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ORIGINAL RESEARCH

Adverse Events Associated with Fosfomycin Use: Review of the Literature and Analyses of the FDA Adverse Event Reporting System Database

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ABSTRACT

Introduction: The growing problem of antibacterial resistance resulted in an increased interest in fosfomycin, especially its parenteral formulation. We reviewed fosfomycin safety profile using the Food and Drug Administration Adverse Event (AE) Reporting System (FAERS) and published literature.

Methods: We conducted a FAERS search and disproportionality analysis of all fosfomycin-associated AEs. We also conducted a FAERS search for AEs implicating fosfomycin as the primary suspect and a search of reports of fosfomycin-associated bone marrow toxicity. We then review the literature for publications reporting AEs associated with fosfomycin by conducting PubMed searches.

Results: The disproportionality analysis of all FAERS reports of fosfomycin-associated AEs produced a higher than expected frequency of agranulocytosis, liver injury, severe skin reactions, and pseudomembranous colitis. Subsequent search for AEs where fosfomycin was the primary suspect and the literature review did not suggest a higher association of fosfomycin with these AEs. The search of bone marrow toxicity reports did not demonstrate an association between aplastic anemia and fosfomycin. The literature review selected 23 trials of parenteral administration of fosfomycin in 1242 patients including 8 comparative and 15 non-comparative trials. For oral fosfomycin, only prospective comparative trials ($n = 28$) in 2743 patients were included. The most frequent AEs associated with parenteral fosfomycin included rash, peripheral phlebitis, hypokalemia, and gastrointestinal disorders. Serious AEs such as aplastic anemia, anaphylaxis, and liver toxicities were reported infrequently. Gastrointestinal disorders were the most common AEs associated with oral fosfomycin.

Conclusion: The identified AEs were consistent with the safety profile of fosfomycin. No new safety signals related to either parenteral or oral fosfomycin were identified.

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INTRODUCTION

Fosfomycin, discovered in Spain in 1969, is a cell wall-acting antibacterial drug that inhibits the formation of *N*-acetylmuramic acid, a precursor of peptidoglycan. Fosfomycin has been available in Europe since the 1970s and was approved in the United States in 1996 [1]. In the US, it is approved as a 3-g sachet of fosfomycin tromethamine to be given orally as a single dose for uncomplicated cystitis due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*. In Europe, fosfomycin is also available as fosfomycin disodium for intravenous (IV) administration and is used for various infections at doses of 12–16 g/day (up to 24 g/day), divided into 3–4 doses.

In vitro, fosfomycin is active against *Enterococci* including vancomycin-resistant strains, *E. coli*, methicillin-resistant *Staphylococcus aureus*, *Citrobacter diversus*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Klebsiella oxytoca* and *Klebsiella pneumoniae*, including some carbapenem-resistant strains, *Proteus mirabilis* and *vulgaris*, *and Serratia marcescens* [2]. Some extended spectrum beta-lactamase-producing strains of *E. coli* and *K. pneumoniae* are susceptible to fosfomycin [3, 4]. Fosfomycin is variably active against *Pseudomonas aeruginosa* and *Acinetobacter spp*. [2, 4, 5].

The oral formulation of fosfomycin is considered to have a favorable safety profile with gastrointestinal disturbances being the most commonly associated adverse event [1, 2]. An IV formulation of fosfomycin, fosfomycin disodium, is associated with a high sodium intake which could be a limitation in patients with heart failure or those on hemodialysis [2]. Adverse reactions such as angioedema, aplastic anemia, cholestatic jaundice, and hepatic necrosis have been reported postmarketing [1].

Because of the growing problem of antibacterial resistance, there has been an increased interest in fosfomycin use, especially its parenteral formulations [6]. This review summarizes the safety profile of fosfomycin using the Food and Drug Administration (FDA) Adverse Event (AE) Reporting System (FAERS) and published literature with an emphasis on AEs associated with its parenteral formulations.

METHODS

The FAERS database was queried for domestic and foreign cases of AEs reported with oral or IV formulations. The FAERS contains information on AE and medication error reports submitted to FDA. AEs and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

We conducted three FAERS searches. The first search included reports regardless of whether fosfomycin was implicated as the primary suspect. The period for the search was from 1996 through September 2012. Data retrieved by this search were subjected to a disproportionality analysis (henceforth referred to as a 'data mining analysis'). This analysis aims to detect over-represented associations of drug–event combinations in the FAERS. The analysis used Empirica Signal® software (version 7.3.3.3.2.359, Oracle, Redwood Shores, CA, USA) and the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm for all events associated with fosfomycin use [7]. MGPS generates adjusted relative reporting

ratios, also known as Empirical Bayes Geometric Mean (EBGM) values, for the entire FAERS database. The EBGM is the value of a ratio of the observed to expected number of AEs indicating the strength of reporting relationships among all drug–AE combinations in the database. Importantly, the process does not adjust for reporting bias.

The EBGM value provides a stable estimate of the relative reporting ratio of any AE for a particular drug relative to all other drugs and AEs in FAERS. MGPS also calculates lower and upper 90% confidence intervals (CI) for the EBGM scores, denoted as EB05 and EB95, respectively. The higher the EBGM value for a particular drug–AE combination, the higher is the reporting association between that drug and AE in the database. Drug–AE pairs with an EB05 (lower bound of the 90% CI for the EBGM) >1 indicate AEs that occur above the expected rate. Furthermore, one may estimate that events with an EB05 >2 occur at least twice the expected ratio relative to the other drugs and events in the database. For our data mining analysis, we selected reports of events with an EB05 >1.

Subsequently, we conducted a FAERS search for reports of AEs where fosfomycin was considered to be the primary suspect [8].

A separate FAERS search was conducted for all cases of possible bone marrow toxicity with the terms of agranulocytosis, neutropenia, febrile neutropenia, aplastic anemia, bone marrow failure, aplasia pure red cell, and pancytopenia associated with the use of fosfomycin. This separate query was prompted by a case of aplastic anemia that was reported to the FDA. Aplastic anemia was defined as a combination of hemoglobin level <10 g/dl, segmented polymorphonuclear and band cells count $<1.5 \times 10^9$/l, platelet count $<100 \times 10^9$/l), and histological evidence of decreased cellularity, absence of infiltration and absence of significant fibrosis on bone marrow examination [9].

