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Gian M, Pacifici *

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Review Article

Clinical Pharmacology of Cefoxitin

Gian M, Pacifici*

Professor of Pharmacology, Via Sant'Andrea 32, 56126 Pisa, Italy.

***Corresponding Author**: Gian Maria Pacifici, Professor of Pharmacology, Via Sant'Andrea 32, 56126 Pisa, Italy.

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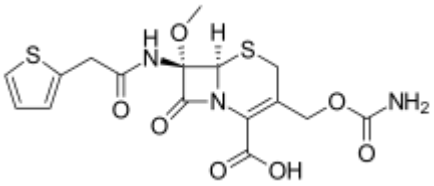
Abstract

Cefoxitin is a second-generation cephalosporin and is resistant to β-lactamases produced by gram-negative rods. Cefoxitin has broad gram-negative activity against most strains of Haemophilus species, indole-positive Proteus species, and Klebsiella species. Cefoxitin is less active than the third-generation cephalosporins against gram-positive bacteria but is more active against anaerobes specially Bacillus fragilis. Cefoxitin effectively and safely treats bacterial infections. The prevention of bacterial infections with cefoxitin, the treatment of bacterial infections with cefoxitin, and the trials conducted with cefoxitin have been reviewed. The pharmacokinetics of cefoxitin have been studied in healthy men volunteers and the elimination half-life of cefoxitin is 0.81+0.04 hours. The concentration of cefoxitin in serum, plasma, and tissues has been reviewed. Cefoxitin achieves lower concentration in fundamental myometrium, in urine segment, and in fallopian tube than in serum. The concentration of cefoxitin in adipose tissue ranges from 3.3% to 6.6% of that in plasma and obese patients undergoing surgery have an inadequate concentration of cefoxitin in adipose tissues to control bacterial infections. Cefoxitin penetrates into the cerebrospinal fluid and the penetration-rate of cefoxitin is higher in inflamed than in uninflamed meninges and cefoxitin sterilizes the cerebrospinal fluid infected by different bacteria. Cefoxitin is a safe cephalosporin and causes little toxicity. The aim of this study is to review cefoxitin efficacy and safely, prevention of bacterial infections, treatment of bacterial infections, trials, pharmacokinetics, penetration into tissues and into the cerebrospinal fluid, treatment of bacterial meningitis, and toxicity.

Keywords: Cefoxitin; molecular; structure

Introduction

Cefoxitin is a second-generation cephalosporin is a technically cephamycin and is resistant to β-lactamases produced by gram-negative rods. Typically of second generation cephalosporin, cefoxitin has broad activity against gram-negative bacteria, including most strains of Haemophilus species, indole-positive Proteus species, and Klebsiella species. Cefoxitin is less active than the third-generation cephalosporins against gram-positive bacteria but is more active against anaerobes especially Bacillus fragilis [1].



Cefoxitin molecular structure (molecular weight = 427.45 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following

Results

Efficacy and safely of cefoxitin in treatment of bacterial infections

Thirty-one patients, aged 60±18 years, had the urinary-tract infected by Escherichia coli or by Klebsiella pneumoniae and received cefoxitin orally at a mean dose of 4 grams daily (range, 2 to 8). The efficacy of cefoxitin was observed in 30 of 31 patients (96.7%) 30-days after start of treatment and in 12 of 14 patients (85.7%) 90-days after start of treatment which was well-tolerated. Cefoxitin effectively and safely treats patients with the urinary-tract infected by Escherichia coli or by Klebsiella pneumoniae [2]. It was assessed the efficacy, safely, and tolerance of cefoxitin in patients with lower respiratory-tract infections. Of 26 patients who could be evaluated clinically, 21 patients (80.8%) responded satisfactorily to treatment and there were neither adverse-effects nor renal or hematologic toxicity. These results suggest that cefoxitin is an efficacious, safe, and well-tolerated antibiotic in treatment of patients with lower respiratory-tract infections [3]. The efficacy and safely of cefmetazole versus those of cefoxitin were assessed in 40 hospitalized patients with lower respiratory-tract infections. The number of patients evaluable for efficacy was 23 of 25 (92.0%) in the cefmetazole group and 13 of 15 (86.7%) in the cefoxitin group. The causative bacteria were eradicated in 23 of 25 patients (92.0%) who received cefmetazole and in 14 of 15 patients (93.3%) who received cefoxitin and both treatments were well-tolerated. Cefmetazole is efficacy and safe as cefoxitin in treatment of hospitalized patients with lower respiratory-tract infections [4]. It was compared the clinical and the microbiological efficacy of cefoxitin versus those of carbapenem in treatment of patients with febrile urinary-tract infections caused by extended spectrum β-lactamase-producing Escherichia coli. The clinical success was observed in 17 of 23 patients (73.9%) who

received cefoxitin and in 22 of 27 patients (81.5%) who received carbapenem and the microbiological success was observed in 11 of 19 patients (57.9%) who received cefoxitin and in 6 of 12 patients (50.0%) who received carbapenem. These results indicate that cefoxitin and carbapenem are effective treatments of patients with urinary-tract infections caused by extended spectrum β-lactamase-producing Escherichia coli [5]. One-hundred-seventeen women had acute pelvic inflammatory disease caused by Neisseria gonorrhoeae or by Chlamydia trachomatis and received either ampicillin/sulbactam or cefoxitin intravenously. Isolates of Neisseria gonorrhoeae were recovered from 59.1% of women and those of Chlamydia trachomatis were recovered from 40.9% of women. Ampicillin/sulbactam cured 75 of 76 women (98.7%) and cefoxitin cured 37 of 41 women (90.2%) and both treatments were well-tolerated. Ampicillin/sulbactam is effective and safe as cefoxitin in treatment of women with pelvic infection caused by Neisseria gonorrhoeae or by Chlamydia trachomatis [6]. Forty-four hospitalized patients received either piperacillin intravenously at the daily dose of 18 grams or cefoxitin intravenously at the daily dose of 12 grams and the treatments lasted for a mean time of 11.5 days. The infection sites were lower respiratory-tract, urinary-tract, gastrointestinal-tract, skin, skin-structures, and bones. Twenty of 23 patients (86.9%) who received piperacillin and 19 of 21 patients (90.5%) who received cefoxitin were cured or improved. Piperacillin and cefoxitin are clinically effective and safe antibiotics for the treatment of bacterial infection in different organs [7].

