Parenteral Fosfomycin in Gastrointestinal Surgery: A Systematic Review

Authors
Siv Fonnes1‡, Masja Klindt Fonnes1‡, Barbara Juliane Holzknecht2,3, Jacob Rosenberg1,3

Affiliations
1 Centre for Perioperative Optimisation, Department of Surgery, Herlev Hospital, University of Copenhagen, Herlev, Denmark
2 Department of Clinical Microbiology, Herlev Hospital, University of Copenhagen, Herlev, Denmark
3 Department of Clinical Medicine, University of Copenhagen, Copenhagen N, Denmark

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Introduction
A great challenge of modern medicine is the rise in antimicrobial resistance. The World Health Organisation ranked antimicrobial resistance as one of the top 10 global public health threats [1]. A possible solution to this threat could be the re-entry of the use of older antibiotics [2] such as fosfomycin. Fosfomycin, a phosphoenolpyruvate analogue [3], is a bactericidal antibiotic agent that interferes with the first step of the bacterial cell wall synthesis, where it irreversibly inhibits the enzyme enolpyruvyl transferase [4]. It has a half-life of 1.9–3.9 hours in plasma [5] and is eliminated by unchanged excretion into the urine [6]. Fosfomycin has shown good...
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A flowchart that shows the process of the systematic review including screening of the articles’ title and abstract, screening of full-text articles, reasons for exclusion of articles, and the total number of included studies in this systematic review. * Five reports were not included as they had overlapping populations with included studies [31–35].

**Table 1** Characteristics of the included studies and fosfomycin administration where n refers to the number of participants undergoing abdominal surgery. IV: intravenous, IP: intraperitoneal, IM: intramuscular, n: number of participants, Pro: prospective cohort study, Q-RCT: Quasi-randomized controlled trial, RCT: randomized controlled trial, Retro: retrospective cohort study.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study design</th>
<th>Type of surgery</th>
<th>Total n</th>
<th>Dose (g)</th>
<th>Total dose (g)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fonnes et al. [16]</td>
<td>2020</td>
<td>Q-RCT</td>
<td>Emergency</td>
<td>12</td>
<td>6</td>
<td>4</td>
<td>IP</td>
</tr>
<tr>
<td>Dorn et al. [17]</td>
<td>2019</td>
<td>Pro</td>
<td>Elective</td>
<td>27</td>
<td>27</td>
<td>8</td>
<td>IV</td>
</tr>
<tr>
<td>Fonnes et al. [18]</td>
<td>2019</td>
<td>Pro</td>
<td>Elective</td>
<td>14</td>
<td>14</td>
<td>4</td>
<td>IP</td>
</tr>
<tr>
<td>Shinagawa et al. [19]</td>
<td>2006</td>
<td>Retro</td>
<td>Elective</td>
<td>162</td>
<td>68</td>
<td>4</td>
<td>6–10</td>
</tr>
<tr>
<td>Unemura et al. [20]</td>
<td>2000</td>
<td>RCT</td>
<td>Elective</td>
<td>242</td>
<td>7</td>
<td>2</td>
<td>2–16</td>
</tr>
<tr>
<td>Andåker et al. [21]</td>
<td>1992</td>
<td>RCT</td>
<td>Elective</td>
<td>517</td>
<td>259</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Nehr et al. [22]</td>
<td>1990</td>
<td>RCT</td>
<td>Elective</td>
<td>149</td>
<td>72</td>
<td>8</td>
<td>IV</td>
</tr>
<tr>
<td>Andåker et al. [23]</td>
<td>1987</td>
<td>RCT</td>
<td>Emergency</td>
<td>381</td>
<td>190</td>
<td>4</td>
<td>4/16/64</td>
</tr>
<tr>
<td>Lindhagen et al. [24]</td>
<td>1984</td>
<td>RCT</td>
<td>Elective</td>
<td>49</td>
<td>26</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Müller et al. [25]</td>
<td>1982</td>
<td>Pro</td>
<td>Elective</td>
<td>40</td>
<td>40</td>
<td>4</td>
<td>4/8b</td>
</tr>
<tr>
<td>Lindhagen et al. [26]</td>
<td>1981</td>
<td>RCT</td>
<td>Elective</td>
<td>58</td>
<td>30</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Cardia et al. [27]</td>
<td>1980</td>
<td>RCT</td>
<td>Mixed</td>
<td>25</td>
<td>12</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Bianca et al. [28]</td>
<td>1979</td>
<td>RCT</td>
<td>Mixed</td>
<td>263</td>
<td>129</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Germiniani et al. [29]</td>
<td>1979</td>
<td>Retro</td>
<td>Mixed</td>
<td>365</td>
<td>120</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

