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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is racecadotril effective for acute diarrhea in children?

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Abstract

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 three systematic reviews including nine randomized trials evaluating the effects of this therapy. 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.

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. Despite understanding physiopathology and its mechanism of action, 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.
- It appears to be a beneficial and safe intervention, but 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 three systematic reviews [1],[2],[3]including nine randomized controlled trials, reported in eight references [4],[5],[6],[7],[8],[9],[10],[11] (one reference reports two studies [10]).
What types of patients were included	All trials included exclusively pediatric patients, between 3 to 71 months old, with acute diarrhea of viral or bacterial etiology. Four studies considered only inpatients [4],[5],[8],[10] and five outpatients only[6],[7],[9],[10],[11]. Stool output and number of diarrheic stools the day before inclusion was 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 every 8 hours [4],[5],[6],[7],[8],[9], two administered 10 mg or 20 mg every 8 hours adjusted by body weight (over or under 9 kg) and one did not specify dosage [11]. All studies compared adding racecadotril to standard treatment (oral rehydration solution). Three were also placebo controlled [4],[5],[8].
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 and number of vomits the first 48 hours of treatment.

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 [3]. The outcome measured was resolution of acute diarrhea before 48 hours of treatment.

- Racecadotril probably reduces the duration of acute diarrhea in pediatric patients. 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 to 2.41)	⨁⨁⨁◯[1] Moderate
	Difference: 262 patients more per 1000 (Margin of error: 194 to 342 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 in the control group of 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 comorbidities.

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 analysis of one of the reviews [3] included in this summary.
- It might be relevant to analyze outcomes as need for hospitalization, need for intravenous hydration, additional emergency department visits, among others.

Balance between benefits and risks, and certainty of the evidence

- None of the studies reported significant adverse effects with racecadotril. It is also an approved therapy for pediatric population [12].
- 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 also 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 could shorten the duration of the disease which might lower risk of dehydration, using racecadotril could decrease healthcare 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

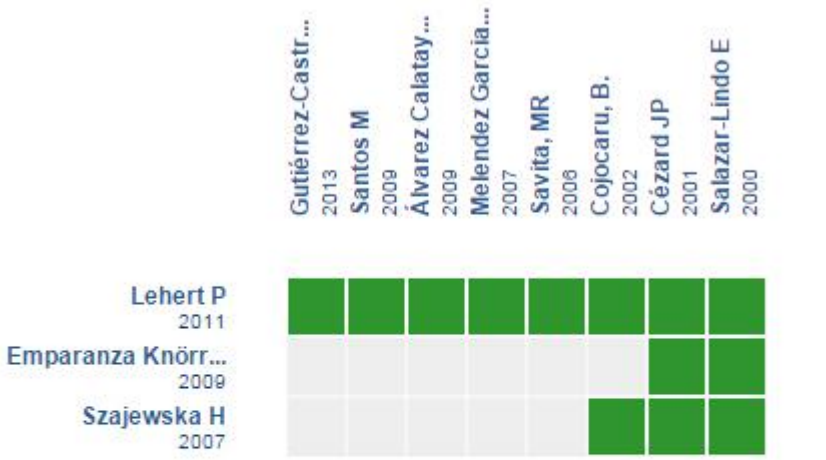
- Our summary is consistent with the systematic reviews identified.
- We reviewed the Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Society for Pediatric Infectious Diseases [13]. Their recommendations are consistent with the conclusions of our summary.

Could this evidence change in the future?

- The certainty of the available evidence is moderate, although only one outcome was analyzed.
- We are aware of ongoing randomized controlled trials about racecadotril for acute diarrhea in children, 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 version:** 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.

Referencias

1. Emparanza Knörr JI, Ozcoidi Erro I, Martínez Andueza MC, Callén Blecua MT, Alústiza Martínez E, Aseguinolaza Iparraguirre I. [Systematic review of the efficacy of racecadotril in the treatment of acute diarrhoea]. An Pediatr (Barc). 2008 Nov;69(5):432-8. | PubMed |
2. Szajewska H, Ruszczyński M, Chmielewska A, Wieczorek J. Systematic review: racecadotril in the treatment of acute diarrhoea in children. Aliment Pharmacol Ther. 2007 Sep 15;26(6):807-13. | PubMed |
3. Lehert P, Chéron G, Calatayud GA, Cézard JP, Castrellón PG, Garcia JM, et al. Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. Dig Liver Dis. 2011 Sep;43(9):707-13. | CrossRef | PubMed |

4. Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, Gutierrez M. Racecadotril in the treatment of acute watery diarrhea in children. N Engl J Med. 2000 Aug 17;343(7):463-7. | PubMed |
5. Cézard JP, Duhamel JF, Meyer M, Pharaon I, Bellaiche M, Maurage C, et al. Efficacy and tolerability of racecadotril in acute diarrhea in children. Gastroenterology. 2001 Mar;120(4):799-805. | PubMed |
6. Santos M, Marañón R, Miguez C, Vázquez P, Sánchez C. Use of racecadotril as outpatient treatment for acute gastroenteritis: a prospective, randomized, parallel study. J Pediatr. 2009 Jul;155(1):62-7. | CrossRef | PubMed |
7. Álvarez Calatayud G, Pinel Simón G, Taboada Castro L, Santos Sebastián M, Rivas Castillo A. Effectiveness of racecadotril in the treatment of acute gastroenteritis. Act Pediatr Esp. 2009 2009;67(3):177–22. | Link |
8. Savita MR. Racecadotril -a novel drug for treatment of acute watery diarrhoea in Indian children. Karnataka Pedicon 2005 Conference Abstracts Pediatric Oncall; 2006.
9. Cojocaru B, Bocquet N, Timsit S, Wille C, Boursiquot C, Marcombes F, et al. [Effect of racecadotril in the management of acute diarrhea in infants and children]. Arch Pediatr. 2002 Aug;9(8):774-9. | PubMed |
10. Gutiérrez-Castrellón P, Acosta-Bastidas M, Llamosas Gallardo B Ensayo clínico aleatorizado y análisis farmacoeconómico del impacto de racecadotrilo (Hidrasec®) como coadyuvante en el tratamiento de la gastroenteritis aguda sobre la reducción de los gastos hospitalarios relacionados en lactantes menores de 24 meses. Rev Invest Clin. 2013. | Link |
11. Meléndez García JM, Rodríguez JT. Racecadotrilo en el tratamiento de la diarrea aguda en niños. Rev Facultad Med (Guatemala). 2007;4:25-8.
12. Rautenberg TA, Zerwes U, Foerster D, Aultman R. Evaluating the cost utility of racecadotril for the treatment of acute watery diarrhea in children: the RAWD model. Clinicoecon Outcomes Res. 2012;4:109-16. | CrossRef | PubMed |
13. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr. 2014 Jul;59(1):132-52. |CrossRef | PubMed |

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