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Is racecadotril effective for acute diarrhea in children? -First update

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Abstract

This article updates the December 2015 Living FRISBEE (Living FRISBEE: Living FRIendly Summary of the Body of Evidence using Epistemonikos), based on the detection of two systematic reviews not identified in the previous version.

Gastroenteritis or acute watery diarrhea is usually a self-limited disease, but it is still associated to substantial healthcare costs and remains a frequent demand for medical care. Racecadotril, an intestinal enkephalinase inhibitor, has been used as treatment because it would decrease the duration of acute diarrhea and fluid loss. However there is still no evidence supporting its routine use. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified five systematic reviews including nine randomized trials relevant for our question. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded racecadotril probably reduces the duration of acute diarrhea in pediatric patients, without increasing adverse effects.

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 December 2015 (doi: 10.5867/medwave.2015.6339), based on two systematic reviews not identified in the previous version [1],[2]. One of them [1] includes a new randomized controlled trial not answering our question because it compares racecadotril with loperamide, not placebo. The same systematic review [1] contributes with a new meta-analysis on adverse effects of racecadotril.

The new evidence incorporated in this summary does not lead to changes in the certainty of the evidence or magnitude of the effects. One systematic review incorporated a new meta-analysis adding new issues to the considerations for decision-making [1].

Problem

Gastroenteritis or acute watery diarrhea is usually a self-limited disease, lasting five to seven days. However, it is still associated to substantial healthcare costs and remains a frequent demand for medical care. The main complication in pediatric population is severe dehydration. Therefore, the main aim of treatment is to prevent it; oral rehydration solution is the cornerstone of therapy, but it does not decrease the duration of diarrhea or fluid loss.

Racecadotril is an antisecretory drug that prolongs endogenous enkephalin action by inhibiting intestinal enkephalinase, decreasing the secretion of water and electrolytes. Even though the mechanism of action seems promising, there is still no evidence to support its routine use for acute diarrhea in children.

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

- Racecadotril probably decreases the duration of acute diarrhea in pediatric population.
- The use of racecadotril for acute diarrhea is probably safe in pediatric population and would not increase adverse effects.
- Even though it would be a beneficial and safe intervention, its cost is still high.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found five systematic reviews [1],[2],[3],[4],[5]including ten randomized controlled trials, reported in nine references [6],[7],[8],[9],[10],[11],[12],[13],[14](one reference reports two studies [12]). One of the trials [14] compares racecadotril with loperamide, so we did not include it in the analysis.
What types of patients were included	All trials restricted inclusion to pediatric population, between 3 to 71 months old, with acute diarrhea of viral or bacterial etiology. Four studies considered inpatients only [6],[7],[10],[12] and five outpatients only [8],[9],[11],[12],[13]. Stool output and number of diarrheic stools per day before inclusion were registered, showing no difference between racecadotril and placebo groups.
What types of interventions were included	Trials evaluated oral racecadotril; in six the dose was 1.5 mg/kg [6],[7],[8],[9],[10],[11], two administered 10 mg or 20 mg three times a day adjusted by body weight (over or under 9 kg) [12] and one did not specify dosage [13] All studies compared adding racecadotril to standard treatment (oral rehydration solution). Three studies were placebo controlled [6],[7],[10].
What types of outcomes were measured	Proportion of responders (defined as diarrhea duration less than 48 hours), proportion of patients not cured at fifth day of therapy, daily stool output and volume, number of vomits the first 48 hours of treatment and adverse effects reported during treatment.

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Summary of findings

The following information about the effects of racecadotril is based on nine randomized trials that included 1384 patients. Our analysis is based on the systematic review that conducted an individual patient data analysis [5]. The outcome measured was resolution of acute diarrhea before 48 hours of treatment. Giving the relevance for decision making, this summary considers the meta-analysis of five randomized controlled trials [6],[7],[8],[12] reported in one systematic review [1] that includes data about adverse effects reported during therapy with racecadotril.

- Racecadotril probably reduces the duration of acute diarrhea in pediatric patients. The certainty of the evidence is moderate.
- Racecadotril probably does not increase adverse effects. The certainty of the evidence is moderate.

Racecadotril for acute diarrhea in children

Patients Children with acute diarrhea
Intervention Racecadotril
Comparison Oral rehydration solution with or without placebo

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT racecadotril	**WITH racecadotril**		
	Difference: patients per 1000			
Proportion of responders	243 per 1000	505 per 1000	RR 2.08 (1.80 a 2.41)	⨁⨁⨁◯[1] Moderate
	Difference: 262 patients more per 1000 (Margin of error: 194 to 342 more)			
Adverse effects	144 per 1000	143 per 1000	RR 0.99 (0.73 a 1.34)	⨁⨁⨁◯[1] Moderate
	Difference: 1 patient less per 1000 (Margin of error: 39 less to 49 more)			

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

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

[1] The certainty was downgraded because of risk of bias; some trials were not blinded and/or did not report allocation concealment.

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

- This evidence applies to pediatric patients with clinical diagnosis of acute diarrhea of viral or bacterial etiology, hospitalized or in ambulatory care.
- This evidence does not apply to immunosuppressed patients or with severe comorbidity.