* Patients were divided into three groups (increasing severity of disease): group A (only one preoperative dose)/ group B (one preoperative dose and three postoperative doses)/ group C (one preoperative dose and three postoperative doses for 5 days). b Patients were divided into two groups: one dose before surgery (n = 23)/ two doses 8–10 days after surgery (n = 17).
and three studies were prospective cohort studies [17, 18, 25]. Nearly half of the studies were carried out in the 1980s to early 1990s [21–27]. Almost half of the studies were carried out in Scandinavia with four from Sweden [21, 23, 24, 26] and three from Denmark [16, 18, 22], respectively. The remaining studies were carried from Italy [27–29], Japan [19, 20], Germany [17, 25], and Spain [30]. The included studies reported on a median (range) of 58 (12–517) patients each, totalling 1,029 patients receiving fosfomycin in connection with gastrointestinal surgery (▶Table 1). The studies included patients of both sexes, however, one study only included males [18] (Supplementary File Table 1). The age of patients was sparsely reported. Most of the patients treated with fosfomycin (51%) had undergone an elective procedure [17, 19–22, 24–26], the most common being colorectal procedures or cholecystectomy (Supplementary File Table 1). Almost one-fourth of patients treated with fosfomycin (23%) underwent an emergency procedure [16, 18, 23, 30] including laparoscopic cholecystectomy or appendectomy. The remaining three studies reported on a mixed population of patients undergoing either an elective or emergency procedure [27–29].

**Fosfomycin and other antimicrobial agents**

Regarding the administration of fosfomycin, the median (range) dose of fosfomycin was 4 g (1–8 g) (▶Table 1). Fosfomycin was administered before surgery in 73% of studies [17, 19–22, 24–29, 36], the median was 1 hour preoperatively but it ranged from 30 minutes to 6 hours preoperatively. Two studies administered fosfomycin during the procedure [16, 18]. In two-thirds of the studies, the postoperative course was also supplemented with fosfomycin. The postoperative regimens listed from fewest to most administrations were as follows: one administration of fosfomycin was given in two studies 8 hours postoperatively [21], two administrations were given either at 5- and 12 hours [28, 37], or 6- and 12 hours [27] postoperatively, and in two studies the patients received fosfomycin three times every 8 hours for 24 hours [24] or with various intervals [36], see ▶Table 1. In one study, the patients received fosfomycin four times daily postoperatively for either 3–7 days [38]. Lastly, three studies gave fosfomycin regularly (time interval not reported) for some days [19] up to 2 days [20], or 5 days [30] after surgery.

Co-administration with another antimicrobial agent was given in some studies and was mostly monotherapy [21–24, 26], however, in 46% of studies fosfomycin was administered as monotherapy [19, 20, 25, 27–30] (Supplementary File Table 1).

**Risk of bias across included studies**

The bias assessment according to Cochrane Handbook Risk of bias assessment tool 1 [12] can be seen in Supplementary File Fig. 1. The nine RCTs [16, 20–24, 26–28] included were assessed, however, one was a quasi-randomized clinical trial [16], thus resulting in a high risk of bias for the domains’ random sequence generation and allocation concealment. For most domains, there was unclear risk of bias in 67% to 89% of included RCTs. The exception was for the domains regarding 1) blinding of participants and 2) personal and incomplete outcome data where 44% and 0%, respectively, had unclear risk of bias. It was also in these two domains where many RCTs had low risk of bias (33–67% of RCTs). Other sources of bias that were noted concerned conflicts of interest and funding. In total, 88% of studies had no conflicts of interest statement [20–24, 26–28]. In most RCTs, a funding statement was either not reported [20, 23, 24] or had insufficient details on the role of funders and/or drug providers [21, 22, 26–28]. In two RCTs [22, 27], the risk of bias for this domain was ultimately assessed to be high, see Supplementary File Fig. 1.

