no benefit on survival, and there is uncertainty about any other clinical benefit, so it is not possible to perform an adequate risk/benefit balance.

Resource considerations

- Although flumazenil is usually available for use in patients with benzodiazepine intoxication, it is a relatively expensive resource, especially compared to other alternatives for the management of hepatic encephalopathy. However, due to the uncertainty associated with the benefits, it is not possible to make an adequate cost/benefit balance.

What would patients and their doctors think about this intervention

- Most physicians should lean against the use of this intervention, as it is an alternative of uncertain benefit and relatively high cost.
- The fact that it is a therapy rarely used in the management of these patients and the existence of other alternatives, such as lactulose or non-absorbable antibiotics [1], probably reinforces this behavior.

Differences between this summary and other sources

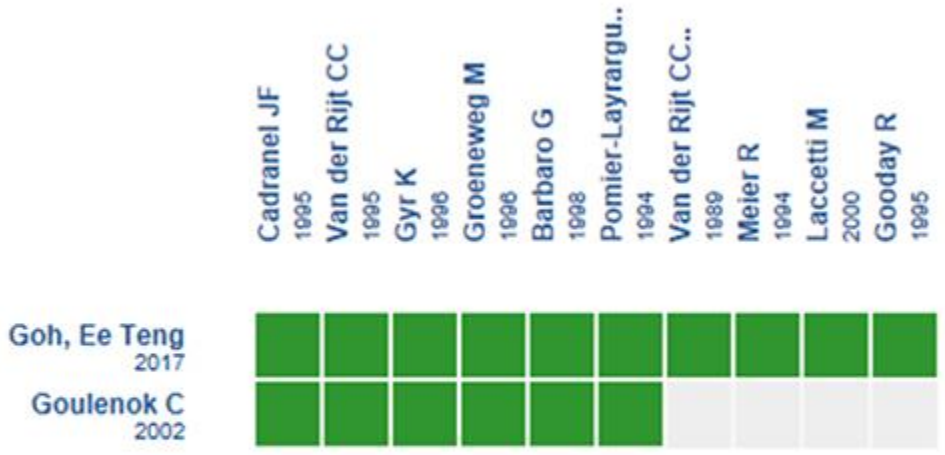
- The conclusions of this summary coincide with those of the identified systematic reviews.
- The conclusions of this summary partially agree with the clinical guideline of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver of 2014 [1]. Although the clinical guideline mentions the use of flumazenil in hepatic encephalopathy would not lead to a higher survival, suggests it could be used in exceptional situations, such as avoiding assisted ventilation and as a diagnostic tool in difficult cases.

Could this evidence change in the future?

- The probability that the conclusions of this summary change with future evidence is high, due to the existing uncertainty of the evidence on most clinical outcomes.
- According to the International Clinical Trials Registry Platform of the World Health Organization, there is at least one trial in progress [29], which could provide relevant information.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

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Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

Potential conflicts of interest
The authors do not have relevant interests to declare.

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