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Is pentoxifylline effective in alcoholic hepatitis? -First update

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Abstract

ABOUT THE UPDATE: This article updates the June 2014 Living FRISBEE (Living FRISBEE: Living FRIendly Summary of the Body of Evidence using Epistemonikos). It incorporates a new systematic review identifying one study not included in previous reviews. The new evidence leads to substantial changes in the existing evidence.

ASBTRACT: Pentoxifylline is an inhibitor of tumor necrosis factor, and has been proposed as treatment for alcoholic hepatitis. However, it is not clear if it is effective, or if it adds benefit to the treatment with corticosteroids. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified three systematic reviews including eight randomized controlled trials addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded pentoxifylline probably leads to little or no difference in mortality in alcoholic hepatitis.

About the update

This article is an update of the Living FRISBEE (Living FRISBEE: Living FRIendly Summary of the Body of Evidence using Epistemonikos) published in June 2014 (doi: 10.5867/medwave.2014.06.6002), based on the publication of a new systematic review including an additional randomized trial larger than all previous studies combined.

The new evidence incorporated in this summary leads to a change in the direction of the effect (from benefit to no benefit) with the corresponding modifications in key messages and considerations for decision-making.

Problem

Alcoholic hepatitis is associated to high morbidity and mortality. During the course of the disease an inflammatory process occurs. Corticosteroids have been

used because of their antiinflammatory properties, but they are associated to important adverse effects. The oral tumor necrosis factor inhibitor pentoxifylline has been postulated as an alternative for the treatment of alcoholic hepatitis. However, its effects are not clear.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this

information we generated a structured summary 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, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Pentoxifylline probably leads to little or no difference in mortality in alcoholic hepatitis.
- The main guidelines have not considered an important proportion of the existing evidence, so their conclusions partially disagree with this summary.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found three systematic reviews [1],[2],[3] including eight randomized controlled trials reported in 13 references [4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16].
What types of patients were included	All studies included patients with severe alcoholic hepatitis, generally based on a Maddrey score > 32. Only three studies required histological confirmation of alcoholic hepatitis as inclusion criteria [4],[11],[16]. One study included patients with advanced cirrhosis, with only some patients presenting severe alcoholic hepatitis [4]. Only data on the latter were used in the analysis.
What types of interventions were included	Pentoxifylline dose was 400 mg t.i.d. in six studies [4],[5],[7],[12],[15],[16]. One study administered 1200 mg q.d. [11] and one study did not report dosification [10]. Duration of treatment was 10 days in one study [11], 28 days in six [5],[9],[10],[14],[15],[16] and 6 months in one [12]. In four studies standard treatment did not include corticosteroids [5],[9],[10],[11] and in three studies both groups received an identical schedule of corticosteroids[4],[14],[16. One trial evaluated both alternatives (pentoxifylline versus placebo, and pentoxifylline plus corticosteroids versus corticosteroids) in different study arms [15]. All of the studies using corticosteroids administered prednisolone.
What types of outcomes were measured	All of the studies measured short-term mortality, and three also measured long-term mortality (three to six months) [4],[14],[16]. Other outcomes assessed in the different systematic reviews were: hepatic mortality, renal dysfunction (hepatorrenal syndrome, serum creatinine elevation), bilirubin plasma levels, and tumor necrosis factor plasma levels.

Summary of findings

Information on the effects of pentoxifylline for alcoholic hepatitis is based on eight randomized controlled studies involving 1,653 patients. All of the studies reported mortality. The summary of findings is the following:

- Pentoxifylline probably leads to little or no difference in mortality in alcoholic hepatitis compared to placebo, or added to standard treatment. The certainty of the evidence is moderate.

Pentoxifylline for alcoholic hepatitis

Patients Severe alcoholic hepatitis
Intervention Pentoxifylline
Comparison Placebo or standard treatment (with or without corticosteroids)

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT pentoxifylline	**WITH pentoxifylline**		
	Difference: patients per 1000			
Mortality	186 per 1000	166 per 1000	RR 0.89 (0.72 to 1.09)	⨁⨁⨁◯[1 2 3] Moderate
	Difference: 20 patients less per 1000 (Margin of error: 52 less to 17 more)			

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

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

[1] We downgraded the certainty of the evidence in one level because of imprecision, since the confidence interval included the possibility of a small benefit.
[2] We did not downgrade the certainty of the evidence for risk of bias even though some studies have substantial limitations. The studies contributing more data had low risk of bias.
[3] We did not downgrade the certainty of the evidence for indirectness, even though some old studies might have not used standard treatment or corticosteroids in the control group. Contemporary studies and those using corticosteroids provided most data to the estimation of the effects.