For the retrospective [19, 29, 30] and prospective [17, 18, 25] cohort studies, bias was assessed using NOS [13]. According to this scale, the studies are graded with a score of zero to nine stars across three categories: 1) selection, 2) comparability, and 3) outcome. A low number of stars equal a high risk of bias and vice versa. The assessed studies were given a median of 3 stars and ranged from 1–5 stars, the bias assessment of the individual studies can be seen in Supplementary File Table 1. For the category selection, all studies demonstrated that the outcome SSI was not present at start of study, thus given a star, but only four studies provided documentation for the ascertainment of preoperative parenteral administration of fosfomycin and could be given a star for this [17, 18, 25, 29]. Only one study was awarded one out of two possible stars for the category comparability [19]. For the last category outcome, none of the studies could be given a star for the item assessment of outcome as it was not blinded, not record linked, or not described. Also, follow-up was only long enough for the outcome SSI to occur in two studies that were each given one star for this item [18, 19].

**Postoperative infectious complications**

The postoperative complications were categorised into four types of complications: SSI, intraabdominal abscess, sepsis, and death due to infectious complications. Five studies did not contribute with data as they did not report on this outcome [17, 20, 25, 30] or they also included patients with other indications for the antimicrobial treatment than gastrointestinal surgery, so relevant data could not be extracted [27–29]. There was a very sparse use of the classification system for postoperative complications according to the Clavien Dindo classification [39] for studies published after 1992.

The rate of SSI was reported by eight studies [16, 18, 19, 21–24, 26] (▶Fig. 2a). SSI was mostly defined as wound infection with the presence of pus/purulent material [21–24, 26]. One study measured the temperature, pulse, and blood pressure together with clinical findings [19]. The rates of SSI for patients receiving fosfomycin vs. comparison group ranged from 0–1% vs. 0–5% for emergency procedures and 0–10% vs. 6–30% for elective procedures, depicted in ▶Fig. 2a. The study with the highest SSI rates (in the comparison group only receiving metronidazole) was terminated prematurely [24].

The rate of intraabdominal abscess was reported by eight studies [16, 18, 19, 21–24, 26] (▶Fig. 2b). An intraabdominal abscess was mostly diagnosed either by imaging (ultrasonography or computer tomography) or laparotomy [21–23] or by “clinical and bacteriological signs of intraabdominal process causing illness” [24, 26]. The rate of intraabdominal abscesses for patients receiving fosfomycin vs. comparison group was 0% vs. 0–1% for emergency procedures and 0–3% vs. 0–10% for elective procedures (▶Fig. 2a).
The rate of sepsis was reported by four studies [16, 18, 21, 22] (data not shown). Sepsis was defined as e.g. “clinical, with malaise and fever” [21] or “temperature > 38.5 °C, together with rigors and poor general condition” [22]. No patients were reported to suffer from sepsis in the two emergency studies with small populations [16, 18]. For elective procedures, the rate of sepsis for patients receiving fosfomycin vs. comparison ranged from 1–2 % vs. 1–3 %.

The mortality rate due to infectious complications was reported by seven studies [16, 18, 19, 21–24] (data not shown). The cause of the reported mortality due to infectious complications was intraabdominal infection [21] or peritonitis [22]. The rate of mortality due to infectious complications was 0 % regardless of antibiotic regimen for emergency procedures and ranging from 0–1 % for elective procedures both for patients receiving fosfomycin and patients receiving any comparison regimen.

**Harms**

Reports on harms were missing in three of the included studies, reporting on a total of 256 patients receiving fosfomycin [20, 28, 29]. Of the studies that reported on harms, six of these described that there were no harms due to treatment with fosfomycin, covering a total of 263 patients [17, 19, 22, 24–26]. Harms of different degrees were reported in six studies that reported on 510 patients in total [16, 18, 21, 23, 27, 30]. An overview of the reported harms is illustrated in ▶ Fig. 3, however, the harms occurring after discharge was not included [18]. All in all, there were few harms, and most were related to the gastrointestinal system (n = 19). One harm was probably a serious adverse reaction, although details were sparse in the study, and it was unclear if the patients had received fosfomycin or the comparison regimen [27]. Most reported harms were deemed to be adverse events or reactions.

**Discussion**

This systematic review found that perioperative parenteral administration of fosfomycin was primarily used in the 1980–1990s for a variety of both elective and emergency gastrointestinal procedures. Often, a dose of 4 g fosfomycin was administered an hour before surgery together with metronidazole, and this was followed by one or more postoperative doses. There were few postoperative infectious complications such as SSIs in patients receiving fosfomycin as well as patients receiving the comparison antimicrobial agents. Harms were inconsistently reported, were few, and most were deemed to be adverse events or reactions that were related to the gastrointestinal system.