About the outcomes included in this summary

- We selected "proportion of responders" as outcome because it was the only outcome critical for decision-making according to the opinion of the authors of this summary. It was also the only one included in all randomized trials available and was subject of individual patient analysis in one of the systematic reviews [5] included in this summary.
- This update includes one meta-analysis reporting adverse effects with racecadotril, providing quantitative data about the safety of this therapy.
- It might be relevant to address outcomes such as need for hospitalization, need for intravenous hydration, additional emergency department visits, among others.

Balance between benefits and risks, and certainty of the evidence

- Racecadotril is a safe therapy for pediatric population [15]. There was no difference in the rate of adverse effects reported between groups. Events reported for placebo and racecadotril groups included vomiting, abdominal distension, abdominal pain, rash and one case of aminotransferase level increase (racecadotril) [1].
- None of the studies reported important adverse effects with racecadotril. It is also an approved therapy for pediatric population [14].
- The certainty of the evidence is moderate, but there is a probable benefit of the intervention in terms of decreasing diarrhea duration and it would be a low risk therapy.

What would patients and their doctors think about this intervention

- Racecadotril is a complement to acute diarrhea treatment and does not replace the use of oral rehydration solutions.
- Pediatric practice involves parents and/or patient caregivers. It is important to consider their concerns about disease. In this scenario and highlighting acute diarrhea is usually a self-limited condition, it is reasonable to suggest racecadotril as an adjuvant therapy that may have benefits but involves costs.

Resource considerations

- Racecadotril is still not widely available and adds costs to standard treatment for acute diarrhea (oral rehydration solution). Considering it would shorten the duration of the disease which might lower risk of dehydration, using racecadotril could decrease costs (hospital bed use, emergency department visits). However, it is not possible to make an appropriate cost-benefit analysis with the evidence available, especially because of the lack of information on other important outcomes.

Differences between this summary and other sources

- Our summary is consistent with the systematic reviews identified.
- The new evidence incorporated in this update does not change conclusions from the previous version. One of the systematic reviews [1] adds a multiple comparisons (network) meta-analysis; it shows racecadotril was better when compared to placebo or other adjuvants. Nevertheless, the difference in methods does not allow comparison with the other systematic reviews considered in this summary.
- We reviewed the Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Pediatric Infectious Diseases [16]. Their recommendations are consistent with the conclusion of our summary.

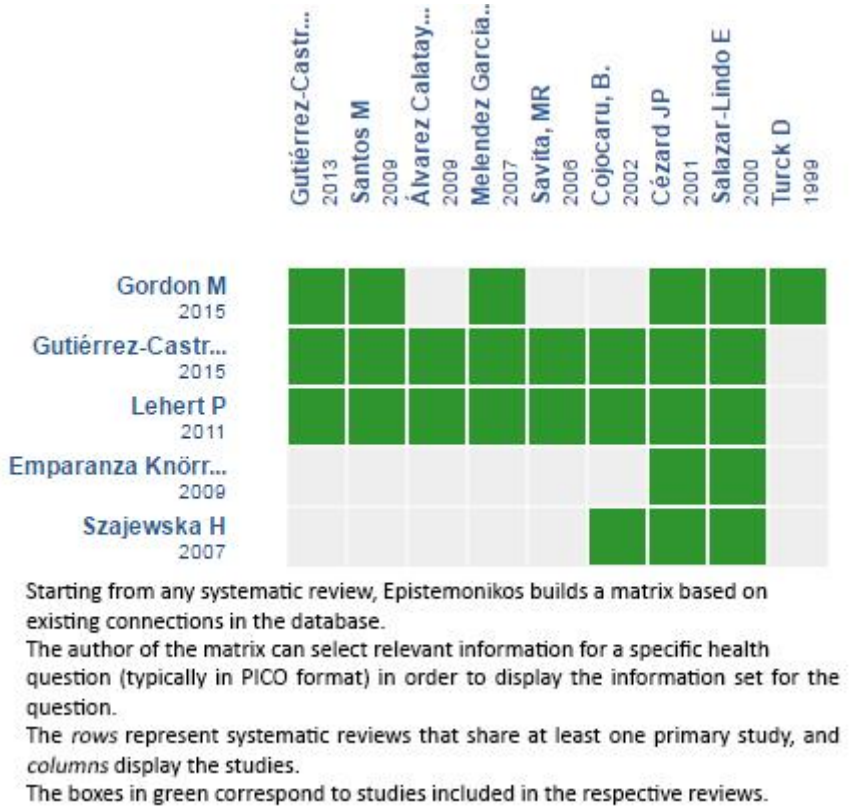
Could this evidence change in the future?

- The certainty of the available evidence is moderate, although only one outcome about efficacy was analyzed.
- We are aware of ongoing randomized controlled trials about racecadotril for acute diarrhea in children and a new systematic review with a network meta-analysis with the aim to

determine the relative effectiveness of pharmacological and nutritional treatments for reducing the duration of acute diarrhea in children[17]. So it is possible that they provide new information for this question in the future.

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 matrix of Evidence**. Racecadotril for acute diarrhea in children

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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