We then supplemented the results of the FAERS searches by the literature review of the safety profile of fosfomycin. The review was conducted by searching articles in English with the term "fosfomycin" via PubMed. We conducted a systematic review aiming to evaluate for possible imbalances in the frequency of AEs associated with fosfomycin as compared to other antibacterial drugs with the focus on fosfomycin AEs over-represented in the data-mining analysis and on safety signals associated with IV administration of fosfomycin.

The reports of clinical trials, meta-analyses, systematic reviews, and case reports of AEs associated with fosfomycin were selected. Individual trials were selected if they included greater than 10 patients. For parenteral formulations of fosfomycin, all clinical trials were selected for analysis and for oral formulations only prospective comparative trials were selected. References of the selected articles were also reviewed. The database was most recently accessed on July 9, 2015.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. No identifiable patient data were provided or accessed.

RESULTS

Data mining for all AEs with EB05 >1 associated with fosfomycin that were reported to FAERS identified a total of 559 reports for 69 events. Two events had an EB05 score greater than 8—pseudomembranous colitis, 5 reports, EBGM

57.4 and agranulocytosis, 16 reports, EBGM 25.8. Two events had an EB05 score from >4 to 8—toxic skin eruption, 7 events, EBGM 16.1 and hepatocellular injury, 10 reports, EBGM 10.

Eighteen events had EB05 score from >2 to 4. These AEs were mainly related to hypersensitivity reactions, liver and bone marrow toxicity. AEs related to hypersensitivity reactions included drug reaction with eosinophilia and systemic symptoms, 6 reports, EBGM 9.2; Stevens Johnson syndrome, 11 reports, EBGM 6.7; eosinophilia, 8 reports, EBGM 6.7; drug eruption, 6 reports, EBGM 5.4; urticaria, 18 reports, EBGM 3.6.

AEs with EB05 score from >2 to 4 related to liver toxicity included hepatitis, 14 reports, EBGM 6.1; hepatic function abnormal, 12 reports, EBGM 4.8; alanine aminotransferase increased, 16 reports, EBGM 4.6; aspartate aminotransferase increased, 13 reports, EBGM 3.8.

AEs with EB05 score from >2 to 4 related to bone marrow toxicity included pancytopenia, 13 reports, EBGM 5.7; leukopenia, 16 reports, EBGM 5.4; thrombocytopenia, 19 reports, EBGM 4.4; neutropenia, 13 reports, EBGM 4.

The other AEs with EB05 score from >2 to 4 included blood urea increased, 10 reports, EBGM of 4.6; blood lactate dehydrogenase increased, 8 reports, EBGM 4.2; disseminated intravascular coagulation, 7 reports, EBGM 4.2; hypokalemia, 8 reports, EBGM 3.9; and pyrexia, 33 reports, EBGM 3.1.

Review of the events with EB05 score from >1 to 2 revealed that many of these events were related to hypersensitivity reactions including anaphylactic reaction ($n = 5$), anaphylactic shock ($n = 4$), toxic epidermal necrolysis ($n = 4$), dermatitis exfoliative ($n = 6$), acute generalized exanthematous pustulosis ($n = 3$), drug hypersensitivity ($n = 6$), hypersensitivity ($n = 8$), vascular purpura ($n = 3$), rash maculopapular ($n = 6$), rash erythematous ($n = 6$), dermatitis allergic ($n = 3$), and face edema ($n = 8$).

Subsequent FAERS query for events where fosfomycin was considered to be the primary suspect identified a total of 146 reports. There were 31 domestic and 115 foreign reports; in 132 cases fosfomycin was given by oral and in 5 cases by IV or intramuscular routes; the route of administration was not reported in 9 reports. In the majority of cases, fosfomycin was used for the treatment of urinary tract infections (UTI) ($n = 131$).

Table 1 presents the most frequently reported AEs (case count of >3). Events related to lack of efficacy or those that were deemed non-significant are not included. Gastrointestinal disorders and allergic reactions were reported most frequently.

There were a total of 38 reports of allergic reactions associated with fosfomycin, although no reports of severe skin reactions such as Stevens Johnson syndrome or drug rash with eosinophilia and systemic symptoms were retrieved by this query.

The seven cases of fetal toxicities reported included stillbirth (1), pyelocalyceal dilation (1), interventricular septal defect and micrognathia (1), spina bifida (1), hydrocele (1), congenital pulmonic stenosis and patent foramen ovale (1), and cranial bone defect with exencephaly (1).

The FAERS search for all cases of cytopenia associated with fosfomycin identified 50 reports. Analysis of these cases identified one case that met criteria for aplastic anemia.

The majority of cases described isolated decreases in white blood cell count ($n = 25$). Time to onset of cytopenia ranged from 1 to 116 days with a median of 11 days. All patients received other medications that could be

Table 1 Most frequently reported MedDRA preferred terms

Event preferred terms	Total cases
Gastrointestinal disorders	
Diarrhea	19
Vomiting	15
Nausea	11
Abdominal pain	8
Allergic reactions	
Urticaria	14
Hypersensitivity	7
Pruritus	7
Anaphylactic reaction	6
Dermatitis allergic	4
Cardiac, Vascular, Respiratory, and General disorders	
Dyspnea	12
Dizziness	8
Fatigue	7
Malaise	7
Hypotension	6
Respiratory failure	5
Pyrexia	5
Palpitations	4
Bone marrow toxicity	
Aplastic anemia[a]	5
Platelet count decreased	4
White blood cell count decreased	4
Nervous system-related disorders	
Headache	5
Loss of consciousness	5
Others	
Maternal drugs affecting fetus	7
Hepatitis	5
Renal failure	4

Preferred terms included in 146 FAERS reports; a report may contain more than one preferred term; PTs are grouped by the authors

PT preferred terms, *MedDRA* Medical Dictionary for Regulatory Activities, *FAERS* Food and Drug Administration Adverse Event Reporting System

[a] Subsequent review of the reports revealed that one case met criteria for aplastic anemia

implicated in the development of bone marrow toxicities. There was no obvious correlation between development of cytopenia and a total dose of fosfomycin and in several cases cytopenia developed after a single dose of the drug.

One case involved a 68-year-old female who took one fosfomycin 3-g sachet for UTI. Concomitant medications included itraconazole and ciprofloxacin. One week after receiving fosfomycin the patient was found to have a decrease in platelet count to 70×10^9/l. On day 17 after fosfomycin administration platelet count was 27×10^9/l, WBC was 1.7×10^9/l and hematocrit was 33. Bone marrow aspiration reported changes "consistent with aplastic anemia". Filgrastim and epoetin alfa were administered and hematological abnormalities resolved by day 44 after fosfomycin dosing.