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 studies included severe alcoholic hepatitis patients, which is the typical situation where this treatment is considered. However, it is reasonable to extrapolate these results to all patients with alcoholic hepatitis.
- This evidence does not apply to other hepatitis etiologies (e.g. non-alcoholic fatty liver disease, viral hepatitis), specially considering there is direct evidence for pentoxifylline for those conditions. This evidence should not be applied to decompensated chronic liver disease not fulfilling criteria for alcoholic hepatitis.

About the outcomes included in this summary

- This summary only synthesized the effects on mortality, which is the outcome critical for decision-making according to the authors of this summary. However, the results are similar for other outcomes evaluated in the different reviews (e.g. renal failure).

Balance between benefits and risks, and certainty of the evidence

- There is probably no benefit in adding pentoxifylline to patients with alcoholic hepatitis, receiving corticosteroids or not. The certainty of the evidence is moderate.
- It is not clear if some benefit migh exist in specific subgroups, so future reviews might address this question. However, based on the existing data this hypothesis seems unlikely.

What would patients and their doctors think about this intervention

- It is expected some variation in the decision made by different patients and doctors; it is a probably ineffective intervention, but it is also safe and not expensive. Patients and doctors putting more value on the scant probability of benefit might be inclined to use the intervention.

Resource considerations

- The cost/benefit judgement does not apply since the evidence shows no benefit.

Differences between this summary and other sources

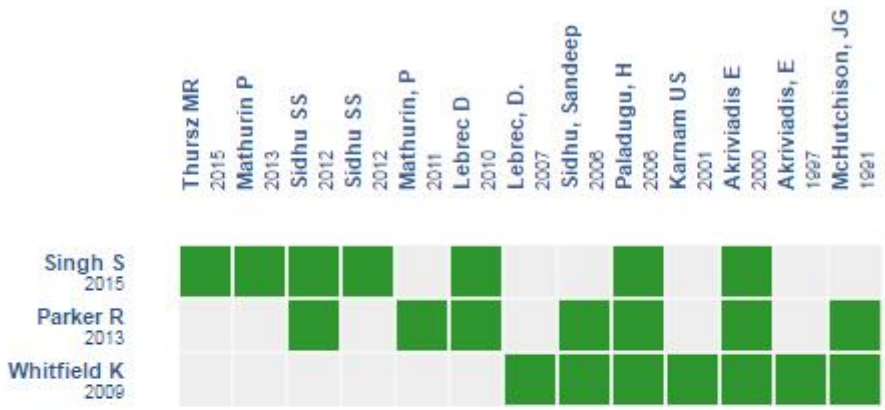
- Key messages of our summary disagree with the existing systematic reviews. In relation with older reviews concluding there might be some benefit but the evidence is no clear [1],[2], the main difference is given by the inclusion of STOPAH trial [15], which weighs more than all other studies combined in the pooled estimated effect.
- The more recent review [3] includes STOPAH and also arrives to a conclusion of possible benefit, but with low certainty of the evidence. The main difference is it addresses the studies of pentoxifylline associated to corticosteroids (versus corticosteroids alone) as a separate comparison. From the methodological point of view this would be justified if some interaction between these drugs could be anticipated (i.e. synergistic or competing) which was not observed in STOPAH. Our summary combined all studies directly comparing pentoxifylline versus plabebo/no treatment, while Singh et al. based their conclusions on indirect comparisons. Indirect comparisons provide a more precise result (narrower margin of error), but with less certainty of the evidence (because it is indirect evidence).
- Our summary is in partial agreement with the main guidelines; the European Association for the Study of the Liver suggests its use only for cases where corticosteroids cannot be employed, while the American Association for the Study of Liver Diseases and the American College of Gastroenterology suggest considering its use in more severe patients, specially if corticosteroids will be not administered. It is important to emphasize the last version of these guidelines is 2012 and 2010 respectively, so most evidence was not available at that moment [17],[18].

Could this evidence change in the future?

- The probability of future evidence changing the conclusions about the effects of pentoxifylline in alcoholic hepatitis is low because of the certainty of the evidence.
- There are several methodological approaches to the synthesis of the existing studies, so new systematic reviews might help clarify this issue. They could also explore if there are subgroups where some benefit might be expected, or if new studies are justified.
- There are no ongoing studies for this question, at least in the International Controlled Trials Registry Platform of the World Health Organization.

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.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Pentoxyfilline (alone or added to corticosteroids) for acute alcoholic hepatitis

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.

The details about the methods used to produce these summaries 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).

These summaries follow a rigorous process of internal peer review.

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

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