Prevention of bacterial infections with cefoxitin

Two-hundred patients with a mean age of 46±12 years and with a mean body-mass-index of 45.8±6.9 kg/m^2 undergoing bariatric surgery received cefoxitin orally at the daily dose of 4 grams. The percentage of patients who met the pharmacokinetic/pharmacodynamic target of cefoxitin was 37.3%, 1.1% and 0% for Staphylococcus aureus, Enterobacteriaceae and anaerobic bacteria, respectively. In these patients, 4 grams daily of cefoxitin led to an inadequate treatment of infections caused by Staphylococcus aureus, Enterobacteriaceae or by anaerobic bacteria [8]. Cefoxitin was administered intravenously at the dose of 2 grams 4 times-daily to 11 patients undergoing colorectal surgery who were infected by anaerobic cocci or by gram-negative bacteria. The serum concentrations of cefoxitin ranged from 107 to 664 µg/ml (mean, 296±610) 15 min after administration. Cefoxitin concentration in the faecal samples ranged from 0 to 57.7 µg/gram and that in tissue samples ranged from 9.0 to 68.3 µg/gram. The number of anaerobic cocci and gram-negative bacteria decreased two days after the start of therapy thus cefoxitin prevents bacterial infection in patients undergoing colorectal surgery [9]. Cefoxitin was administered intravenously at the dose of 2 grams 4 times-daily to 20 patients undergoing colorectal surgery who were infected by anaerobic bacteria, Bacteroides, and other gram-negative bacteria. The maximum serum concentration of cefoxitin during surgery ranged from 25 to 100 µg/ml, that in faecal samples ranged from 1.5 to 35 µg/gram, and that in tissue samples ranged from 2.0 to 50 µg/gram. The number of anaerobic bacteria, Bacteroides, and other gram-negative bacteria decreased significantly during cefoxitin therapy thus cefoxitin prevents bacterial infections in patients undergoing colorectal surgery [10]. Sixty-eight infants and children (9 neonates, 34 infants, and 25 children) undergoing cardiopulmonary bypass received cefoxitin intravenously. The mean unbound cefoxitin concentration in serum was 1.7 µg/ml and varied 150-fold and 340-fold at admission of cardiac intensive care unit and after 24 hours, respectively. The variability of unbound cefoxitin serum concentration prevents the use of cefoxitin for the prevention of bacterial infections in infants and children undergoing cardiac surgery [11]. The prophylaxis with piperacillin-tazobactam or with cefoxitin was assessed in patients undergoing surgery. Of 778 patients 378 patients (48.6%) received piperacillin-tazobactam intravenously and 400 patients (51.4%) received cefoxitin intravenously. The percentage of surgical-site infection at 30-days of treatment was lower in patients who received piperacillin-tazobactam than in patients who received cefoxitin (19.8% and 32.8%, respectively, P-value < 0.001). Patients treated with piperacillin-tazobactam had lower-rate of postoperative sepsis than patients treated with cefoxitin (P-value = 0.02). Piperacillin-tazobactam is more effective than cefoxitin in the prophylaxis of patients undergoing surgery [12]. The prophylaxis of surgical-site infections was assessed with piperacillin-tazobactam or with cefoxitin. Patients received either 1 to 2 grams of cefoxitin intravenously or 3.375 to 4.5 grams of piperacillin-tazobactam intravenously within 60 min of surgical incision. The primary outcome was 30-days postoperative infection and the secondary outcome included 30-days postoperative mortality. Piperacillin-tazobactam is more effective and safe than cefoxitin in the prophylaxis of postoperative surgical-site infections [13]. It was examined the efficacy of prophylactic cefotetan and that of cefoxitin in treatment of postoperative wound infections in patients undergoing appendectomy. One-hundred-thirty-six patients with a clinical diagnosis of appendicitis were divided into three groups: patients of group A received 2 grams of cefotetan preoperatively, patients of group B received 2 grams of cefoxitin preoperatively, and patients of group C received 2 grams of cefoxitin preoperatively followed by three postoperative doses. Single-dose cefotetan is more effective than single-dose of cefoxitin and single-dose of cefotetan is effective as multiple-doses cefoxitin in preventing infections in patients undergoing appendectomy [14]. One-hundred-sixty-four patients received 2 grams of cefotetan preoperatively and 75 patients received 2 grams of cefoxitin preoperatively and all patients were submitted to colorectal surgery. The mean concentration of cefotetan in plasma, in specimens of colon, and in specimens of subcutaneous fat was 128±61.8 µg/ml, 57.2±40.4 µg/gram, and 26.8±19.4 µg/gram, respectively. The adverse-effects occurred in 12% patients who received cefotetan and in 12% of patients who received cefoxitin. A single-dose of 2 grams of cefotetan administered preoperatively is effective and safe as a single-dose of 2 grams of cefoxitin give preoperatively in reducing postoperative wound infections in patients undergoing colorectal surgery [15]. It was compared the efficacy of a single-dose of cefotetan versus multiple-doses of cefoxitin in preventing infections in patients undergoing colorectal surgery. Two-hundred-six patients received 1 gram of cefoxitin preoperatively and this dose was also administered 3, 6, and 12 hours after the start of surgery (group A) and 197 patients received a single-dose of 2 grams of cefotetan (group B) and both drugs were administered intravenously. The abdominal wound infection-rate was 11.2% in patients of group A and 9.1% in patients of group B (P-value > 0.05). The number of patients with infections at nonsurgical-sites was significantly greater in patients of group A than in patients of group B (17.0% versus 9.1%, P-value < 0.05). The mean postoperative hospital stay was similar in both groups of patients (15.1 versus 15.9 days). Both drugs were inadequate in preventing infections in the operative field [16]. Clinical practice guidelines recommend 2 grams of cefotetan or cefoxitin for surgical prophylaxis. One-hundred-seventy-five patients undergoing surgery were included in the study, 141 patients (80.6%) received 2 grams of cefotetan intravenously and 34 patients (19.4%) received 2 grams of cefoxitin intravenously. Surgical-site infections occurred in 20.7% of patients who received cefotetan and in 22.9% of patients who received cefoxitin (P-value = 0.78). There was no difference in the number of drug-related adverse-effects in patients who received cefotetan and in those who cefoxitin thus the prophylaxis of surgery infections with cefotetan is equivalent to that with cefoxitin [17]. One-hundred-thirty-three patients undergoing abdominal surgery were enrolled, 62 patients (46.6%) received 3 grams of ampicillin-sulbactam intravenously and 71 patients (53.4%) received 2 grams of cefoxitin intravenously, and both drugs were administered before surgery. The overall postoperative infection-rate was 12.9% in patients who received ampicillin-sulbactam and 9.8% in patients who received cefoxitin (P-value > 0.05) and the adverse-effects occurred in 13.2% of patients who received ampicillin-sulbactam and in 19.1% of patients who received cefoxitin (P-value > 0.05). Both drugs are similarly effective and safe in preventing infections in patients undergoing abdominal surgery [18].

Treatment of bacterial infections with cefoxitin

A study evaluated the prolonged or continuous infusion of cefoxitin to treat patients with urinary-tract infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae which had a minimum inhibitory concentration (MIC) ranging from 0.5 to 64 µg/ml. In patients infected by extended-spectrum-β-lactamase-producing Enterobacteriaceae which had a MIC ≤ 6 µg/ml the pharmacokinetic/pharmacodynamic (PK/PD) objectives were achieved with prolonged or continuous infusion. In contrast, when the MIC was ≥ 8 µg/ml only the continuous infusion achieved the PK/PD objectives [19]. A total of 136 patients with uncomplicated gonorrhoea were

enrolled, 25 patients (18.4%) received cefoxitin intramuscularly at the dose of 2 grams and 111 patients (81.6%) received cefoxitin intramuscularly at the dose of 1 gram and all patients had uncomplicated gonococcal urethritis caused by penicillinase-producing Neisseria gonorrhoeae. One gram of cefoxitin cured 95.0% of patients and 2 grams of cefoxitin cured 98.2% of patients (P-value > 0.05). One gram of cefoxitin is sufficient to treat patients with uncomplicated gonococcal urethritis caused by penicillinase-producing Neisseria gonorrhoeae [20]. Ten men and 15 women were infected by β-lactamase-producing Neisseria gonorrhoeae and received either 1 gram or 2 grams of cefoxitin intramuscularly. All cases of gonococcal cervicitis and urethritis were cured and there was no discernible difference between the efficacy of 1 gram and 2 grams of cefoxitin thus 1 gram of intramuscular cefoxitin is sufficient to treat gonococcal cervicitis and urethritis caused by β-lactamase-producing Neisseria [21]. A single intramuscular dose of 2 grams of cefoxitin effectively treats patients with urethritis caused by penicillinase-producing Neisseria gonorrhoeae [22]. One-hundred-twenty-eight patients had gonococcal urethritis caused by penicillinase-sensitive or by penicillinase-resistant Neisseria gonorrhoeae and received 2 grams of cefoxitin intramuscularly and all patients were cured [23]. Cefoxitin was administered intravenously at a dose of 1 gram or 2 grams thrice-daily or 6 times-daily to 47 patients with orthopaedic infections. Thirty-one patients (66.0%) had acute or chronic infections of bones, joint, muscle, and tendon and were cured. Sixteen patients (34.0%) with spinal cord infections caused by Serratia or by indole-positive Proteus were cured thus cefoxitin effectively treats patients with orthopaedic infections [24]. Cefoxitin was intravenously infused at the dose of 2 grams 4 times-daily for 1 hour (group A), or 2 grams 4 times-daily of cefoxitin were infused for 4 hours (group B), or 8 grams of cefoxitin were continuously infused (group C) to patients with urinary-tract infections due to extended-spectrum-β-lactamase-producing Escherichia coli. The treatment success was greater in patients of group C than in those of groups A and B [25]. Fifty-nine patients with skin and soft-tissue infections received either cefmenoxime or cefoxitin intravenously at the dose of 0.5 and 2 grams, respectively, 4 times-daily for 7 days. Eight patients (13.5%) had concomitant bacteraemia and 10 patients (16.9%) had serious underlying disease. All patients were cured and both treatments were well-tolerated [26]. Cefmenoxime was administered intravenously at the daily dose of 0.5 to 1 gram and cefoxitin was administered intravenously at the daily dose of 1 to 2 grams and both drugs were administered 4 times-daily for 10 days to patients with serious bacterial infections. All patients were cured and both antibiotics were well-tolerated [27]. Amdinocillin and cefoxitin were co-administered intravenously at the daily dose of 40 and 100 mg/kg, respectively, for 5 to 14 days to 17 patients with complicated urinary-tract infections and this drug combination efficaciously and safely treated these patients [28].