Literature Search

The search resulted in selection of 20 trials of parenteral fosfomycin and 25 trials of oral fosfomycin. Details of the retrieved articles are presented in Tables 2 and 3.

The trials of parenteral fosfomycin reported on 1242 patients enrolled in 8 comparative, 7 prospective non-comparative, and 8 retrospective non-comparative trials. A total of 2052 patients were enrolled in prospective comparative trials of oral formulations of fosfomycin. Our review included 6 trials in 254 pediatric patients (3 trials of parenteral and 3 of oral fosfomycin) and 5 trials in 291 pregnant patients (all received oral fosfomycin).

The eight comparative trials of parenteral fosfomycin enrolled 664 patients in the fosfomycin and 626 patients in the

Table 2 Adverse events associated with parenteral use of fosfomycin in individual trials

References	Trial design	FOM *N*	Patients' gender and age Indication	FOM dosing regimen	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Andaker et al. [15]	Prospective randomized controlled[a]	*N* = 259	F and M; mean age 67 years Prophylaxis of infection after colorectal surgery	FOM IV 8 g + metronidazole 1 g once and FOM 8 g 8 h later	16 g	*N* = 258 Doxycycline + metronidazole once	5% (12/259) Death 2% (5/259) Urticaria/purpura 1% (3/259) Nausea 1% (3/259) Thrombophlebitis 0.5% (1/259)	4% (11/258) Death 2% (5/259) Urticaria 1% (2/258) Nausea 0.5% (1/258) Leucopenia 0.5% (1/258) Vaginitis 0.5% (1/258) Pulmonary edema 0.5% (1/258)
Ishizaka et al. [13]	Prospective randomized controlled	*N* = 101	F and M >20 years Prevention of infection after urological surgery	FOM IV 2 g once + 2 g twice daily × 3 days Follow-up 14 days	14 g	*N* = 101 Cefotiam × 4 days	3 (3%) Eosinophilia—2 (2%) Elevated LDH—1 (1%)	6 (6%) Eosinophilia—2 (2%) Elevated LDH—1 (1%) Elevated GTP—1 (1%) GI disorders—2 (2%)
Nohr et al. [10]	Prospective randomized controlled	*N* = 84	F and M 24–90 years Prophylaxis of infection after colorectal surgery	FOM IV 8 g + metronidazole 1 g once	8 g	*N* = 88 Bacitracin + neomycin × 2 days + metronidazole and ampicillin once	2 (2%) Rash—1 (1%) GI disorders—1 (1%)	7 (8%) Rash—1 (1%) GI disorders—6 (7%)
Chareancholvanich [14]	Prospective randomized controlled	*N* = 56	F and M 57–86 years Prevention of surgical infection after elective total knee arthroplasty	FOM IV 2 g 12 h apart Follow-up 6 months	4 g	*N* = 56 Cefuroxime, 3 g total divided in 3 doses q 8 h	0% (0/56)	0% (0/56)

Table 2 continued

References	Trial design	FOM *N*	Patients' gender and age Indication	FOM dosing regimen	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Sirijatuphat and Thamlikitkul [17]	Prospective randomized controlled	$N = 47$	F and M 31–96 years Treatment of carbapenem-resistant *Acinetobacter baumannii* infection including pneumonia (79%), primary bacteremia, UTI, cIAI, SSI	FOM IV 4 g every 12 h plus colistin at 5 mg of colistin base activity/kg × median duration 12 days (range 3–14)	56–168 g	$N = 47$ Colistin at 5 mg of colistin base activity/kg × median duration 12 days (range 3–56)	28-days all cause mortality 46.8% AKI- 53.4% Abnormal liver tests 12.8%	28-days all cause mortality 57.4% AKI—59.6% Abnormal liver tests 12.8%
Lindhagen et al. [16]	Prospective randomized controlled	$N = 30$	Prophylaxis of infection after elective colorectal surgery	FOM 2 g + metronidazole 0.5 g Q6 h × 3 days for the total dose of FOM of 32 g and metronidazole of 8 g	32 g	$N = 28$ Cephalotin + metronidazole × 3 days for the total dose of cephalotin of 32 g and metronidazole of 8 g	0% (0/30)	0% (0/28)
Nissen et al. [12]	Prospective randomized controlled	$N = 17$	F and M ≥ 18 years of age Mean age 57 years Pneumonia requiring mechanical ventilation in 22 out 32 patients	FOM IV 4 g every 8 h + AMP 1 g q 6 h Mean treatment duration 5.5 days	About 180 g	$N = 15$ Gentamicin 80 mg every 8 h + AMP 1 g q 6 h	Peripheral phlebitis—2 (12%) 'mild transient" AST elevation—1 (6%)	0
Pontiki et al. [31]	Prospective non-comparative	$N = 66$	F and M 56.7 ± 17.2 years (age ± SD) Infections due to resistant pathogens including primary bacteremia ($n = 18$), VAP ($n = 14$), CR-BSI ($n = 7$), cIAI, UTI, meningitis.	FOM IV + colisitin ($n = 32$), tigecycline ($n = 19$), gentamicin ($n = 15$), meropenem ($n = 12$), and piperacillin-tazobactam ($n = 4$) for median duration of 14 days (IQR 8–17 days) at a median dose 24 g/day (IQR 16–24 g/day)	About 336 g	NA	Hypokalemia 10 (15.2%) Renal toxicity 3 (4.5%) Thrombocytopenia 4 (6%) Diarrhea 2 (3%) Rash 1 (1.5%) Neutropenia 1 (1.5%)	NA
Meissner et al. [20]	Prospective non-comparative	$N = 60$	F and M 17–78 years Chronic post-traumatic osteomyelitis	FOM IV 10 g once, then 5 g 3 times daily Mean duration 13.9 days (5–28)	50–420 g	NA	Peripheral phlebitis—7 (12%) GI disorders—4 (7%) Exanthema—2 (3%)	NA

