RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.2018.36
Mediterr J Infect Microb Antimicrob 2018;7:36
Erişim: http://dx.doi.org/10.4274/mjima.2018.36

Cefoxitin: Interesting Perspectives on a Neglected Intravenous Beta-lactam

Sefoksitin: Göz Ardı Edilen Bir İntravenöz Beta-laktama Farklı Bir Bakış

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Abstract

Cefoxitin is a beta-lactam antibiotic belonging to the cephamycins class, up to now only used in clinical practice for prophylaxis during surgery. Recently, its use has increased due to the spread of infections caused by extended-spectrum beta-lactamase-producing bacteria, particularly urinary tract infections. It has a broad antimicrobial spectrum and is also effective in polymicrobial bone and joint infections or skin and soft tissue infections. Stability data allows its use as a continuous infusion in intensive care units or with elastomeric diffuser for outpatients. Cefoxitin is well tolerated. The aim of this article was to highlight the interesting aspects of this old and inexpensive intravenous beta-lactam.
Keywords: Cephamycins, osteomyelitis, extended-spectrum beta-lactamase, continuous infusion, infection

Öz

Sefoksitin, sefamisin sınıfına ait bir beta-laktam antibiyotiktir ve şimdiye kadar klinik uygulamada sadece ameliyatlarda profilaksi amacıyla kullanılmaktadır. Yakın zamanda, genişlemiş spektrumlu beta-laktamaz üreten bakterilerin neden olduğu özellikle idrar yolu enfeksiyonları gibi enfeksiyonların yaygınlaşması nedeniyle kullanımı artmıştır. Geniş bir antimikrobiyal spektruma sahiptir ve polimikrobiyal kemik ve eklem enfeksiyonları veya deri ve yumuşak doku enfeksiyonlarında da etkilidir. Stabilite verileri yoğun bakım ünitelerinde sürekli infüzyon olarak veya ayakta tedavi gören hastalarda elastomerik difüzör ile kullanımına olanak sağlamaktadır. Sefoksitin iyi tolere edilen bir antibiyotiktir. Bu makalenin amacı, bu eski ve ucuz intravenöz beta-laktam antibiyotiğin ilgi çekici yönlerini vurgulamaktır.
Anahtar Kelimeler: Sefamisinler, osteomiyelit, genişlemiş spektrumlu beta-laktamaz, sürekli infüzyon, enfeksiyon

Cite this article as: Cavalli Z, Dhelft F, Dupieux C, Richard JC, Ferry T. Cefoxitin: Interesting Perspectives on a Neglected Intravenous Beta-lactam. Mediterr J Infect Microb Antimicrob. 2018;7:36.

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Received/Geliş Tarihi: 18.06.2018 **Accepted/Kabul Tarihi:** 27.11.2018

Published: 29 November 2018

Introduction

Cefoxitin is a semi-synthetic beta-lactam antibiotic belonging to the cephamycin class, derived from cephamycin C, an antibacterial substance produced by *Streptomyces lactamdurans*[1-3]. It is characterized by a 7 alpha-methoxy side chain[4]. It exerts its bactericidal activity by inhibiting bacterial cell wall synthesis and is administered parenterally.

Cefoxitin was developed in the early 1970s and has several interesting features, including broader Gram-negative coverage compared to cephalotin[1,3,4], better stability against hydrolysis from various beta-lactamases such as penicillin amido-beta-lactamhydrolase (EC 3.5.2.6)[2,5,6], and activity against anaerobes[7]. Various clinical trials showed its efficacy in lower respiratory tract infections, urinary tract infections, intraabdominal infections, gynecologic infections, and bacteremia[4,8]. However, since 1979, cefoxitin was accused of inducing resistance in Gram-negative bacilli; indeed, the use of cefoxitin can lead to selection of a porin-deficient mutant of *Klebsiella pneumoniae* producing a TEM-3 beta-lactamase[9,10]. Soon after commercialization, it was replaced for most indications by third-generation cephalosporins. For this reason, the use of cefoxitin in clinical practice was also limited for years to chemoprophylaxis in gastrointestinal surgery, due to its activity against *Enterobacteriaceae* and anaerobes[11]. However, there is now renewed interest in cefoxitin due to the increasing rate of infections with extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.