Trials conducted with cefoxitin

A clinical trial was conducted in 266 pregnant women undergoing Caesarean section, 138 pregnant women (51.9%) received 2 grams of cefoxitin intravenously before the Caesarean section and 128 pregnant women (48.1%) were not treated. Treated pregnant women had significantly fewer serious infections (4.3% versus 19.5%), fewer urinary tract infections (4.4% versus 10.7%), less standard febrile morbidity (3.6% versus 9.4%), and fewer courses of antibiotics postoperatively (11.6% versus 23.4%) than untreated pregnant women. The use of perioperative cefoxitin effectively prevents infections in pregnant women undergoing Caesarean section [29]. A clinical trial was conducted in 657 patients infected by gram-positive cocci, gram-negative bacilli, or by anaerobes bacteria and 92.3% of patients were cured or improved. Bacteriologic response to therapy with cefoxitin occurred in 94.3% of patients infected by gram-positive cocci, in 87.5% of patients infected by gram-negative bacilli, and in 95.2% of patients infected by anaerobes bacteria [30]. A clinical trial was conducted in 86 patients with severe (66.3%), moderate (31.4%) and mild (1.2%) bacterial infections caused by gram-positive cocci or by aerobic gram-negative bacilli. The patients received cefoxitin orally at the daily dose of 2 grams and the clinical cure-rate occurred in 93.0% of patients [31]. A single-site, randomized, prospective, blind, comparative, parallel-treatment trial was conducted in 93 women with a diagnosis of pelvic inflammatory disease. Forty-seven women (50.5%) received ampicillin/sulbactam intravenously at the dose of 2 gram/1 gram 4 times-daily and 46 women (49.5%) received cefoxitin intravenously at the dose of 2 grams 4 times-daily. Ampicillin/sulbactam and cefoxitin have similar bacteriological efficacy in treatment of women with acute pelvic inflammatory disease [32]. A randomized, double-blind trial compared the clinical and bacteriologic efficacy of ampicillin/sulbactam administered intravenously at the dose of 2 grams/1 gram 4 times-daily versus those of cefoxitin administered intravenously the dose of 2 grams 4 times-daily in 96 patients with cutaneous or with soft-tissue bacterial infections. The cure or improvement occurred in 89.8% of patients who received ampicillin/sulbactam and in 93.6% of patients who received cefoxitin (P-value > 0.05). The median time to resolution of all symptoms was 10.5 days with ampicillin/sulbactam treatment and 15.5 days with cefoxitin treatment (P-value > 0.05). Ampicillin/sulbactam and cefoxitin are equally effective in treatment of patients with cutaneous and soft-tissue bacterial infections [33]. A double-blind, randomized trial was conducted in 70 women who were treated with cefotetan intravenously at the dose of 2 grams twice-daily and in 70 women who received cefoxitin intravenously at the dose of 2 grams 4 times-daily. All women had endometritis following Caesarean section and the cure-rate was 83.2% in women treated with cefotetan and 79.5% in women treated with cefoxitin (P-value = 0.56). Cefotetan and cefoxitin are equally effective and well-tolerated in treating women with endometritis [34]. An open-label, multicentre, randomized phase 3 clinical trial was conducted to test the efficacy of piperacillin-tazobactam versus that of cefoxitin in treating surgical-site infection in 778 patients undergoing surgery. Of 778 patients 378 patients (48.6%) received piperacillin-tazobactam intravenously at the daily dose of 4 grams and 400 patients (51.4%) received cefoxitin intravenously at the daily dose of 2 grams. Patients treated with piperacillin-tazobactam had lower-rate of postoperative sepsis than patients treated with cefoxitin (4.2% versus 7.5%; P-value = 0.02) and had lower clinically relevant postoperative pancreatic fistula (12.7% versus 19.0%; P-value = 0.03). In patients undergoing open pancreatoduodenectomy piperacillin-tazobactam is more effective than cefoxitin in reducing the postoperative surgical-site infection [35]. A clinical trial was conducted in 1052 pregnant women undergoing Caesarean section who received either ceftriaxone intravenously at the daily dose of 1 gram (N = 520, 49.4%) or cefoxitin intravenously at the dose of 1 gram thrice-daily (N = 532, 50.6%). Urinary-tract infection was significantly more frequent in patients who received cefoxitin than in patients who received ceftriaxone (17.8% versus 9.7%; P-value < 0.001). A single-dose of 1 gram of ceftriaxone is more effective than 3 doses of 1 gram of cefoxitin in treating urinary-tract infections in pregnant women undergoing Caesarean section [36].

Pharmacokinetics of cefoxitin

Ko et al. [37] studied the pharmacokinetics of cefoxitin in 16 healthy men volunteers who received a single intravenous dose of 2 grams of cefoxitin. Volunteers were aged 20 to 49 years (mean, 31), the height of volunteers ranged from 166 to 186 centimetres (mean, 175), and the body-weight of volunteers ranged from 61 to 105 kg (mean, 77). Table 1 summarizes the pharmacokinetic parameters of cefoxitin.

Peak conc. (µg/ml)	Elimination half-life (h)	Distribution volume (L)	AUC (µg*h/ml)	Urinary recovery (%)	TBC (ml/min)	Renal clearance (ml/min)
244±10	0.81±0.04	12.8±0.42	129±5.4	76.7±5.2	279±12	221±34

AUC = area under the concentration-time curve. TBC = total body clearance.

Table 1. Pharmacokinetic parameters of cefoxitin which have been obtained in 16 healthy men volunteers following a single intravenous dose of 2 grams of cefoxitin. The values are the mean±SD, by Ko et al. [37].

This table shows that cefoxitin is rapidly eliminated as the mean elimination half-life is 0.81 hours, the distribution volume of cefoxitin is lower than the water volume, two-thirds of the dose of cefoxitin are recovered in the urine, and the renal clearance is similar to the total body clearance.

Bawdon et al. [38] administered a single intramuscular dose of 2 grams of cefoxitin to 32 women scheduled for elective abdominal hysterectomy. Table 2 summarizes the concentration of cefoxitin in serum and tissues at different times after cefoxitin administration.

Concentration of cefoxitin in serum, plasma, and tissues

		Cefoxitin concentration (µg/ml)				Tissue to serum ratio of cefoxitin concentration		
Time after hysterectomy (min)	No of women	Serum	Fundal myometrium	Lower uterine segment	Fallopian tube	Fundal myometrium	Lower uterine segment	Fallopian tube
110 – 139	4	21.2±10.9	12.0±4.6	11.9±8.6	14.7±5.3	0.566	0.561	0.693
140 – 169	8	19.1±6.5	9.9±4.8	9.7±4.8	9.1±4.7	0.471	0.506	0.476
170 – 199	11	12.9±7.4	6.7±2.3	7.0±2.3	7.0±3.3	0.532	0.556	0.556
200 – 229	7	12.7±7.3	5.7±2.7	4.6±1.2	4.6±1.8	0.449	0.362	0.362
230 – 259	1	6.3	4.5	4.5	6.5	0.714	0.714	1.031
260 – 330	1	1.7	0.3	0.3	0.3	0.176	0.176	0.176

Table 2. Serum and tissue concentrations of cefoxitin which have been obtained in 32 women submitted to abdominal hysterectomy. A single-dose of 2 grams of cefoxitin was administered intramuscularly to all women. Values are the mean±SD, by Bawdon et al. [38].

This table shows that the concentration of cefoxitin is lower concentration in fundal myometrium, in lower uterine segment, and in fallopian tube than in serum and the concentration of cefoxitin in these tissues decays at the same rate as that in serum.