Table 2 continued

References	Trial design	FOM *N*	Patients' gender and age Indication	FOM dosing regimen	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Stengel et al. [21]	Prospective non-comparative	$N = 52$	F and M ≥18 years; mean age 63 years DFI with high risk of major amputation	FOM IV 8-24 g × 14 days (range 3–40) in combination with carbapenems and other β-lactams, quinolones, clindamycin	Varied	NA	Nausea and rash—4 (8%)	NA
Rio et al. [32]	Prospective non-comparative	$N = 16$	Rescue therapy for MRSA bacteremia or infective endocarditis ($n = 12$)	FOM IV 2 g every 6 h plus imipenem 1 g every 6 h Median duration 28 days (range 4–75)	48–900 g	NA	Deaths—5 (31%); 1 death due to sodium overload, hypernatremia and acute renal failure was considered FOM related Leucopenia—1 Sodium overload—3	NA
Portier et al. [18]	Prospective non-comparative	$N = 16$	8 days–73 years (five children aged 8 days 14 years) Meningitis (3); bone and joint infections (6); persistent bacteremia (7)	IV 50 mg/kg 3–4 times daily for 11–21 days in combination with cefotaxime 25 mg/kg 3–4 times daily	About 115–295 g	NA	Neutropenia—3 (19%) (not specified) AST increase—1 (6%) (not specified)	NA
Mirakhur et al. [19]	Prospective non-comparative	$N = 15$	F and M mean age 23 years (18–37) Pulmonary exacerbations of *Pseudomonas aeruginosa* infection in patient with cystic fibrosis	FOM IV 5 g three times daily Mean course length 16.6 days (7–36); mean 2 courses per patient (range 1–3), FOM given in combination with 1–2 other intravenous antibacterial drugs	Varied	NA	Nausea—1 (7%)	NA
Michalopoulos et al. [22]	Prospective non-comparative	$N = 11$	Adults Carbapenem-resistant *Klebsiella pneumoniae* infections: VAP, BSI, UTI, and wound infection	FOM IV 2–4 g every 6 h × 14 ± 5.6 days in combination with colistin, gentamicin, or piperacillin/tazobactam	72–320 g	NA	0 (0%)	NA

Table 2 continued

References	Trial design	FOM *N*	Patients' gender and age Indication	FOM dosing regimen	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Hernandez Casado [26]	Retrospective non-comparative	$N = 99$	M and F 7–74 years (No. of children is not reported) At risk of bone fracture infection or established osteomyelitis	$N = 39$ IV 8–16 g × 4 days, then IM 2–8 g × 2–6 days, then PO 2–4 g × 2–6 days $N = 60$ IM or PO, doses are not specified	Varied	NA	Rash—1 (1%)	NA
Florent et al. [23]	Retrospective non-comparative	$N = 72$	M and F 55 ± 19 years Infections of bone and joint ($n = 33$); CNS ($n = 11$); ear and sinus ($n = 9$); UTI ($n = 9$); bacteremia ($n = 5$); SSTI ($n = 4$); pneumonia ($n = 1$)	FOM IV 12 g a day in 86% of cases with a median duration of 11 days; co-administered with another antibacterial in all cases	About 132 g	NA	27 (38%) Hypokalemia—19 (26%) Injection site pain—3 (4%) Heart failure—2 (3%) Hypertension—2 (3%) ALT elevated—1 (1.4%)	NA
Gallardo et al. [28]	Retrospective non-comparative	$N = 33$	M and F 10–79 years cIAI ($n = 29$) SSI ($n = 4$[e])	IM/IV 4–6 daily × 5 days in the cIAI ($n = 29$) group and IM 3–6 daily ($n = 4$) in the SSI group	IM/IV 18–30 g	Historical control; but no safety data are reported for the control	Petechial rash—1 (3%)	Not reported
Ruiz Garcia et al. [30]	Retrospective non-comparative	$N = 31$	Females 16–39 years Endometritis	FOM IM 4 g/day ($N = 29$) FOM IV 8–12 g/day ($N = 2$) for 7 days	28–84 g	NA	0	NA
Hutzler et al. [24]	Retrospective non-comparative	$N = 30$	M and F 4–77 years UTI ($n = 13$), pneumonia ($n = 14$), osteomyelitis ($n = 2$), septicemia ($n = 1$)	IM or PO 2–8 g daily (100–230 mg/kg/day) divided in 4 doses given every 6 h × 5–58 days	20–200 g	NA	Pain at the injection site 1 (3%) Transaminase elevation—2 (7%) Eosinophilia—1 (3%)	NA
Menendez et al. [27]	Retrospective non-comparative	$N = 27$	M and F 11–80 years Pneumonia and bronchitis	Parenterally $N = 19$ PO $N = 8$ (calcum salt) 4–12 g daily for 1–2 weeks;	28–168 g	NA	Rash—1 (4%) Diarrhea—1 (4%)	NA

Table 2 continued

References	Trial design	FOM *N*	Patients' gender and age Indication	FOM dosing regimen	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Children								
Corti et al. [11]	Retrospective comparative	*N* = 70 FOM (23) FOM+(47)[b]	Children <16 years of age acute hematogenous osteomyelitis	IV 200 mg/kg daily Mean duration 2.5–3 weeks	Varied	*N* = 33 Flucloxacillin, amoxicillin, amoxicillin/clavulanic acid, clindamycin	FOM Exanthema—0 Diarrhea—1 (4%) Leucopenia —0[c] FOM+ Exanthema—10 (21%) Diarrhea—1 (2%) Leucopenia—1 (2%)	Exanthema—14 (42%) Diarrhea—7 (21%) Leucopenia—3 (9%)[c]
Baquero et al. [29]	Retrospective non-comparative	*N* = 26 (number of treatments in 24 patients)	F and M *Serratia marcescens* bacteremia Children; 22 out of 24 were <1 year including 11 <1 month	IV 75 mg/kg every 6 h for 2–4 weeks, FOM alone (*n* = 6), in combination with gentamicin (*n* = 18) and carbenicillin (2)[f]	Varied	NA	0—"no significant side effects"	NA
Llorens et al. [25]	Retrospective non-comparative	*N* = 24	Children of 11 months to 12 years Pneumonia, empyema, bronchitis	200 mg/kg/day given in 4 injections every 6 h; IV—10, IM—14; co-administered with ampicillin in 1 case Duration 4–23 days	Varied	NA	Transient "slight" transaminase elevation—6 (25%)—resolved without stopping FOM Nicolau syndrome—1 (4%)[d]	NA

AC amoxicillin clavulanate, *AE* adverse events, *AKI* acute kidney injury, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AMP* ampicillin, *AST* aspartate aminotransferase, *BSI* bloodstream infection, *CA* cefuroxime axetil, *cIAI* complicated intra-abdominal infection, *CNS* central nervous system, *COMP* comparator, *CR-BSI* catheter-related bloodstream infection, *CTX* cotrimoxazole, *DFI* diabetic foot infection, *F* female, *FOM* fosfomycin, *F-up* follow-up, *GI* gastrointestinal, *GTP* γ-guanosine triphosphate, *IM* intramuscularly, *IQR* interquartile range, *IV* intravenously, *LDH* lactate dehydrogenase, *M* male, *MRSA* methicillin-resistant *Staphylococcus* aureus, *NA* not applicable, *PO* orally, *SSTI* skin and soft tissue infection, *TID* three times daily, *TMP* trimethoprim, *UTI* urinary tract infection, *VAP* ventilator-associated pneumonia