The aim of this review was to highlight the interesting aspects of this old and inexpensive intravenous beta-lactam.

Pharmacokinetics/Pharmacodynamics (PK/PD)

Dose

Standard cefoxitin dose is 1-2 g every eight hours, i.e. 3-6 g per day. This dose must be adjusted in cases of renal failure to 1-2 g every 8-12 hours for creatinine clearance of 30-50 ml/min, 1-2 g every 12-24 hours for creatinine clearance of 10-30 ml/min, 0.5-1 g every 12-24 hours for creatinine clearance of 5-10 ml/min, and 0.5-1 g every 24-48 hours for creatinine clearance lower than 5 ml/min. For patients in hemodialysis, the recommended dose is 0.5-1 g every 24-48 hours or 1-2 g after each dialysis. For patients under continuous renal replacement therapies, the recommended dose is 1-2 g every 8-12 hours[12].

Obesity

Cefoxitin use in obese people requires a higher dose. Various studies showed insufficient concentrations in fat when cefoxitin is used as prophylaxis in bariatric surgery. In a study by Toma et al.[13], adipose tissue cefoxitin concentrations in obese patients undergoing abdominal and pelvic surgery were below the minimum inhibitory concentration (MIC) despite giving twice the normal dose. Similarly, Brunetti et al.[14] reported that subcutaneous adipose tissue concentrations of cefoxitin at the time of surgical closure were subtherapeutic in six patients undergoing sleeve gastrectomy. Moine showed that a single dose of cefoxitin at 40 mg/kg failed to achieve the desired probability of target attainment in fat tissue for *Staphylococcus aureus*, *Escherichia coli*, and *Bacteroides fragilis* over 4-h periods postdose[15]. In bariatric surgery, a starting dose of 4 g is recommended instead of 2 g for people weighing more than 100 kg[16]. Data for other surgery types do not exist.

Distribution

In healthy volunteers, the terminal elimination half-life is 45 minutes[12]. Plasma protein binding accounts for 65 to 80%, and cefoxitin is eliminated by the kidney as unchanged drug. Cefoxitin diffusion is fast in fluid compartments but poor in brain, which is why cefoxitin is not indicated for neurologic infection[12]. Indeed, the degree of penetration of cefoxitin approaches 10% in aseptic meningitis[17]. Bone diffusion is similar to that of other cephalosporins such as cefazolin or ceftriaxone[18]. Cefoxitin concentrations measured in bone and synovial fluid one hour after administration achieve 20% of the serum level[19,20]. In colonic tissue, a study on cefoxitin used in colorectal cancer surgery prophylaxis showed that an infusion of 2 g given one hour before incision is required to achieve free plasma concentrations above 8 mg/l (the concentration threshold for susceptible bacteria)[21].

Administration

Cefoxitin is compatible with the following solutions: NaCl 0.9%, glucose 5% and 10%, and sterile water[12].

Pharmacodynamics

Cefoxitin is a time-dependent antibiotic. Various studies have shown that cefoxitin is stable for at least 24 h at 24 °C[22-24], allowing its administration as continuous infusion. A study of cefoxitin in the treatment of urinary tract infections due to ESBL-producing *E. coli* showed that only prolonged infusions of 4 hours could achieve free cefoxitin concentrations above the MIC or 4xMIC during 100% of the administration interval with 76% and 68% probability, respectively, whereas continuous infusion provided 100% probability of achieving MIC and 4xMIC[25]. Another controlled trial with one hundred sixteen adults showed a reduction of postoperative infections after colorectal surgery with continuous infusion (over 20 hours) versus intermittent infusion (every eight hours)[26].

Potential Use in Outpatient Settings

Stability data allow the use of cefoxitin as a continuous infusion at home with an elastomeric diffuser, an interesting feature that can reduce hospital length of stay. Elastomeric infusers are devices where the fill volume of the drug reservoir and the flow

rate are preset. The elastomer, which makes up the reservoir walls, is what makes the infusate flow due to the pressure it exerts. Those made of polyisoprene are superior to silicone for constant and stable infusion because the relaxation time is shorter and does not significantly impact infusion kinetics[27]. The following elastomeric pumps may be used in this setting: LV10® (Baxter), Easypump® II (Braun), DOSI-FUSER® (Asept Inmed), and Accufuser® (Vygon).