Brunetti et al. [39] administered a single intravenous dose of 2 grams of cefoxitin to 6 patients aged 48.7±6.2 years, weighing 48.9±5.9 kg, with a body-mass-index of 42.8±7.1 kg/m^2. Specimens of adipose tissue were sampled at the time of skin incision. Four patients had a mean concentration of cefoxitin in adipose tissue of 16 µg/ml and 2 patients had a mean concentration of cefoxitin in adipose tissue of 8 µg/ml. The mean concentration of cefoxitin in plasma was 244 µg/ml thus the concentration of cefoxitin in adipose tissue ranges from 3.3% to 6.6% of that in plasma.

Toma et al. [40] enrolled 27 obese patients who underwent surgery. Fourteen patients with a body-mass-index of 43.2±10 kg/m^2 received a single intravenous dose of 2 grams of cefoxitin and 13 patients with a body-mass-index of 20.0±2 kg/m^2 received a single intravenous dose of 1 gram of cefoxitin. Specimens of adipose tissue were sampled at surgery and there was an inverse relationship between the penetration of cefoxitin in adipose tissue (AUC-tissue to AUC-plasma ratio) and the body-mass-index (0.08±0.07 versus 0.37±0.26; P-value < 0.05). The concentration of cefoxitin in adipose tissue was 7.8±7.3 and 2.7±1.4 µg/gram at skin incision and closure, respectively. Obese patients who have an impaired penetration of cefoxitin in adipose tissue have an inadequate tissue concentration of cefoxitin which is a risk of infections at surgery.

Penetration of cefoxitin into the cerebrospinal fluid (CSF)

Galvao et al. [41] administered cefoxitin intravenously at the dose of 2 grams 4 times-daily to 25 patients with purulent meningitis caused by Streptococcus pneumoniae (N = 9), Staphylococcus aureus (N = 2), Neisseria meningitidis (N = 5), Haemophilus influenzae (N = 1), Proteus species (N = 2), and 6 patients had negative culture. CSF samples were obtained before and 2, 4, or 6 hours after the first-dose and the third-dose of cefoxitin. The concentration of cefoxitin in the CSF ranged from 1.2 to 22.0 µg/ml with a majority of the concentration falling within the range of 1.2 to 6.2 µg/ml. The concentration of cefoxitin tended to be higher in CSF sampled after the third-dose than after the first-dose indicating that cefoxitin accumulates in the CSF. The peak concentration of cefoxitin in CSF occurred between 2 and 6 hours after administration. In patients with bacterial meningitis, it should be possible to achieve therapeutic cefoxitin concentrations in CSF by using nontoxic doses of cefoxitin. Humbert et al. [42] measured the concentration of cefoxitin in serum and in the CSF of 3 groups of patients. Twelve patients had aseptic meningitis (group A) and 17 patients (group B) and 14 patients (group C) had bacterial meningitis. The patients of group A received a single intravenous dose of 2 grams of cefoxitin and patients of groups B and C received 2 grams of cefoxitin intravenously 6 times-daily on days 3 and 4 of therapy and on day 10. The concentration of cefoxitin in the CSF was undetectable (< 1.5 µg/ml) in 11 of 12 patients (91.7%) of group A and the concentration of cefoxitin of 2.8 and 30 µg/ml was measured in the CSF and in serum, respectively, in the 12th patient of group A. In patients of group B, the mean CSF concentration was 3.3, 4.7, and 2.9 µg/ml on days 3, 4, and 10, respectively, of treatment, with simultaneous serum concentration of 8, 9, and 8 µg/ml. At similar time periods, the mean concentration of cefoxitin in patients of group C was 8.6, 12.3, and 4.3 µg/ml in the CSF and 57, 35, and 27 µg/ml in serum. These results indicate that in patients of groups B and C the ratio of the concentration of cefoxitin in CSF to that in serum ranges from 15% to 50%. A total of 25 patients with bacterial meningitis received cefoxitin intravenously at the dose of 4 grams thrice-daily or 4 times-daily. In patients with uninflamed meninges, the concentration of cefoxitin in the CSF was about 7% of that in serum. In patients with inflamed meninges, the concentration of cefoxitin in the CSF ranges from 30% to 70% of that in serum [43]. Feldman et al. [44] administered 3 consecutive intravenous doses of 75 mg/kg of cefoxitin 4 times-daily to 24 patients with meningitis on days 4, 5, 9, and 10 of therapy. Haemophilus influenzae type b was isolated in the CSF of 21 patients, Streptococcus pneumoniae was isolated in the CSF of 2 patients, and Neisseria meningitidis was isolated in the CSF of 1 patient. The median minimal inhibitory concentration and the median bactericidal concentration of cefoxitin for strains of Haemophilus influenzae type b were 0.312 and 0.625 µg/ml, respectively. Twenty of 21 strains of Haemophilus influenzae type b (95.2%) and the strains of Streptococcus pneumoniae and Neisseria meningitidis were killed by a concentration of 2.5 µg/ml of cefoxitin. The mean concentration of cefoxitin in the CSF was 4.9 µg/ml which appeared from 1 to 6 hours on days 5 and 10 of treatment. These data indicate that following this dosage, cefoxitin reaches sufficient concentration in the CSF required for killing susceptible strains of Haemophilus influenzae type b, Streptococcus pneumoniae, and Neisseria meningitidis [44].

Treatment of bacterial meningitis with cefoxitin

Little is known about the treatment of bacterial meningitis with cefoxitin. Galvao et al. [41] administered cefoxitin intravenously at the dose of 2 grams 4 times-daily to 25 patients with purulent meningitis caused by Streptococcus pneumoniae (N = 9), Staphylococcus aureus (N = 2), Neisseria meningitidis (N = 5), Haemophilus influenzae (N = 1), Proteus species (N = 2), and 6 patients had negative culture and this treatment sterilized the cerebrospinal fluid. Feldman et al. [44] administered 3 consecutive intravenous doses of 75 mg/kg 4 times-daily of cefoxitin on days 4, 5, 9, and 10 of therapy to 24 patients with meningitis. Haemophilus influenzae type b was isolated from the CSF of 21 patients, Streptococcus pneumoniae was isolated in the CSF of 2 patients, and Neisseria meningitidis was isolated from the CSF of 1 patient and this treatment sterilized the cerebrospinal fluid.

Toxicity induced by cefoxitin

Cefoxitin is a safe cephalosporin thus little is known about the toxicity induced by cefoxitin. The hypersensitivity reactions caused by cefoxitin are

observed in a frequency similar to that found with cephalosporins. No case of anaphylactic shock has been observed. In contrast to cephalosporins, cefoxitin does not to cause any impairment of the renal function. The few gastrointestinal disturbances reported indicate that cefoxitin does not significantly affect the normal bowel flora. In a small percentage of patients, reversible, mild, or moderate increases of liver transaminases and/or alkaline phosphatase are noted. Positive direct Coombs test without haemolysis is found in a frequency similar to that found with cephalosporins. Clinical superinfections caused by cefoxitin-resistant microorganisms, mainly by Pseudomonas, Enterobacter, and fungi are observed at the same extent as can be expected with broad-spectrum antibiotics. The available experience clearly demonstrates that cefoxitin shares the safely of other β-lactam antibiotics without causing high frequency of rashes observed with ampicillin and cefoxitin is free of serious nephrotoxicity [45]. A 77-year-old man received cefoxitin for the treatment of peritonitis. He developed haemolytic anaemia and became clinically jaundiced. The patient was switched from cefoxitin to doxycycline, his total bilirubin concentration decreased, and his haematocrit increased [46].