[a] Including blinded and open label trials

[b] FOM+ fosfomycin was combined with flucloxacillin (38), amoxicillin (2), amoxicillin/clavulanic acid (4), clindamycin (2), and with gentamicin (1)

[c] Leucopenia was defined as a leukocyte count <1G/l

[d] Nicolau syndrome—necrosis of the skin and underlying tissues at the site on intramuscular injection

[e] Additional 21 patients received FOM orally

[f] Patients could receive more than one course of treatment

Table 3 Adverse associated with oral use of fosfomycin in individual trials

References	Trial type	FOM *N* Study population	Indication FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Stein et al. [59]	Prospective randomized controlled[a]	$N = 375$ F ≥12 years	Uncomplicated UTI PO 3 g once Follow-up 4-6 weeks	3 g	$N = 374$ Nitrofurantoin × 7 days	20 (5.3%) GI disorders 12 (3%)[b] Vaginitis 7 (1.8%)	21 (5.6%) GI disorders 9 (2%) Vaginitis 6 (1.6%) Dizziness 3 (0.8%)
Lista et al. [57]	Prospective randomized controlled	$N = 359$	Prophylaxis in transrectal prostate biopsy PO 3 g twice 48 h apart Follow-up 3 months	6 g	$N = 312$ Ciprofloxacin × 5 days	GI disorders 10 (2.8%)	GI disorders 9 (2.9%) Anaphylaxis 1 (0.3%)
Periti et al. [58]	Prospective randomized controlled	$N = 256$	Prophylaxis in transurethral prostatic surgery PO 3 g twice 27 h apart (before and after surgery) Follow-up 2 weeks	6 g	$N = 419$ Amoxicillin $n = 207$ 3 g × 2 q 24 h CTX $n = 212$ 1.92 g × 2 q 24 h	12/256 (5%) GI disorders 8 (3%) Allergy 4 (1.5%)	33 (8%) Amoxicillin 17/207 (8%) GI disorders—15 (7%) Allergy—2 (2%) CTX 16/212/ (7.5%) all GI disorders

Table 3 continued

References	Trial type	FOM *N*	Indication Study population	FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Naber et al. [35]	Prospective randomized controlled	$N = 250$	Uncomplicated UTI F 18–75 years	PO 3 g once Follow-up 4 weeks	3 g	$N = 246$ Ofloxacin $n = 119$ CTX $n = 127$	17 (6.8%) GI disorders—16 (6.4%) Rash—1 (0.4%)	17 (6.9%) Ofloxacin 7 (5.9%), all GI disorders CTX 10 (7.9%); GI disorders—8 (6%) Headache—1 Exanthema—1
Rudenko and Dorofeyev [33]	Prospective randomized controlled	$N = 166$	Prophylaxis of recurrent uncomplicated UTI F 25–63 years	PO 3 g every 10 days × 6 months Follow-up 360 days	54 g	$N = 151$ Placebo	2 (1%) Dyspnea—1 (0.6%) Rash—1 (0.6%)	4 (2.6%) Rash—1 (0.7%) GI disorders—1 (0.7%) Cough—1 (0.7%) Joint pain—1(0.7%)
Van Pienbroek et al. [47]	Prospective randomized controlled	$N = 113$	Uncomplicated UTI F >18 years	PO 3 g once Follow-up 6 weeks	3 g	$N = 114$ Nitrofurantoin × 7 days	65 (58%) GI disorders—47 (42%) CNS—8 (7%) Urogenital—4 (3%) Skin—2 (2%) Other—4 (3%)	37 (32%) GI disorders—24 (21%) CNS—7 (6%) Skin—1 (1%) Other—5 (4)%

Table 3 continued

References	Trial type	FOM *N*	Indication Study population	FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Neu [71]	Prospective randomized controlled	$N = 80$	Uncomplicated UTI F 18–65 years	PO 3 g once Follow-up 16–32 days	3 g	$N = 78$ Amoxicillin 3 g once	GI disorders 7 (9%)	9 (11.5%) GI disorders—8 (10%) Rash—1 (1%)
Boerema and Willems [37]	Prospective randomized controlled	$N = 79$	Uncomplicated UTI F 16–50 years of age	PO 3 g once Follow-up 6 weeks	3 g	$N = 79$ Norfloxacin × 7 days	16 (20%) GI disorders—14 (18%) Fatigue—1 (1.3%) Dizziness -1 (1.3%)	2 (2.5%) GI disorders—2 (2.5%)
Ceran et al. [53]	Prospective randomized controlled	$N = 77$	Uncomplicated UTI F 18–65 years	PO 3 g once Follow-up 60 days	3 g	$N = 65$ Ciprofloxacin × 5 days	GI disorders—3 (3.9%)	GI disorders—2 (3.1%)
Costantini et al. [34]	Prospective randomized controlled	$N = 76$	Prophylaxis of recurrent UTI F 58 ± 16.7 years (age ± SD)	PO 3 g weekly × 12 weeks Follow-up 12 months	36 g	$N = 71$ Prulifloxacin one tablet weekly × 12 weeks	8 (10%) GI disorders—7 (9%) Vaginitis—1 (1.3%)	5 (7%) GI disorders—2 (3%) Vaginitis—3(4%)

Table 3 continued

References	Trial type	FOM *N*	Indication Study population	FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Cooper et al. [38]	Prospective randomized controlled	*N* = 72	Dysuria M and F 17–75 years	PO 3 g once Follow-up 1 month	3 g	*N* = 69 Amoxicillin clavulanate × 5 days	6 (8%) GI disorders—5 (7%) Rash—1 (1.4%)	7 (10%) GI disorders—3 (4%) Vaginitis—3 (4%) Rash—1 (1.5%)
Elhanan et al. [48]	Prospective randomized controlled	*N* = 58	Uncomplicated UTI F >16 years	PO 3 g once Follow-up 1 month	3 g	*N* = 54 Cephalexin × 5 days	0 (0%)	3 (5.5%) Vaginitis—3
Selvaggi [39]	Prospective randomized controlled	*N* = 45	Uncomplicated UTI F 16–70 years	PO 3 g once Follow-up 3 weeks	3 g	*N* = 44 Norfloxacin once	0 (%)	0 (%)
Crocchiolo [40]	Prospective randomized controlled	*N* = 38	Uncomplicated UTI F 16-70 years	PO 3 g once Follow-up 30 days	3 g	*N* = 35 CTX × 3 days	GI disorders—3 (8%)	2 (6%) Rash—1 Asthenia—1
De Jong et al. [46]	Prospective randomized controlled	*N* = 33	Uncomplicated UTI F >16 years	PO 3 g once Follow-up 30 days	3 g	*N* = 30 Norfloxacin × 5 days	9 (27%) GI disorders—8 (24%) Dizziness—1 (3%)	8 (27%) GI disorders 5 (17%) Dizziness—1 (3%) Headache—1(3%) Hepatic function abnormal—1(3%)