Serum cefoxitin level measurement

The measurement of cefoxitin levels in serum is possible by liquid chromatography/high-resolution mass spectrometry. This is of interest in terms of continuous infusion.

Antimicrobial Spectrum

Cefoxitin has a broad antimicrobial spectrum relative to second-generation cephalosporins. Bacterial susceptibility data for cefoxitin are shown in Table 1[12]. Cefoxitin is also used for the treatment of *Mycobacterium abscessus*[12]. MIC distributions of main bacteria are shown in Table 2[28].

In microbiological laboratories, cefoxitin may be used to detect methicillin resistance in staphylococci. Indeed, *in vitro*, cefoxitin is a better predictor of methicillin-resistance than oxacillin. Staphylococcal isolates that are resistant to cefoxitin are considered resistant to all beta-lactam antibiotics (except ceftaroline and ceftobiprole). Cefoxitin clinical breakpoints are presented in Table 3; for other susceptible bacteria such as streptococci, there is no defined cut-off[28-30].

A substantial proportion of ESBL-producing *Enterobacteriaceae* (*E. coli, K. pneumoniae*, mainly producing TEM, CTX-M or SHV beta-lactamases) remains susceptible to cefoxitin[31] and this allows clinicians to avoid the use of carbapenems in these cases. However, when clinicians consider using this molecule for antimicrobial therapy, the cefoxitin MIC should be measured precisely before administration. Some studies reported that cefoxitin could induce resistance in Gram-negative bacilli, for example by inducing beta-lactamases or impermeability by selecting mutants with modified porins[9,10,32].

Indications

Cefoxitin is licensed for prophylaxis of postoperative infection and treatment of infection due to susceptible bacteria, except in meningitis[12]. Main clinical trials are shown in Table 4. One of the first clinical trials, published in 1977, was performed on 143 patients treated with cefoxitin in two phases, the first was randomized while the second was an open trial. Infections were due to various bacterial species including staphylococci, streptococci, and Gram-negative bacilli and were mainly skin and soft tissue infections, pneumonia, and urinary tract infections. The rate of cure or improvement was 93% (of note, 20 of these patients had bacteremia including three with endocarditis) with a clinical success amounting to 95%[8]. A review of clinical studies performed on 657 patients showed a cure rate of 69% and improvement in 92% of patients with various infections such as lower respiratory tract infections, urinary tract infections, intraabdominal infections, gynecologic infections, and bacteremia[33].

Table 1. Cefoxitin susceptibility data of main bacteria

	Susceptible pathogens	Resistant pathogens
Gram-positive bacteria	*Staphylococcus* spp. (methicillin-susceptible isolates) *Streptococcus pneumoniae* *Streptococcus* spp.	*Staphylococcus* spp. (methicillin-resistant isolates) *Enterococcus* spp. *Listeria monocytogenes*
Gram-negative bacteria	*Branhamella catarrhalis* *Citrobacter koseri* *Escherichia coli* *Haemophilus influenzae* *Klebsiella* spp. *Morganella morganii* *Neisseria gonorrhoeae* *Proteus* spp. *Providencia* spp. *Salmonella* spp. *Shigella* spp.	*Acinetobacter* spp. *Burkholderia cepacia* *Campylobacter* spp. *Citrobacter freundii* *Enterobacter* spp. *Legionella* *Pseudomonas aeruginosa* *Serratia marcescens* *Stenotrophomonas* spp. *Yersinia enterocolitica*
Anaerobic bacteria	*Actinomyces* spp. *Bacteroides* spp. *Clostridium perfringens* *Fusobacterium* spp. *Peptostreptococcus* spp. *Prevotella* *Propionibacterium acnes* *Veillonella* spp.	*Clostridium difficile*
Intracellular		*Chlamydia* spp. *Mycoplasma* spp.