Discussion

Cefoxitin is a second-generation cephalosporin is a technically cephamycin and is resistant to β-lactamases produced by gram-negative rods. Cefoxitin has a broad activity against gram-negative bacteria including most strains of Haemophilus species, indole-positive Proteus species, and Klebsiella species. Cefoxitin is less active than the third-generation cephalosporins against gram-positive bacteria but is more active against anaerobes especially Bacillus fragilis [1]. The efficacy and safely of cefoxitin in treatment of bacterial infections have been reviewed. Cefoxitin administered orally at a mean dose of 4 grams daily effectively and safely treats patients with urinary-tract infections caused by Escherichia coli or by Klebsiella pneumoniae [2], and cefoxitin effectively and safely treats patients with lower respiratory-tract infections [3], cefmetazole is efficacy and safe as cefoxitin in treatment of patients with lower respiratory-tract infections [4], cefoxitin is similarly efficacy and safe as cefoxitin in treatment of patients with febrile urinary-tract infections caused by extended spectrum β-lactamase-producing Escherichia coli [5], ampicillin/sulbactam is efficacy and safe as cefoxitin in treatment of women with pelvic infections caused by Neisseria gonorrhoea or by Chlamydia trachomatis [6], piperacillin administered intravenously at the daily dose of 18 grams is efficacy and safe as cefoxitin administered intravenously at the daily dose of 12 grams in treatment of patients with lower respiratory-tract, urinary-tract, gastrointestinal-tract, skin, skin-structure, and bone infections [7]. The prevention of bacterial infections with cefoxitin has been reviewed. Cefoxitin was administered orally at the daily dose of 4 grams to patients undergoing bariatric surgery and the percentages of patients who met the pharmacokinetic/pharmacodynamic target of cefoxitin was 37.3%, 1.1%, and 0% for Staphylococcus aureus, Enterobacteriaceae, and anaerobic bacteria, respectively. Four grams daily of cefoxitin lead to an inadequate treatment of infections caused by these bacteria [8], cefoxitin was administered intravenously at the dose of 2 grams 4 times-daily to patients undergoing colorectal surgery who were infected by anaerobic cocci or by gram-negative bacteria. The mean concentration of cefoxitin in serum was 296±610 μg/ml and that in tissue samples ranged from 9.0 to 68.3 μg/ml and the number of anaerobic cocci and gram-negative roads decreased two days after the start of therapy thus cefoxitin prevents infections caused by anaerobic cocci or by gram-negative roads in patients undergoing colorectal surgery [9], cefoxitin was administered intravenously at the dose of 2 grams 4 times-daily to patients undergoing colorectal surgery who were infected by anaerobic bacteria, Bacteroides, and other gram-negative bacteria. The maximum serum concentration of cefoxitin ranged from 25 to 100 μg/ml, that in faecal samples ranged from 1.5 to 35 μg/ml, and that in tissue samples ranged from 2.0 to 40 μg/gram. The number of anaerobic bacteria, Bacteroides, and other gram-negative bacteria decreased significantly during cefoxitin therapy thus cefoxitin prevents infections caused by anaerobic bacteria, Bacteroides, and other gram-negative bacteria in patients undergoing colorectal surgery [10], infants and children undergoing cardiopulmonary bypass received cefoxitin intravenously and the unbound serum concentration of cefoxitin varied 150-fold and 340-fold at admission of cardiac intensive care unit and after 24 hours, respectively. This variability of unbound cefoxitin concentration prevents the use of cefoxitin for the prevention of infections in infants and children undergoing cardiac surgery [11], the prophylaxis with piperacillin-tazobactam or with cefoxitin was assessed in patients undergoing surgery and the percentage of surgical-site infection at 30-days of treatment was lower in patients who received piperacillin-tazobactam than in patients who received cefoxitin (P-values < 0.001). Patients who received piperacillin-tazobactam had lower-rate of postoperative sepsis than patients who received cefoxitin (P-value = 0.02). Piperacillin-tazobactam is more effective than cefoxitin in the prophylaxis of patients undergoing surgery [12]. The prophylaxis of surgical-site infections was assessed with piperacillin-tazobactam or with cefoxitin. Patients received either 1 to 2 grams of cefoxitin intravenously or 3.3375 to 4.5 grams of piperacillin-tazobactam intravenously within 60 min of surgical incision. The primary outcome was 30-days postoperative infection and the secondary outcome was 30-days postoperative mortality. Piperacillin-tazobactam is more effective and safe than cefoxitin in the prophylaxis of postoperative surgical-site infections [13], a study was performed to examine the efficacy of prophylactic cefotetan and cefoxitin in treatment of patients undergoing appendectomy. Patients were divided into three groups: patients of group A received 2 grams of cefotetan preoperatively, patients of group B received 2 grams of cefoxitin preoperatively, and patients of group C received 2 grams of cefoxitin preoperatively followed by three postoperative doses. Single-dose cefotetan is more effective than single-dose of cefoxitin and multiple-doses cefoxitin and single-dose of cefotetan are equally effective in preventing bacterial infections in patients undergoing appendectomy [14], patients undergoing colorectal surgery received either a single-dose of 2 grams of cefotetan preoperatively or a single-dose of 2 grams of cefoxitin preoperatively. The incidence of adverse-effects was 12% in patients who received cefotetan and in patients who received cefoxitin. A single-dose of 2 grams of cefotetan given preoperatively is effective as a single-dose of 2 grams of cefoxitin given preoperatively in reducing postoperative wound infections in patients submitted to colorectal surgery [15], patients undergoing colorectal surgery received either 1 gram of cefoxitin preoperatively and this dose was also given 3, 6, and 12 hours after the start of surgery or a single-dose of 2 grams of cefotetan preoperatively. The number of patients with infections at nonsurgical-sites was significantly higher in patients treated with cefoxitin than in patients treated with cefotetan (P-value < 0.05). The mean postoperative hospital stay was similar in patent who received cefoxitin and in patients who receive cefotetan. Both drugs are inadequate in preventing infections in the operative field [16], patients undergoing surgery received either 2 grams of cefotetan intravenously or 2 grams of cefoxitin intravenously and the surgical-site infections occurred in 20.7% of patients who received cefotetan and in 22.9% of patients who received cefoxitin (P-value = 0.78) thus cefotetan prevents surgical infections as cefoxitin [17], patients undergoing abdominal surgery received either 3 grams of ampicillin-sulbactam preoperatively or 2 grams of cefoxitin preoperatively and both drugs were administered intravenously. The overall postoperative infection-rate was 12.9% in patients who received ampicillin-sulbactam and 9.8% in patients who received cefoxitin (P-value > 0.05) and both treatments were well-tolerated. Ampicillin-sulbactam and cefoxitin are similarly effective in preventing infections in patients undergoing abdominal surgery [18]. The treatment of bacterial infections with cefoxitin has been reviewed. A study evaluated the prolonged or continuous infusion of cefoxitin to treat patients with urinary-tract infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae which had a MIC ranging from 0.5 to 64 μg/ml. In patients infected by extended-spectrum-β-lactamase-producing Enterobacteriaceae which had a MIC ≤ 6 μg/ml the pharmacokinetic/pharmacodynamic objectives were achieved with prolonged or continuous infusion. In contrast, when the MIC was ≥ 8 μg/ml only continuous infusion achieved the pharmacokinetic/pharmacodynamic objectives [19], patients with uncomplicated gonorrhoea urethritis caused by penicillinase-producing Neisseria gonorrhoea received either 2 grams of cefoxitin or 1 gram of cefoxitin intramuscularly. One gram of cefoxitin cured 95.0% of patients and 2 grams of cefoxitin cured 98.2% of patients (P-value > 0.05) thus 1 gram of cefoxitin is sufficient to treat patients with uncomplicated gonococcal urethritis caused by penicillinase-producing Neisseria gonorrhoeae [20], 10 men and 15 women were infected by β-