Table 3 continued

References	Trial type	FOM *N*	Indication Study population	FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Baert et al. [41]	Prospective randomized controlled	$N = 31$	Prevention of infection after prostate resection Males 48–83 years	PO 3 g daily before and after procedure for a total of 2 doses Follow-up 1 month	6 g	$N = 30$ Placebo	0 (%)	0 (%)
Ferraro et al. [43]	Prospective randomized controlled	$N = 30$	Uncomplicated UTI F and M >50 years	PO 3 g once Follow-up 35 days	3 g	$N = 30$ Norfloxacin 400 mg BID × 7 days	GI disorders—1 (3%)	GI disorders—2 (7%)
Caramalli et al. [45]	Prospective randomized controlled	$N = 20$	Complicated and uncomplicated UTI M and F >60 years	PO 3 g once Follow-up up to 18 months		$N = 76$ Netilmicin 5 mg/kg IM once ($n = 53$) Amikacin 15 mg/kg IM once ($n = 23$)	0 (%)	0 (%)
Reynaert et al. [42]	Prospective randomized controlled	$N = 16$	Uncomplicated UTI F 16–75 years	PO 3 g once Follow-up 5 weeks	3 g	$N = 16$ Norfloxacin × 3 days	GI disorders—1 (6%)	GI disorders—1 (6%)

Table 3 continued

References	Trial type	FOM *N*	Indication Study population	FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Jardin [55]	Prospective comparative	$N = 144$	Uncomplicated UTI F 16–75 years	PO 3 g once Follow-up 28 days	3 g	$N = 144$ Pipemidic acid	37 (27%) Diarrhea—11 (8%) Other AE described as medium and slight and were not specified	27 (19%) Nausea—16 (11%) Other AE described as medium and slight and were not specified
Children								
Principi et al. [44]	Prospective randomized controlled	$N = 71$	UTI F and M 1 month–16 years	PO 2 g once (1 g in children <1 year) Follow-up 30 days	2 g	$N = 64$ Netilmicin 5 mg/kg IM once	4 (6%) GI disorders—3 (4%) Rash—1 (1.5%)	0(%)
Varese [50]	Prospective randomized controlled	$N = 39$	Uncomplicated UTI F and M 6 months–14 years	PO 2 g once Follow-up 30 days	2 g	$N = 35$ Netilmicin 5 mg/kg IM once	0 (0%)	0 (0%)
Careddu et al. [49]	Prospective randomized controlled	$N = 24$	Recurrent UTI M ($n = 2$) and F ($n = 22$) 1–14 years	PO 2 g once Follow-up for 1 month	2 g	$N = 27$ Pipemidic acid 400 or 800 mg (for children > 25 kg) daily × 7 days	0 (0%)	0 (0%)

Table 3 continued

References	Trial type	FOM *N*	Indication Study population	FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Pregnancy								
Zinner [36]	Prospective randomized controlled	$N = 153$	Bacteriuria in pregnancy F 28 ± 5 years	PO 3 g once Follow-up 30 days	3 g	$N = 138$ Pipemidic acid × 7 days	14 (9%) Mainly GI disorders No fetal AEs	20 (15%) Mainly GI disorders
Estebanez et al. [52]	Prospective randomized controlled	$N = 53$	Asymptomatic bacteriuria in pregnancy	PO 3 g once Follow-up 10–14 days, then until the end of pregnancy	3 g	$N = 56$ AC 500/125 mg × 7 days	GI disorders—1 (2%)	GI disorders—11 (20%)
Bayrak et al. [51]	Prospective randomized controlled	$N = 44$	Asymptomatic bacteriuria in the second trimester of pregnancy	PO 3 g once Follow-up 1 week	3 g	$N = 40$ Cefuroxime axetyl 250 mg PO twice daily × 5 days	Rash—1 (2%)	Vaginal candidiasis—2 (5%)
Usta et al. [54]	Prospective randomized controlled	$N = 28$	Uncomplicated UTI Pregnant F with a mean age of 26 years	PO 3 g once Follow-up 2 weeks	3 g	$N = 56$ AC = 27 CA = 29 Both drugs × 5 days	7 (25%) GI disorders—6 (24%) Vaginitis—1 (4%)	20 (36%) GI disorders—14 (25%) Vaginitis—6 (11%)

Table 3 continued

References	Trial type	FOM *N*	Indication Study population	FOM dosing regimen Duration of follow-up after the start of therapy	FOM total dose	COMP *N* Regimen	FOM AE No of events (%)	COMP AE *n* (%)
Thoumsin et al. [56]	Prospective randomized controlled	$N = 13$	Asymptomatic bacteriuria in pregnancy	PO 3 g once Follow-up until birth	3 g	$N = 10$ Nitrofurantoin × 7 days	0 (0%)	GI disorders—2 (20%)

AC amoxicillin clavulanate, *AE* adverse events, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *BSI* bloodstream infection, *CA* Cefuroxime axetil, *CTX* cotrimoxazole, *cIAI* complicated intra-abdominal infection, *CNS* central nervous system, *COMP* comparator, *F* female, *FOM* fosfomycin, *F-up* follow-up, *GI* gastrointestinal, *GTP* γ- guanosine triphosphate, *IM* intramuscularly, *IV* intravenously, *LDH* lactate dehydrogenase, *M* male, *NA* not applicable, *PO* orally, *SD* standard deviation, *SSI* surgical site soft tissue infection, *TID* three times daily, *TMP* trimethoprim, *UTI* urinary tract infection, *VAP* ventilator-associated pneumonia

[a] Including blinded and open label trials

[b] The most common AE reported

comparator arms [10–17]. Seven trials were randomized controlled trials [10, 12–17] and one was a retrospective study [11]. Fosfomycin was used for the treatment of pneumonia including ventilator-associated pneumonia [12, 17], primary bacteremia [17], complicated intra-abdominal infection, UTI [17], skin and soft tissue infections [17], acute hematogenous osteomyelitis in children [11], prevention of infection after urological surgery [13], prophylaxis of surgical site infection after elective total knee arthroplasty [14] and colorectal surgery [10, 15, 16]. Fosfomycin was administered up to 3 weeks at a dose up to 12 g but the majority of patients in these trials (530/664) received fosfomycin for 1–3 days as prophylaxis for surgical site infections.