Table 2. Cefoxitin minimum inhibitory concentration distributions of main bacteria[28]

	MIC 50 (mg/L)	MIC 90 (mg/L)
Acinetobacter baumannii	64	64
Acinetobacter lwoffii	32	64
Acinetobacter spp.	64	64
Bacteroides fragilis	8	32
Bacteroides fragilis group	16	64
Bacteroides ovatus	32	128
Bacteroides thetaiotaomicron	16	64
Bacteroides vulgatus	16	128
Citrobacter freundii	64	64
Citrobacter koseri	2	8
Citrobacter spp.	64	64
Enterobacter aerogenes	64	128
Enterobacter cloacae	64	256
Escherichia coli	4	8
Haemophilus influenzae	2	4
Hafnia alvei	8	32
Klebsiella oxytoca	2	8
Klebsiella pneumoniae	4	16
Morganella morganii	8	32
Prevotella spp.	2	16
Proteus mirabilis	4	4
Proteus vulgaris	4	8
Providencia rettgeri	2	32
Providencia stuartii	2	32
Salmonella enteritidis	2	4
Salmonella spp.	2	8
Salmonella typhi	2	4
Salmonella typhimurium	2	8
Serratia marcescens	16	64
Serratia spp.	32	128
Shigella flexneri	4	4
Shigella sonnei	2	4
Staphylococcus aureus	2	4
Staphylococcus aureus methicillin-resistant	32	128
Staphylococcus aureus methicillin-susceptible	4	4
Staphylococcus lugdunensis	2	4
Staphylococcus saprophyticus	4	8

MIC: Minimum inhibitory concentration

Table 3. Cefoxitin clinical breakpoints according to the 2018 guidelines of the Antibiogram Committee of the French Society for Microbiology, the European Committee on Antimicrobial Susceptibility Testing, and Clinical and Laboratory Standards Institute

	CA-SFM / EUCAST				CLSI			
	MIC breakpoint (mg/L)		Zone diameter breakpoint (mm)[a]		MIC breakpoint (mg/L)		Zone diameter breakpoint (mm)[a]	
	Susceptible if ≤	Resistant if >	Susceptible if ≤	Resistant if >	Susceptible if ≤	Resistant if >	Susceptible if ≤	Resistant if >
Enterobacteriaceae	8	16	19	15	8	16	18	15
Staphylococcus aureus and *S. lugdunensis*[b]	4	4	22	22	4	4	22	22
Staphylococcus saprophyticus[b]	-	8	22	22	-	-	-	-
Staphylococcus epidermidis[b]	-	-	28	28	-	-	-	-
Others coagulase-negative staphylococci	-	-	22	22	-	-	25	25
Neisseria gonorrhoeae	-	-	-	-	2	4	28	24
Anaerobes	-	32	-	-	16	32	-	-
Mycobacterium abscessus	-	-	-	-	16	-	-	-

[a]Disk content 30 µg.
[b]For staphylococci, the disk diffusion test using cefoxitin allows to predict methicillin resistance. For staphylococci other than *S. aureus, S. lugdunensis* and *S. saprophyticus*, the cefoxitin minimum inhibitory concentration is a poorer predictor of methicillin resistance than the disk diffusion test.
CA-SFM: Antibiogram Committee of the French Society for Microbiology, EUCAST: European Committee on Antimicrobial Susceptibility Testing, CLSI: Clinical and Laboratory Standards Institute