lactamase-producing Neisseria gonorrhoea and received either 1 gram or 2 grams of cefoxitin intramuscularly. All cases of gonococcal cervicitis or urethritis are cured thus 1 gram of cefoxitin is sufficient to treat all cases of gonococcal cervicitis and urethritis [21], a single intramuscular dose of 2 grams of cefoxitin effectively treats patients with urethritis caused by Neisseria gonorrhoeae [22], patients had gonococcal urethritis caused by penicillinase-sensitive or by penicillinase-resistant Neisseria gonorrhoeae and received 2 grams of cefoxitin intramuscularly and all patients are cured [23], cefoxitin was administered intravenously at the dose of 1 gram or 2 grams thrice-daily or 6 times-daily to patients with orthopaedic infections. Patients with acute or chronic infections of bones, joint, muscle, and tendon or with spinal cord infections caused by Serratia or by indole-positive Proteus are cured thus cefoxitin effectively treats patients with orthopaedic infections [24], cefoxitin was intravenously infused at the dose of 2 grams 4 times-daily for 1 hour (group A), or 2 grams 4 times-daily of cefoxitin were infused for 4 hours (group B), or 8 grams of cefoxitin were continuously infused (group C) to patients with urinary-tract infections caused by extended-spectrum-β-lactamase-producing Escherichia coli and the treatment success is greater in patients of group C than in patients of groups A and B [25], patients with skin and soft-tissue infections received either cefmenoxime or cefoxitin intravenously at the dose of 0.5 and 2 grams, respectively, 4 times-daily for 7 days. Some patients had concomitant bacteraemia and some patients had serious underlying diseases but all patients are cured and both treatments are well-tolerated [26], cefmenoxime was administered intravenously at the daily dose of 0.5 to 1 gram and cefoxitin was administered intravenously at the daily dose of 1 to 2 grams, both treatments were given 4 times-daily for 10 days to patients with serious bacterial infections, and all patients are cured and both treatments are well-tolerated [27], amdinocillin and cefoxitin were co-administered intravenously at the daily dose of 40 and 100 mg/kg, respectively, for 5 to 14 days to patients with complicated urinary-tract infections and this treatment effectively and safely treats the patients [28]. Trials conducted with cefoxitin have been reviewed. A clinical trial was conducted in 266 pregnant women undergoing Caesarean section, 138 pregnant women (51.9%) received 2 grams of cefoxitin intravenously and 128 pregnant women (48.1%) were not treated. Treated pregnant women have significantly fewer serious infections, fewer urinary-tract infections, less febrile morbidity, and fewer courses of antibiotics postoperatively than untreated pregnant women. Use of perioperative cefoxitin effectively prevents infections in pregnant women undergoing Caesarean section [29], a clinical trial was conducted in 657 patients infected by aerobic and anaerobic bacteria and 92.3% of patients are cured or improved. Excellent bacteriologic response occurs in patients infected by gram-positive cocci, by gram-negative bacilli, or by anaerobes bacteria [30], a clinical trial was conducted in patients with severe (66.3%), moderate (31.4%), and mild (1.2%) infections caused by gram-positive cocci or by aerobic gram-negative bacilli. The patients received cefoxitin orally at the daily dose of 2 grams and the clinical cure occurs in 93.0% of patients [31], a single-site, randomized, prospective, blind, comparative parallel-treatment trial was conducted in 96 women with pelvic inflammatory diseases, 50.5% of women received ampicillin/sulbactam intravenously at the dose of 2 grams/1 gram 4 times-daily and 49.5% of women received cefoxitin intravenously at the dose of 2 grams 4 times-daily. Ampicillin/sulbactam is efficacy as cefoxitin in treatment of women with acute pelvic inflammatory disease [32], a randomized, double-blind trial compared the clinical and bacteriologic efficacy of ampicillin/sulbactam administered intravenously at the dose of 2 grams/1 gram 4 times-daily versus those of cefoxitin administered intravenously the dose of 2 grams 4 times-daily to patients with cutaneous or with soft-tissue bacterial infections. The median time of resolution of all symptoms was 10.5 days with ampicillin/sulbactam treatment and 15.5 days with cefoxitin treatment (P-value > 0.05). The cure or improvement and the median time of resolution of all symptoms are similar in patients who received ampicillin/sulbactam and in those who received cefoxitin [33], a double-blind, randomized trial was conducted in 70 women who were treated with cefotetan intravenously at the dose of 2 grams twice-daily and in 70 women who received cefoxitin intravenously at the dose of 2 grams 4 times-daily. All women had endometritis following Caesarean section and the cure-rate is similar in women who received cefotetan and in those who received cefoxitin [34], an open-label, multicentre, randomized phase 3 clinical trial was conducted to test the efficacy of piperacillin-tazobactam versus that of cefoxitin in treating surgical-site infections in patients undergoing surgery. Some patients received piperacillin-tazobactam intravenously at the daily dose of 4 grams and other patients received cefoxitin intravenously at the daily dose of 2 grams. Patients treated with piperacillin-tazobactam have lower-rate of postoperative sepsis and lower clinically relevant postoperative pancreatic fistula than patients treated with cefoxitin. In patients undergoing open pancreatoduodenectomy piperacillin-tazobactam is more effective than cefoxitin in reducing the postoperative surgical-site infections [35], a clinical trial was conducted in pregnant women undergoing Caesarean section who received either ceftriaxone intravenously at the daily dose of 1 gram or cefoxitin intravenously at the dose of 1 gram thrice-daily. Urinary-tract infections were significantly more frequent in patients who received cefoxitin than in patients who received ceftriaxone. A single-dose of ceftriaxone is more effective than 3 doses of cefoxitin in treating urinary-tract infections in pregnant women undergoing Caesarean section [36]. Ko et al. [37] studied the pharmacokinetics of cefoxitin in 16 healthy men volunteers who received a single intravenous dose of 2 grams of cefoxitin. Cefoxitin is rapidly eliminated as the elimination half-life is 0.81 ± 0.04 hours, the distribution volume of cefoxitin is lower than the water volume, two-thirds of cefoxitin are recovered in the urine, and the renal clearance of cefoxitin is similar to the total body clearance of cefoxitin. The concentration of cefoxitin in serum, plasma, and tissues has been reviewed. Bawdon et al. [38] administered a single intramuscular dose of 2 grams of cefoxitin to women undergoing abdominal hysterectomy and measured the concentration of cefoxitin in serum, fundal myometrium, lower urine segment, and fallopian tube. The concentration of cefoxitin in these tissues is about one-half of that in serum and cefoxitin decays in these tissues at the same rate as in serum. Brunetti et al. [39] administered a single intravenous dose of 2 grams of cefoxitin to 6 patients and sampled specimens of adipose tissue at surgery. The concentration of cefoxitin in adipose tissue ranges from 3.3% to 6.6% of that in plasma. Toma et al. [40] enrolled 27 obese patients submitted to surgery. Fourteen patients with a body-mass-index of 43 ± 10 kg/m^2 received a single intravenous dose of 2 grams of cefoxitin and 13 patients with a body-mass-index of 20 ± 2 kg/m^2 received a single intravenous dose of 1 gram of cefoxitin. Specimens of adipose tissue were sampled at surgery and there is an inverse relationship between the penetration of cefoxitin in adipose tissue (AUC-tissue to AUC-plasma ratio) and the body-mass-index (0.08 ± 0.07 versus 0.37 ± 0.26; P-value < 0.05). The concentration of cefoxitin in adipose tissue was 7.8 ± 7.3 and 2.7 ± 1.4 µg/gram at skin incision and closure, respectively. Obese patients have impaired penetration of cefoxitin in adipose tissue and inadequate tissue concentration of cefoxitin is a risk of infections at surgery. The penetration of cefoxitin into the cerebrospinal fluid has been reviewed. Galvao et al. [41] administered cefoxitin intravenously at the dose of 2 grams 4 times-daily to 25 patients with purulent meningitis caused by different bacteria. Samples of blood and cerebrospinal fluid were obtained before and also at 2, 4, and 6 hours after the first-dose and the third-dose of cefoxitin. The concentration of cefoxitin in the cerebrospinal fluid ranged from 1.2 to 22.0 µg/ml with a majority of the concentration falling within a range of 1.2 and 6.2 µg/ml. The concentration of cefoxitin tended to be higher in cerebrospinal fluid sampled after the third-dose than after the first-dose indicating that cefoxitin accumulates in the cerebrospinal fluid. The peak concentration of cefoxitin in cerebrospinal fluid occurred between 2 and 6 hours after administration. In patients with bacterial meningitis, it should be possible to achieve therapeutic cefoxitin concentration in the cerebrospinal fluid by using nontoxic doses of cefoxitin. Humbert et al. [42] measured the concentration of cefoxitin in serum and in the cerebrospinal fluid of 3 groups of patients. Twelve patients had aseptic meningitis (group A), 17 patients (group B), and 14 patients (group C) had bacterial meningitis. The patients of group A received a single intravenous dose of 2 grams of cefoxitin and patients of groups B and C received 2 grams of cefoxitin intravenously 6 times-daily on days 3 and 4 of study and on day 10. The concentrations of cefoxitin in the cerebrospinal fluid did not reach detectable concentration (< 1.5 µg/ml) in 11 of 12 patients (91.7%) of group A. In patients of group B, the mean concentration of cefoxitin in the cerebrospinal fluid concentration was 3.3, 4.7, and 2.9 µg/ml on days 3, 4, and 10, respectively, of treatment, with

