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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is it worth adding loperamide to antibiotic treatment of traveler's diarrhea?

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Abstract

Travelers' diarrhea is a frequent condition, especially in those traveling to high-risk areas. Although antibiotic treatment reduces the duration of diarrhea, it has been suggested adding loperamide could further reduce the symptoms. 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 identified two systematic reviews including 28 studies overall, of which 15 were randomized trials relevant for the question of interest. We extracted data from the systematic reviews, reanalysed data of primary studies and generated a summary of findings table using the GRADE approach. We concluded adding loperamide to antibiotic treatment might accelerate resolution of symptoms in traveler's diarrhea with minimal or no adverse effects.

Problem

Travelers' diarrhea is a common condition affecting approximately 20-60% of those traveling to high-risk areas, usually low-income regions. Although it is not generally associated to serious complications, it entails morbidity, disability, and costs.

Antibiotic treatment is considered the standard treatment, but despite its use a substantial number of people persist with symptoms at 48 hours.

Loperamide is an antimotility agent that acts at the level of intestinal opioid receptors, reducing peristalsis. It has been suggested that adding it to antibiotic treatment could reduce the time of symptoms, as well as the duration of antimicrobial treatment, which would result in lower costs, adverse effects and antibiotic resistance.

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 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 if data are suitable, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Adding loperamide to antibiotic treatment might accelerate resolution of traveler's diarrhea.
- There are probably minimal or no adverse effects of loperamide when used in the treatment of traveler's diarrhea.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematic reviews [1],[2] including 28 studies relevant for the question of interest [3],[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],[29],[30], including 15 randomized controlled trials [3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16], [17]. This table and the summary in general are based on the latter.
What types of patients were included*	Four trials included military personnel sent abroad for military operations [12],[13],[15],[16].The rest of the trials included regular people traveling. The destinations were: • Mexico in 9 trials [3],[4],[5],[6],[7],[8],[9],[10],[11]. • Turkey in 2 trials [13],[16]. • Egypt in 2 trials [14],[15]. • Latin America in 1 trial [17]. • Thailand in 1 trial [12].
What types of interventions were included*	Loperamide was used in all trials, with a maximum dose of 16 mg per day. Only two trials compared antibiotic treatment versus loperamide alone [4],[6], and one trial compared loperamide versus education, with co-interventions in both groups [16]. In the rest of the trials, antibiotic monotherapy was compaired to loperamide plus antibiotic, using the following antibiotic schemes: • Ciprofloxacin 500 mg bid for 3 days [15]. • Ciprofloxacin 500 mg bid for 3 days, or 750 mg single dose [12]. • Azithromycin single dose 500 mg [10] • Azithromycin single dose 1000 mg or levofloxacin 500 mg single dose [13]. • Sulfamethoxazole-trimethoprim 800/160 mg for 3 days [6] • Sulfamethoxazole-trimethoprim at different doses (1600/320 mg single dose; 1600/320 mg single dose then 800/160 mg bid for 5 doses [8]. • Ofloxacin 400 mg single dose [9]. • Ofloxacin initial dose 400 mg followed by 200 mg bid for 3 days [11]. • Rifaximin 200 mg tid for 3 days [4]. In some trials other cointerventions were used, such as the use of zaldaride [11],[14] or bismuth [16],[17].
What types of outcomes were measured	The outcomes studied were: • Cure rate of diarrhea at 24 h after treatment initiation [4],[6],[9],[10],[12],[15]. • Cure rate of diarrhea at 48 hours after treatment initiation [4],[6],[9],[10],[12],[15]. • Cure rate of diarrhea at 72 hrs after treatment initiation [4],[6],[9],[10],[12]. • TLUS: time until the last semiformated diarrheal deposition [4],[6],[9],[10],[12]. Adverse events were not reported in any of the trials.

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

Summary of findings

Information on the effects of adding loperamide to the antibiotic treatment of traveler's diarrhea is based on 15 randomized trials involving 2527 patients. It was not possible to conduct meta-analysis from the data extracted from the different reviews, so the meta-analysis provided by an individual review was used [2].