This systematic review has several strengths. We performed a systematic search for articles after a medical research librarian had been consulted to help ensure a broad and specific literature search. We had no language bias, as all relevant articles no matter the language were included. A protocol was registered at PROSPERO [10] to keep stringency, thoroughness, and transparency through the conduct of the systematic review. Furthermore, registering a protocol at PROSPERO reduced the risk of selective reporting. The screening of articles was conducted independently by blinded reviewers, hence, not influencing each other in the screening process. Finally, we reported according to PRISMA 2020 guideline [9]. However, this review also has some limitations. Despite our best efforts, one report [40] found by searching the reference list of included report with overlapping data [33] could not be retrieved despite expert assistance from the Royal Danish Library. It was an abstract from 1988 on 371 participants in a controlled clinical trial that possibly could have contributed with data [40]. We had no language bias, but some information or nuances could have been lost during translation due to the inclusion of all languages. Some of this systematic review’s limitations were due to a lack of transparency in the reporting of the included studies. Most of the studies were conducted in the 1980–1990s, thus before the implementa-
tion of reporting guidelines such as STROBE [41] for cohort studies, CONSORT [42] for RCTs, and ClinPK statement [43] for pharmacokinetic studies. This was especially evident for the risk of bias assessment for RCTs where most domains had unclear risk of bias due to insufficient information in 67% to 89% of the included RCTs. For bias assessment of the cohort studies, the total number of awarded stars was low due to the lack of a comparison group (comparability can be awarded up to two stars). Furthermore, there was often no description of how the outcomes were assessed, and follow-up was not long enough for SSIs to occur [13]. Also, harms and postoperative complications were sparsely reported and not always well-defined by the authors for instance by using definitions by ICH-GCP [44] or the Clavien-Dindo classification of complications [39].

This systematic review provides an important overview of the use of fosfomycin in gastrointestinal surgery that could become relevant, e.g. due to the emerging resistance to currently used antimicrobial agents. In urology, fosfomycin has been used as antimicrobial prophylaxis during prostate biopsies [45] as fluoroquinolones were associated with harms and emerging resistance [46]. A meta-analysis of 1,239 patients undergoing prostate biopsy found that fosfomycin compared with fluoroquinolones halved the risk of infectious complications [45]. The combination of fosfomycin and metronidazole could be a potential option to consider in gastrointestinal surgery as prophylaxis or empiric treatment in conjunction with surgical source control. For now, however, the use of systemic fosfomycin is restricted by the European Medical Agency as a reserve agent for the treatment of serious infections [47]. However, systemic fosfomycin has been used for several indications, resulting in few harms, and these were mainly gastrointestinal such as diarrhoea and nausea (5%) [7] as also seen in this systematic review. One single oral dose of fosfomycin to treat uncomplicated urinary tract infections in adults has been widely used for several years, and this indication was left untouched by the European Medicines Agency [47]. Oral fosfomycin is generally well tolerated and side effects are mainly gastrointestinal [48]. Recently, fosfomycin was confirmed to be safe also in pregnant women regarding the risk of congenital anomalies in a larger register-based French study where more than 2,700 women received fosfomycin during their first trimester [49]. All in all, the European Medicines Agency currently allows oral fosfomycin in uncomplicated urinary tract infections and prostate biopsies [47].

**Conclusion**

There were few postoperative infectious complications after perioperative parenteral administration of fosfomycin in various gastrointestinal procedures, though the studies were primarily published in the 1980–1990s. One dose of 4 g fosfomycin sometimes supplemented with a few postoperative doses was often used together with metronidazole. Harms were few and mild but inconsistently reported.

![Distributions and types of the harms in the studies that reported harms (total n = 510 patients) with reference in brackets. * not clearly reported whether this was after fosfomycin or comparison treatment, “Allergic manifestation” was further elaborated as “modest hypotension, skin rashes, pruritus and laryngospasm” [27].](image-url)
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Conflicts of Interest

Fonnes J, Rosenberg: Protocol and registration

A protocol was registered at PROSPERO, registration number: CRD42020201268, before data extraction [10].

Authorship contribution statement


References


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