simultaneous serum concentration of 8, 9, and 8 µg/ml. At similar time periods, the mean concentration of cefoxitin in patients of group C was 8.6, 12.3, and 4.3 µg/ml in the cerebrospinal fluid and 57, 35, and 27 µg/ml in serum. These results indicate that in patients of groups B and C the ratio of the concentration of cefoxitin in the cerebrospinal fluid to that in serum ranges from 15% to 50%. In patients with uninflamed meninges the concentration of cefoxitin in the cerebrospinal fluid was about 7% of that in serum and in patients with inflamed meninges the concentration of cefoxitin in the cerebrospinal fluid ranged from 30% to 70% of that in serum [43], Feldman et al. [44] administered 3 consecutive intravenous doses of 75 mg/kg 4 times-daily of cefoxitin on days 4, 5, 9, and 10 of therapy to patients with meningitis. The meninges were infected by Haemophilus influenzae type b (N = 21), by Streptococcus pneumoniae (N = 2), and by Neisseria meningitidis (N = 1). The mean concentration of cefoxitin in the cerebrospinal fluid is 4.9 µg/ml 1 to 6 hours after dosing on days 5 and 10 of treatment and this dosage of cefoxitin killed the susceptible strains of Haemophilus influenzae type b, Streptococcus pneumoniae, and Neisseria meningitidis [44]. Little is known about the treatment of meningitis with cefoxitin. Cefoxitin was administered intravenously at the dose of 2 grams 4 times-daily to 25 patients with purulent meningitis caused by Streptococcus pneumoniae, Staphylococcus aureus, Neisseria meningitidis, Haemophilus influenzae, or by Proteus species and this treatment of cefoxitin sterilizes the cerebrospinal fluid [41]. Three consecutive doses of 75 mg/kg of cefoxitin were given intravenously 4 times-daily to 24 patients with meningitis on days 4, 5, 9, and 10 of therapy. The organisms causing the meningitis were Haemophilus influenzae, Streptococcus pneumoniae, or Neisseria meningitidis and this treatment of cefoxitin sterilizes the cerebrospinal fluid [44]. The toxicity induced by cefoxitin has been reviewed. Cefoxitin is a safe cephalosporin thus little is known about the toxicity induced by cefoxitin. The hypersensitivity reactions caused by cefoxitin are observed in a frequency similar to that found with cephalosporins. Neither anaphylactic shock nor renal impairment is caused by cefoxitin and cefoxitin induces few gastrointestinal disturbances. Reversible mild or moderate increases of transaminases and/or alkaline phosphatase are observed in few patients. Positive direct Coombs test without haemodialysis is found in a frequency similar to that observed in cephalosporins. Clinical superinfections caused by cefoxitin-resistant Pseudomonas, Enterobacter, and fungi occur at the same frequency as can be expected with other broad-spectrum antibiotics. Cefoxitin is safe as β-lactam antibiotics and does not induce high rashes as observed with ampicillin and cefoxitin is free of serious nephrotoxicity [45]. An old patient received cefoxitin for treatment of peritonitis and developed haemolytic anaemia and became jaundice. The patient was switched to doxycycline and the bilirubin concentration decreased and the haematocrit increased [46].

In conclusion, cefoxitin is a second-generation cephalosporin is a technically cephamycin and is resistant to β-lactamases produced by gram-negative rods. Cefoxitin has broad gram-negative activity including most strains of Haemophilus species, Proteus species, and Klebsiella species. Cefoxitin is less active than the third-generation cephalosporins against gram-positive bacteria but is more active against anaerobes especially Bacillus fragilis. The efficacy and safely of cefoxitin in treatment of bacterial infections have been reviewed. The prevention of bacterial infections with cefoxitin, the treatment of bacterial infections with cefoxitin, and the trials conducted with cefoxitin have been reviewed. The pharmacokinetics of cefoxitin have been reviewed. A single-dose of cefoxitin was administered intravenously to healthy men volunteers and cefoxitin is rapidly eliminated as the mean elimination half-life is 0.81 hours and about two-thirds of the dose of cefoxitin are recovered in the urine. The concentration of cefoxitin in serum, plasma, and tissues has been reviewed. Cefoxitin penetrates into the cerebrospinal fluid in significant amounts, the penetration-rate of cefoxitin is higher in inflamed than in uninflamed meninges, and cefoxitin sterilizes the cerebrospinal fluid infected by different bacteria. Cefoxitin is a safe cephalosporin and the toxicity caused by cefoxitin is similar to that induced by cephalosporins. The aim of this study is to review the clinical pharmacology of cefoxitin.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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References

1. MacDougal C. (2023). Cell Envelope Disruptors: β-lactam, Glycopeptide, and Lipopeptide Antibacterials. In Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 14th Edition. Laurencel LB and Knollann BC, editors, pp 1147-1165.
2. Senard O, Bouchand F, Deconinck L, Matt M, Fellous L, et al. (2018). Efficacy of cefoxitin for the treatment of urinary tract infection due to extended-spectrum-beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae isolates. Ther Adv Infect Dis; 11.
3. Weinstein MP, Eickhoff TC. Clinical evaluation of cefoxitin in the treatment of respiratory tract and other acute bacterial infections. *Rev Infect Dis;* 1(1): 158-164.
4. Yangco BG, Kenyon VS, Halkias KD, Toney JF, Chmel H. (1979). Comparative evaluation of safety and efficacy of cefmetazole and cefoxitin in lower respiratory tract infections. *J Antimicrob Chemother*; 23(Suppl D): 39-46.
5. Senard O, Lafaurie M, Lesprit P, Nguyen Y, Lescure X, et al. (2020). Efficacy of cefoxitin versus carbapenem in febrile male urinary tract infections caused by extended spectrum beta-lactamase-producing Escherichia coli: a multicenter retrospective cohort study with propensity score analysis. *Eur J Clin Microbiol Infect Dis;* 39(1): 121-129.
6. Hemsell DL, Wendel GD Jr, Hemsell PG, Heard ML, Nobles BJ. (1993). Inpatient Treatment for Uncomplicated and Complicated Acute Pelvic Inflammatory Disease: Ampicillin/Sulbactam Vs. Cefoxitin. Infect *Dis Obstet Gynecol;* 1(3): 123–129.
7. McCloskey RV. Clinical (1986). comparison of piperacillin and cefoxitin in patients with bacteriologically confirmed infections. Antimicrob Agents Chemother; 30(3): 354–358.
8. Belveyre T, Guerci P, Pape E, Thilly N, Hosseini K, et al. (2019). Antibiotic prophylaxis with high-dose cefoxitin in bariatric surgery: an observational prospective single center study. Antimicrob Agents Chemother. 63(12): e01613-1619.
9. Kager L, Malmborg AS, Nord CE, Pieper R. (1982). The effect of short-term cefoxitin prophylaxis on the colonic microflora in patients undergoing colorectal surgery. Infection; 10(6): 338-340.
10. Kager L, Ljungdahl I, Malmborg AS, Nord CE, Pieper R, et all., (1981). Antibiotic prophylaxis with cefoxitin in colorectal surgery: effect on the colon microflora and septic complications--a clinical model for prediction of the benefit and risks in using a new antibiotic in prophylaxis. Ann Surg.; 193(3): 277-282.
11. Ricci Z, Benegni S, Cies JJ, Marinari E, Haiberger R, et al. (2019). Cefoxitin Prophylaxis During Pediatric Cardiac Surgery: Retrospective Exploration of Postoperative Trough Levels. Pediatr *Infect Dis J;* 38(5): 484-489.
12. D'Angelica MI, Ellis RJ, Liu JB, Brajcich BC, Gönen M, et al. (2023). Piperacillin-Tazobactam Compared With Cefoxitin as Antimicrobial Prophylaxis for Pancreatoduodenectomy: A Randomized Clinical Trial. *JAMA.;* 329(18): 1579-1588.
13. Nevarez NM, Brajcich BC, Liu J, Ellis R, Ko CY, et al. (2021). Cefoxitin versus piperacillin-tazobactam as surgical antibiotic prophylaxis in patients undergoing pancreatoduodenectomy:

protocol for a randomised controlled trial. *BMJ Open;* 11(3): e048398.
14. Liberman MA, Greason KL, Frame S, Ragland JJ. (1995). Single-dose cefotetan or cefoxitin versus multiple-dose cefoxitin as prophylaxis in patients undergoing appendectomy for acute nonperforated appendicitis. *J Am Coll Surg;* 180(1): 77-80.
15. Jagelman DG, Fabian TC, Nichols RL, Stone HH, Wilson SE, et all., (1988). Single-dose cefotetan versus multiple-dose cefoxitin as prophylaxis in colorectal surgery. Am J Surg. ; 155(5A): 71-76.
16. Periti P, Mazzei T, Tonelli F. (1989). Single-dose cefotetan vs. multiple-dose cefoxitin--antimicrobial prophylaxis in colorectal surgery. Results of a prospective, multicenter, randomized study. *Dis Colon Rectum;* 32(2): 121-127.
17. Banoub M, Curless MS, Smith JM, Jarrell AS, Cosgrove SE, et al. (2018). Higher versus Lower Dose of Cefotetan or Cefoxitin for Surgical Prophylaxis in Patients Weighing One Hundred Twenty Kilograms or More. *Surg Infect (Larchmt);* 19(5): 504-509.
18. Paladino JA, Rainstein MA, Serrianne DJ, Przylucki JE, Welage LS, et al. (1994). Ampicillin-sulbactam versus cefoxitin for prophylaxis in high-risk patients undergoing abdominal surgery. *Pharmacotherapy;* 14(6): 734-739.
19. Pilmis B, Mizrahi A, Mory C, Le Monnier A, El Helali N. (2021). How to optimize administration of cefoxitin for the treatment of extended spectrum producing Enterobacteriaceae-related infection? *Eur J Clin Microbiol Infect Dis;* 40(7): 1393-1397.
20. Lim KB, Thirumoorthy T, Lee CT, Tham SN, Sng EH, et all., (1986). Single-dose cefoxitin in treating uncomplicated gonorrhoea caused by penicillinase producing Neisseria gonorrhoeae (PPNG) and non-PPNG strains. *Genitourin Med;* 62(4): 224-227.
21. Jones RB, Stimson J, Counts GW, Holmes KK. (1979). Cefoxitin in the treatment of gonorrhoea. *Sex Transm Dis;* 6(4): 239-242.
22. Berg SW, Kilpatrick ME, Harrison WO, McCutchan JA. (1979). Cefoxitin as a single-dose treatment for urethritis caused by penicillinase-producing Neisseria gonorrhoeae. *N Engl J Med;* 301(10): 509-511.
23. Zajdowicz TR, Sanches PL, Berg SW, Kerbs SB, Newquist RL, et all., (1983). Comparison of ceftriaxone with cefoxitin in the treatment of penicillin-resistant gonococcal urethritis. *Br J Vener Dis;* 59(3): 176-178.
24. Schurman DJ, Dillingham M. (1979). Clinical evaluation of cefoxitin in treatment of infections in 47 orthopedic patients. *Rev Infect Dis*; 1(1): 206-209.
25. Guet-Revillet H, Emirian A, Groh M, Nebbad-Lechani B, Weiss E, et al. (2014). Pharmacological study of cefoxitin as an alternative antibiotic therapy to carbapenems in treatment of urinary tract infections due to extended-spectrum-β-lactamase-producing Escherichia coli. *Antimicrob Agents Chemother;* 58(8): 4899-4901.
26. Bechard DL, Hawkins SH, Sutherland SC. (1984). Comparative evaluation of cefmenoxime versus cefoxitin in serious infections. *Am J Med;* 77(6A): 13-16.
27. Tan JS, File YM Jr. (1984). Cefmenoxime versus cefoxitin in the treatment of serious bacterial infections. *Am J Med;* 77(6A): 51-52.
28. Ward TT, Amon MB, Krause LK. (1983). Combination amdinocillin and cefoxitin therapy of multiply-resistant Serratia marcescens urinary tract infections. *Am J Med;* 75(2A): 85-89.
29. Polk BF, Krache M, Phillippe M, Muñoz A, Hutchinson D, Miao L, et al. (1982). Randomized clinical trial of perioperative cefoxitin in preventing maternal infection after primary cesarean section. *Am J Obstet Gynecol;* 142(8): 983-987.
30. Neu HC. (1979). Cefoxitin: an overview of clinical studies in the United States. Rev Infect Dis; 1(1): 233-239.
31. McCloskey RV. (1977). Results of a clinical trial of cefoxitin, a new cephamycin antibiotic. *Antimicrob Agents Chemother;* 12(5): 636-641.
32. Jemsek JG, Harrison F. (1997). Ampicillin/Sulbactam vs. Cefoxitin for the treatment of pelvic inflammatory disease. *Infect Dis Obstet Gynecol*. 5(5): 319-325.
33. Talan DA, Summanen PH, Finegold SM. (2000). Ampicillin/sulbactam and cefoxitin in the treatment of cutaneous and other soft-tissue abscesses in patients with or without histories of injection drug abuse. *Clin Infect Dis;* 31(2): 464-471.
34. MacGregor RR, Graziani AL, Samuels P. (1992). Randomized, double-blind study of cefotetan and cefoxitin in post-cesarean section endometritis. *Am J Obstet Gynecol*; 167(1): 139-143.
35. D'Angelica MI, Ellis RJ, Liu JB, Brajcich BC, Gönen M, Thompson VM, et al. (2023). Piperacillin-Tazobactam Compared With Cefoxitin as Antimicrobial Prophylaxis for Pancreatoduodenectomy. *JAMA*; 329(18): 1579–1588.
36. von Mandach U, Huch R, Malinverni R, Huch A. Ceftriaxone (single-dose) versus cefoxitin (multiple-doses): success and failure of antibiotic prophylaxis in 1052 cesarean sections. *J Perinat Med;* 21(5): 385-397.
37. Ko H, Cathcart KS, Griffith DL, Peters GR, Adams WJ. (1989). Pharmacokinetics of intravenously administered cefmetazole and cefoxitin and effects of probenecid on cefmetazole elimination. *Antimicrob Agents Chemother*; 33(3): 356-361.
38. Bawdon RE, Hemsell DL, Guss SP. (1982). Comparison of cefoperazone and cefoxitin concentrations in serum and pelvic tissue of abdominal hysterectomy patients. Antimicrob Agents Chemother; 22(6): 999-1003.
39. Brunetti L, Kagan L, Forrester G, Aleksunes LM, Lin H, et al. (2016). Cefoxitin Plasma and Subcutaneous Adipose Tissue Concentration in Patients Undergoing Sleeve Gastrectomy. *Clin Ther;* 38(1): 204-210.
40. Toma O, Suntrup P, Stefanescu A, London A, Mutch M, Kharasch E. (2011). Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical-site infection. Anesth Analg; 113(4): 730-737.
41. Galvao PA, Lomar AV, Francisco W, de Godoy CV, *Norrby R.* (1980). Cefoxitin penetration into cerebrospinal fluid in patients with purulent meningitis. *Antimicrob Agents Chemother;* 17(4): 526-529.
42. Humbert G, Leroy A, Rogez JP, Cherubin C. (1980). Cefoxitin concentrations in the cerebrospinal fluids of patients with meningitis. *Antimicrob Agents Chemother;* 17(4): 675-678.
43. Nair SR, Cherubin CE, Weinstein M. (1979). Penetration of cefoxitin into cerebrospinal fluid and treatment of meningitis caused by gram-negative bacteria. *Rev Infect Dis; 1*(1): 134-143.
44. Feldman WE, Moffitt S, Manning NS. (1982). Penetration of cefoxitin into cerebrospinal fluid of infants and children with bacterial meningitis. *Antimicrob Agents Chemother*; 21(3): 468-471.
45. Norrby R, Martin CM, Winzum CV, Brown KR. (1979). The toxicity of cefoxitin in man. *J Inf.*; 1(Suppl 1): 57-66.
46. DeTorres OH. (1983). Hemolytic anemia and pancytopenia induced by cefoxitin. *Drug Intell Clin Pharm;* 17(11): 816-818.

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