The summary of finding is as follows:

- Adding loperamide to antibiotic treatment might accelerate resolution of traveler’s diarrhea, but the certainty of the evidence is low.
- There are probably minimal or no adverse effects of loperamide when used in the treatment of traveler's diarrhea.The certainty of the evidence is moderate.
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Adding loperamide to antibiotic treatment of traveler's diarrhea				
Patients	Traveler's diarrhea			
Intervention	Loperamide + antibiotic			
Comparison	Placebo + antibiotic			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT loperamide	**WITH loperamide**		
	Difference: patients per 1000			
Cure rate at 48 h	750 per 1000	866 per 1000	OR 2.15 (1.50 a 3.09)	⨁⨁◯◯[1,2] Low
	Difference: 116 patients more per 1000 (Margin of error: from 68 to 160 more)			
Adverse events	Although adverse effects were not clearly reported in the trials, these were non-specific, minimal or nonexistent in all trials.		--	⨁⨁⨁◯[1] Moderate

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 loperamide** is based on the risk in the control group of the trials. The risk **WITH loperamide** (and its margin of error) is calculated from relative effect (and its margin of error)

[1] The certainty of the evidence was downgraded for risk of bias, since the studies presented serious limitations.
[2] The certainty of the evidence was downgraded because it was considered indirect since all the trials used different interventions and comparisons.

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 adult patients, both military and civilians, who travel to high-risk countries and develop non-dysenteric or febrile traveler's diarrhea.
- Although there are multiple antibiotic schemes, it is clinically reasonable to extrapolate this evidence to any scheme.

About the outcomes included in this summary

- The outcomes presented in the table are those considered critical for decision making by the authors of this summary.
- The clinical cure at 48 hours was considered as the more important outcome for the patient who is traveling. Cure at a longer period was considered less relevant given the high probability of spontaneous resolution or in relation to the use of antibiotics.

Balance between benefits and risks, and certainty of the evidence

- Adding loperamide to the treatment regimen is an intervention that probably has an effect on reducing the duration of symptoms, but the certainty of the evidence is low.
- Considering that it is a probably safe strategy in these patients, the risk / benefit balance is favorable.

What would patients and their doctors think about this intervention

- Adding loperamide to antibiotic treatment is a low-cost intervention, so it would not be a limitation for decision-making.

Resource considerations

- With the evidence presented in this summary, most patients and clinicians should be inclined to add loperamide to antibiotic treatment for the treatment of traveler's diarrhea.
- However, it will depend on how much value patients give to the duration of the symptoms - self-limiting and without serious complications in the vast majority of cases - and the uncertainty of the benefits.

Differences between this summary and other sources

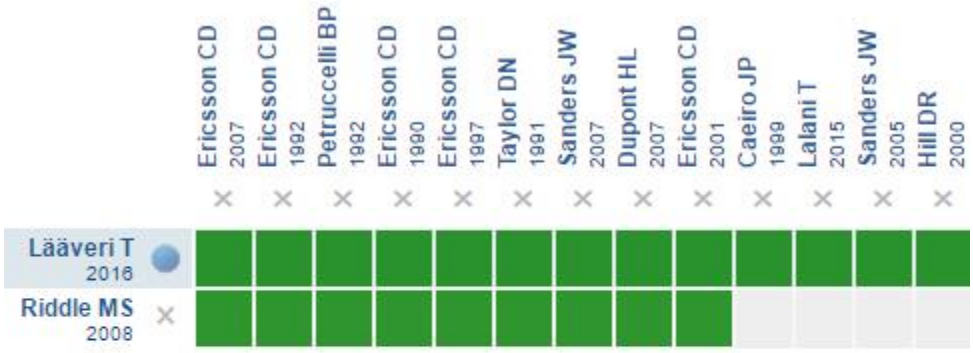
- The conclusions of this summary are consistent with those presented in the systematic reviews identified.
- We did not identify international clinical guidelines, but the main non-systematic reviews also reached a similar conclusion [31],[32],[33].

Could this evidence change in the future?

- The probability of the conclusions of this summary changing with future trials is high because of the existing uncertainty.
- We did not identify ongoing trials in the International Clinical Trials Registry Platform of the World Health Organization aiming to answer the question of this summary.

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:** Loperamide for traveler's diarrhea

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 matrices 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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