Travel Medicine and Infectious Disease (2016) 14, 299–312

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

REVIEW

Systematic review of loperamide: No proof of antibiotics being superior to loperamide in treatment of mild/moderate travellers' diarrhoea

Tinja Lääveri [a,1], Jesper Sterne [b,1], Lars Rombo [b,c], Anu Kantele [a,c,d,*]

[a] *Inflammation Center, Division of Infectious Diseases, University of Helsinki and Helsinki University Hospital, Helsinki, POB 348, FIN-00029 HUS, Finland*
[b] *Centre for Clinical Research, Sörmland County Council, Eskilstuna and University of Uppsala, SE 631 88 Eskilstuna, Sweden*
[c] *Karolinska Institutet, Department of Medicine/Solna, Unit for Infectious Diseases, SE 17176 Stockholm, Sweden*
[d] *Department of Medicine, University of Helsinki, Finland*

Received 9 May 2016; received in revised form 19 June 2016; accepted 20 June 2016
Available online 27 June 2016

KEYWORDS
Adverse drug event;
Safety;
Antibiotics;
Antidiarrhoeals;
Antibiotic resistance

Summary Looking at the worldwide emergency of antimicrobial resistance, international travellers appear to have a central role in spreading the bacteria across the globe. Travellers' diarrhoea (TD) is the most common disease encountered by visitors to the (sub)tropics. Both TD and its treatment with antibiotics have proved significant independent risk factors of colonization by resistant intestinal bacteria while travelling. Travellers should therefore be given preventive advice regarding TD and cautioned about taking antibiotics: mild or moderate TD does not require antibiotics. Logical alternatives are medications with effects on gastrointestinal function, such as loperamide. The present review explores literature on loperamide in treating TD. Adhering to manufacturer's dosage recommendations, loperamide offers a safe and effective alternative for relieving mild and moderate symptoms. Moreover, loperamide taken singly does no predispose to contracting MDR bacteria. Most importantly, we found no proof that would show antibiotics to be significantly more effective than loperamide in treating mild/moderate TD.

* Corresponding author. Inflammation Center, Division of Infectious Diseases, University of Helsinki and Helsinki University Hospital, Helsinki, POB 348, FIN-00029 HUS, Finland.
E-mail addresses: tinja.laaveri@hus.fi (T. Lääveri), jesper.sterne@gmail.com (J. Sterne), lars.rombo@gmail.com (L. Rombo), anu.kantele@hus.fi (A. Kantele).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.tmaid.2016.06.006

1. Introduction

Travellers' diarrhoea (TD) remains the most common medical problem encountered by travellers. WHO defines TD as three or more loose or liquid stools per day, or more frequently than is normal for the individual [1]. Although rarely severe and almost always spontaneously resolving [2—5], TD incurs significant morbidity and causes inconvenience to a high number of individuals: of all travellers to the (sub)tropics [6], 40—60% are expected to contract TD [2—4,7]. The inconvenience may not remain short-term: recent studies suggest that 3.0—13.6% of travellers with TD develop post-infectious irritable bowel syndrome (IBS) [8—13].

Antimicrobials have for decades been considered the primary option in treatment [14] — and even prevention [15—17] — of TD. One justification for this approach has been its presumed potential to prevent postinfectious IBS. However, we did not find any investigations that would have shown antibiotic treatment of TD to prevent IBS. On the contrary, one study suggests that taking antimicrobials actually increases the risk of post-travel IBS [9]. The increase of antimicrobial resistance raises serious concern over excessive antibiotic use [18—20]. The use of antibiotics for TD adds to this problem, as the drugs predispose travellers to contracting multidrug-resistant (MDR) bacteria which they may eventually spread to their home countries [21—23]. Besides global health care, antibiotics may harm individuals, not only by increasing the risk of infections by MDR bacteria, but by causing long-lasting changes in the intestinal microbiota [24]. Therefore, many current guidelines do not encourage treating TD with antibiotics [25]. In recent research, however, fairly little attention has been paid to non-antibiotic drugs with effects on the gastrointestinal function. These include loperamide, diphenoxylate plus atropine, and rasecondrontil, drugs of which loperamide has been available for decades, whereas racecadotril, despite its indication for acute diarrhoea [26], has so far not been studied among travellers. In a recent study, loperamide taken singly did no predispose to contracting MDR bacteria [27].

In this review we discuss the effectiveness and safety of loperamide in treating TD.

1.1. Loperamide — pharmacological aspects

Loperamide is an oral opioid-like agent which is considered nonabsorbable: only insignificant amounts reach the systemic circulation and even less penetrate the blood-brain barrier [28]. Therefore, at recommended dosages, the drug lacks central opioid-like effects, including centrally mediated blockade of intestinal propulsion [29]. In the intestine, it has an antisecretory effect mediated via μ-opioid receptors and non-opioid-receptor mechanisms. At higher dosages, however, loperamide also decreases motility, an effect mediated via μ-opioid receptors in the myenteric plexa of the bowel. Both of these mechanisms may be covered by dosage recommendations: low doses exploit the antisecretory and higher ones the antimotility effect [30]. Loperamide undergoes first-pass metabolism by CYP3A4 and CYP2C8 [31], a point of potential relevance when concomitantly using medicines metabolized through the same enzyme systems.

Loperamide is currently marketed in 110 countries. The recommended regimen is a 4-mg loading dose followed by 2 mg after every episode of diarrhoea. Some manufactures recommend that in acute disease the maximum dose would be 12 mg/day and the drug should not be used for longer than 48 h [32], while others allow 16 mg and even five-day-use [33].

1.2. Effects of various pathogens on bowel functions

The total fluid turnover of the intestine is about eight litres per day, most of which will be re-absorbed. The various intestinal pathogens may disturb the normal intestinal functions in differing ways as described below.

Many intestinal pathogens, with enterotoxinogenic *Escherichia coli* (ETEC) and *Vibrio cholerae* as two well-known examples, produce enterotoxins which stimulate the active water transport mechanisms of the enterocytes via ATP-dependant sodium/potassium pumps (secretory diarrhoea) [34]. As obvious, the antisecretory effect of loperamide is especially advantageous in this setting.

The main pathogenetic mechanism of some other pathogens, such as *Campylobacter* spp. and *Salmonella* spp., is not enterotoxin-mediated but, instead, the invasive nature of the bacteria determines the clinical picture: the bacteria invading the mucous membrane cause inflammation and ulcerations [35]. Blood and plasma leaking into the lumen draw even more fluid from the systemic circulation through osmosis. In addition, the widespread apoptosis of enterocytes leads to a decrease in the total resorptive ability of the bowel. Loperamide appears to have some effect even in this setting [36], probably by diminishing fluid secretion from the remaining viable enterocytes. Loperamide has been suggested to be harmful in infections with invasive pathogens: through its antimotility effect it may prevent the natural mechanism where pathogens are washed out. Accordingly, the drug is not recommended for cases with high fever or overtly bloody diarrhoea [14,25,32,33].

In cases with *Clostridium difficile* as a potential pathogen, loperamide and all other agents decreasing intestinal motility should be avoided, at least initially. If the diagnosis is confirmed, administering loperamide in conjunction with antibiotics effective against *C. difficile* is probably safe [37], although many experts advise against it [38—42]. Most importantly: when *C. difficile* is suspected, loperamide should not be used without an effective anti-clostridial agent [37].

2. Methods

2.1. Loperamide and travel — systematic search for studies

PubMed search with terms "loperamide" and "travel" yielded 86 articles, 71 of which were in English. From them we excluded five letters and 34 reviews on a subject other than loperamide; one case report did not focus on