Parenteral fosfomycin was given in combination with other antibacterial drugs in 6 comparative trials [10–12, 15–17]; antibacterial drugs that were used in combination with fosfomycin and those that were used as comparators are presented in Table 2. The cumulative rate of AEs was similar in fosfomycin and comparator arms. The most common AEs observed in these trials are presented in Table 4.

AEs observed in 15 non-comparative trials of parenteral fosfomycin [18–32] are presented in Table 5. These trials enrolled 578 patients, mainly adults. in combination with other antibacterial drugs in 9 trials (Table 5). Fosfomycin was used at a daily dose of up to 24 g for the treatment of various infections including bloodstream, central nervous system infections and ventilator-associated pneumonia. The duration of treatment ranged from 4 days to 2 months.

AEs associated with oral administration of fosfomycin are presented in Table 6. The majority of these trials studied a single dose of fosfomycin for the treatment of uncomplicated

Table 4 Adverse events associated with parenteral fosfomycin in 8 comparative trials [10–17]

Adverse event	Fosfomycin $N = 664$ n (%)	Comparators $N = 626$ n (%)
Death	32 (5%)	34 (5%)
Acute kidney injury	25 (4%)	28 (4%)
Skin reactions	14 (2%)	17 (3%)
GI disorders	6 (1%)	16 (3%)
Phlebitis	3 (<1%)	0
Eosinophilia	2 (<1%)	2 (<1%)
Abnormal liver tests	6 (1%)	6 (1%)
Leucopenia[a]	1 (<1%)	4 (<1%)

[a] Leucopenia was defined as a leukocyte count <1G/l on one trial [11] and not defined in another [15]

Table 5 Adverse events associated with parenteral administration of fosfomycin in 15 non-comparative trials [18–32]

Adverse event	Fosfomycin $N = 578$ n (%)
Hypokalemia	28 (5%)
Transaminase elevation	10 (2%)
GI disorders	12 (2%)
Rash	11(2%)
Peripheral phlebitis	7 (1%)
Deaths	5 (1%)
Sodium overload and heart failure	5 (1%)
Neutropenia (not defined)	5 (1%)
Injection site pain	4 (1%)
Thrombocytopenia	4 (1%)
Renal toxicity	3 (<1%)
Heart failure	2 (<1%)
Hypertension	2 (<1%)

Table 6 Adverse events associated with oral administration of fosfomycin in 28 prospective comparative trials [33–59, 71]

	Fosfomycin $N = 2743$ n (%)	Comparator $N = 2863$ n (%)
Adverse events	219 (8%)	229 (8%)
GI disorders (nausea, vomiting, diarrhea, abdominal pain)	179 (6.5%)	177 (6%)
Vaginitis	13 (0.5%)	23 (1%)
Central nervous system (headache, dizziness)	10 (<0.5%)	13 (<0.5%)
Rash	11 (<0.5%)	9
Other (asthenia, dyspnea, cough, joint pain)	6 (<0.5%)	8 (<1%)
Hepatic function abnormal	0	1 (<1%)

UTIs. In two trials of prophylaxis of recurrent UTI, fosfomycin was administered for 3–6 months [33, 34]. The most frequently reported adverse reactions (8%) were gastrointestinal disorders. More details are provided in Table 6.

One placebo-controlled trial for prophylaxis of recurrent uncomplicated UTI evaluated safety of a prolonged exposure to oral fosfomycin [33]. The trial compared 166 females treated with 3 g of oral fosfomycin every 10 days for 6 months with 155 subjects treated with placebo. After a follow-up of 360 days including 6 interim evaluations there were 2 (1%) AEs (rash and mild dyspnea) in the treatment arm as compared with 4 events in the placebo arm. Hematology and chemistry laboratory parameters at the end of the study did not show any significant difference between the two arms.

Trials conducted in pediatric population included 3 retrospective trials of parenteral

fosfomycin ($n = 118$) [11, 25, 29] and 3 prospective randomized trials of oral fosfomycin ($n = 134$) [44, 49, 50]. In trials of parenteral fosfomycin, the drug was given up to 4 weeks for the treatment of acute hematogenous osteomyelitis, bacteremia, and lung infection. Oral fosfomycin was administered as a single time dose for the treatment of UTI. There were also several studies of parenteral [18, 24, 26–28] and oral [28, 59, 60] fosfomycin that included children that did not present safety data in children separately. Four pediatric trials were comparative [11, 44, 49, 50]. Overall, no specific safety issues related to the use of fosfomycin in children were identified.

Five trials of a total of 291 patients reported on the use of fosfomycin in pregnancy for the treatment of asymptomatic bacteriuria [36, 51, 52, 54, 56]. One of these trials in 153 patients specifically indicated that no serious fetal AEs were observed [36].

Our review of the literature also identified several reviews reporting on the efficacy and safety of fosfomycin. A meta-analysis of 27 randomized controlled trials compared fosfomycin ($n = 2188$) with other antibacterial drugs ($n = 2052$) for the treatment of cystitis [61]. The authors reported that fosfomycin had a comparable safety profile with the evaluated comparators in non-pregnant women, mixed and pediatric populations, and was associated with fewer AEs in pregnant women [61].

Information on the efficacy and safety of fosfomycin was provided by the Japan Research Committee of Fosfomycin in a report evaluating 1191 and 503 patients who received oral and IV fosfomycin, respectively [62]. For the oral formulation, AEs were observed in 122 of 1191 cases (10%) and included mainly gastrointestinal disturbances.

The report notes that side effects were observed in 17% of patients and included aspartate aminotransferase and glutamic-pyruvate transaminase elevations (although infrequent), pain at the injection site, gastrointestinal disorders, palpitations, and rash.

Mayama et al. analyzed postmarketing experience with oral fosfomycin in Japan by reviewing clinical records of 35,481 patients who were prescribed fosfomycin calcium capsules in 1981–1986 [63]. The overall incidence of side effects was 3.5%. The incidence of side effects was higher at a daily dose >3 g and was not dependent on the duration of administration. The most common side effects were related to gastrointestinal disorders (2.7%), hepatobiliary disorders (0.2%), and skin disorders (0.2%). There was one case of thrombocytopenia and one case of anemia.

There have been a few reports of liver toxicity associated with fosfomycin [64, 65]. An acute painful hepatomegaly, transaminase elevation and a hyperechogenic liver on ultrasound were reported in a 30-year-old female with cystic fibrosis and normal baseline liver function tests and liver ultrasound [64]. The liver abnormalities reoccurred three times during repeated courses of IV fosfomycin for *Pseudomonas aeruginosa* bronchitis. Laboratory and ultrasound abnormalities resolved every time after discontinuation of fosfomycin.

Another report of fosfomycin-induced liver injury described a 50-year-old male with no underlying liver diseases who developed mixed hepatocellular and cholestatic liver injury 3 days after being started on fosfomycin (route is not reported) [65]. His alanine aminotransferase peaked at 12.8 times the upper limit of normal and total bilirubin increased to 42 μmol/L (normal range

<26 μmol/L). Liver function tests normalized 1 week after the withdrawal of the drug.

There have been four case reports of anaphylaxis associated with fosfomycin administration [66–68]. All reported cases were associated with oral formulations of fosfomycin and occurred within minutes to an hour after fosfomycin intake.

DISCUSSION

Fosfomycin has been in clinical use for about 25 years and its safety profile has been previously described [6, 61, 69]. Our review did not identify new safety concerns related to fosfomycin. The most frequent AEs associated with parenteral administration of fosfomycin included rash, peripheral phlebitis, hypokalemia, and gastrointestinal disorders. Gastrointestinal disorders were the most common AEs associated with oral administration.

While the initial results of data mining for all reports of AEs associated with fosfomycin in the FAERS database revealed a higher than expected frequency of reports of agranulocytosis, liver injury, severe skin reactions, and pseudomembranous colitis, subsequent searches for adverse reactions implicating fosfomycin as the primary suspect as well as the literature review did not suggest an association of the drug with these AEs. Serious AEs of cytopenias, liver toxicities, and hypersensitivity reactions were not more frequent in fosfomycin-treated patients in comparative trials and were not common in non-comparative trials.

A separate search and detailed analysis of all FAERS reports of cytopenia identified one case that met pre-defined criteria of aplastic anemia that was associated with the use of oral fosfomycin. No cases of aplastic anemia associated with either oral or parenteral administration of fosfomycin were found by literature search. Considering more than 40-year experience with the drug, fosfomycin-associated aplastic anemia seems to be a rare event.

With regard to liver toxicities, we did not see an imbalance between fosfomycin- and comparator-treated patients in the comparative trials. However, several cases of liver toxicities associated with fosfomycin have been reported and monitoring of liver functions in patients receiving parenteral fosfomycin when the drug is administered for several days may be warranted.

The rates of hypersensitivity reactions were also comparable in fosfomycin- and comparator-treated patients in comparative trials and also four cases of anaphylactic reactions associated with fosfomycin have been reported. Of note, the package insert for oral fosfomycin lists the AEs of aplastic anemia, angioedema, cholestatic jaundice, and hepatic necrosis in the Adverse Reactions/ Postmarketing Experience section [1].

Important safety consideration for parenteral fosfomycin is its high sodium content which may result in sodium overload and heart failure [23, 70]. Thus, each gram of fosfomycin contains 14.35 mEq (330 mg) of sodium. Considering that an average dose of fosfomycin is about 12 g, the sodium load associated with its use may be significant, especially for patients with underlying heart failure. In comparison, piperacillin and tazobactam, the antibacterial drug that is considered to have high sodium content contains 2.36 mEq (54.28 mg) of sodium per gram of piperacillin. A pooled analysis of comparative trials in our review did not demonstrate a higher rate of heart failure in fosfomycin-treated patients. However, a

publication that specifically addressed AEs associated with IV fosfomycin reported that 6% of patients experienced cardiovascular AEs related due to sodium overload [23]. Hypokalemia was the most common AE in this study (26%). Another publication reports on the case of fosfomycin-associated heart failure that promptly resolved after the discontinuation of the drug [70].

Although, fosfomycin was suspected to be the cause of fetal toxicities in 7 cases in the FAERS database, the data mining search demonstrated EB05 scores of 1–2 for these types of AEs, indicating an overall expected frequency of reporting of this adverse reaction. Our review of the literature also did not identify cases of fetal toxicities. Of note, oral fosfomycin is labeled as pregnancy category B.

Our analyses have several limitations. FAERS contains spontaneously submitted data on AEs by the public and reporting biases such as under- and over-reporting of drug events can occur. Because of the spontaneous nature of reporting, the results of this analysis should not be interpreted as a formal comparison of treatment groups or of their relative risks and does not allow one to determine adverse event incidence rates.

The effects of concomitant illnesses or therapy cannot be fully controlled in this data mining analysis. Other factors such as the length of time of marketing, drug usage, and changes in coding practices over time should also be considered when interpreting these data mining results. Given the limitations inherent in the FAERS data, the high scores do not prove causality or an increased relative risk of the drug–AE in all patients exposed to fosfomycin. Another limitation of the FAERS search is that only 5 reports with parenteral administration of fosfomycin were retrieved.

Limitations of the literature review are related to a small number of randomized comparative prospective trials for parenteral fosfomycin and that in 5 out of 7 of these trials the drug was given for up to 3 days for prophylaxis of surgical site infection [10, 13–16]. Only 64 patients were treated with fosfomycin in randomized prospective comparative trials [12, 17]. Another comparative trial was retrospective and enrolled 70 patients in the fosfomycin arm [11].

CONCLUSION

In conclusion, no new safety concerns related to fosfomycin have been identified by this review. In comparative trials serious AEs such as cytopenia, anaphylaxis, and liver toxicities were not more common in fosfomycin-treated patients as compared with those treated with comparator. The most frequently reported AEs associated with parenteral administration of fosfomycin were rash, peripheral phlebitis, hypokalemia, and gastrointestinal disorders. High sodium content of parenteral fosfomycin should be taken into consideration in treating patients with underlying heart disease. An important limitation of the available safety data regarding the parenteral formulation of fosfomycin is that only in a very small number of randomized comparative trials was parenteral fosfomycin administered for a duration that would be expected in the treatment of the majority of infections. Oral formulations of fosfomycin were mostly associated with gastrointestinal disturbances.

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