Table 4. Main clinical trials of cefoxitin

Year	Author	Type of study	Number of patients	Type of infection	Rate of cure or improvement
1977	McCloskey[8]	Phase 1: randomized controlled trial Phase 2: prospective cohort study	143	Skin and soft tissue infections, pneumonia, urinary tract infections	93%
1979	Jacobson et al.[56]	Prospective cohort study	26 children	Cellulitis, pneumonia, bone and joint infection	100%
1979	Neu et al.	Prospective cohort study	657	Lower respiratory tract infections, urinary tract infections, intraabdominal infections, gynecologic infections and bacteremia	69% cure 92% improvement
1979	Neu et al.	Randomized controlled trial	320	Various	91%
1979	Perkins et al.[44]	Prospective cohort study	27	Skin and soft tissue infections (including 3 osteomyelitis)	93%
1979	Schurman and Dillingham[45]	Retrospective series	77	Infections of bone, joint or muscle and tendon (including 15 bone and joint infections)	84%
1979	Webb et al.[43]	Prospective cohort study	30	Endocarditis, lung abscess, empyema, liver and subhepatic abscess, osteomyelitis, pancreatic abscess	93%
1980	Feldman et al.[57]	Prospective cohort study	32 children	Cellulitis, abscess, arthritis, bacteremia	89%
1996	Stiglmayer et al.[52]	Randomized controlled trial	76	Pelvic inflammatory disease	79%
1997	Erstad and McIntyre[46]	Randomized controlled trial	18	Diabetic foot infection (including 28% with osteomyelitis)	39%
1997	Jemsek and Harrison[51]	Randomized controlled trial	93	Pelvic inflammatory disease	68%
2000	Talan et al.[50]	Randomized controlled trial	63	Skin and soft tissue abscess	94%
2009	Jeon et al.[54]	Retrospective series	65	*Mycobacterium abscesses* in lung disease of cystic fibrosis	83%
2016	Mambie et al.[40]	Prospective cohort study	15	ESBL urinary tract infection	100%
2015	Kernéis et al.[37]	Retrospective series	33	ESBL urinary tract infection and catheter-related bloodstream infections	91%
2018	Demonchy et al.[39]	Prospective cohort study	23	ESBL prostatitis	83%

ESBL: Extended-spectrum beta-lactamase

Another review of comparative studies showed that cefoxitin was as efficient as cephalothin for the treatment of serious infections, with overall cure/improvement rates of 93% for cephalothin versus 91% for cefoxitin[4].

ESBL Infections

Infection with ESBL-producing *Enterobacteriaceae* (E-ESBL) has been an emergent public health concern since the 1990s[34,35]. The most common E-ESBL are *E. coli* and *K. pneumoniae*. One of the first studies was performed with the cephamycin flomoxef, whose use in ESBL-producing *K. pneumoniae* bacteremia showed non-inferiority to carbapenem[36]. In a murine model of E-ESBL urinary tract infection, cefoxitin was shown not significantly different from carbapenems regarding bactericidal activity (significant reduction in bacterial counts greater than 2 log10 CFU in kidney and bladder) or selection of resistant mutants[31]. Kernéis et al.[37] studied 33 patients infected with E-ESBL (including 16 patients with bacteremia) with unreported disease severity (mainly urinary tract infections), and reported favorable clinical outcomes in 91% and microbiological cure in 70%. However, emergence of *K. pneumoniae* resistance to cefoxitin was observed in two patients with microbiological relapse. In a retrospective study of 53 patients with E-ESBL bloodstream and/or urinary tract infections, the rate of clinical or microbiological relapse did not differ between carbapenems or alternative antibiotics (mainly cefoxitin), but relapses were more frequent with *K. pneumoniae*[38]. Cefoxitin is particularly interesting in urinary tract infections because of its high urinary concentrations[12]. Various studies confirmed that cefoxitin is an efficient alternative to carbapenems in urinary tract infections due to E-ESBL[39,40]. Nevertheless, a meta-analysis of studies performed in E-ESBL bacteremia showed that mortality was significantly lower in both carbapenem-treated and beta-lactam/beta lactam inhibitor-treated patients when compared with cefoxitin, thus casting doubt on its efficacy in this setting (although the latter group was not exclusively composed of cefoxitin-treated patients)[41]. Carbapenem may remain the reference treatment in E-ESBL bacteremia, in keeping with the

results of the recent MERINO trial, which identified greater mortality in patients with E-ESBL bacteremia treated with piperacillin-tazobactam as compared to carbapenem[42]. Even if an isolate is reported susceptible to cefoxitin, this molecule must be used carefully and its efficiency in bacteremia remains to be evaluated.

Pharmacodynamic optimization is critical when treating E-ESBL-infected patients in order to achieve effective blood concentrations. A recent pharmacological simulation study showed that continuous infusion of 8 g cefoxitin daily was the was the only regimen able to achieve levels consistently above the MIC in all patients with normal renal function (assuming a theoretical MIC of 8 mg/L), while bolus and extended perfusion were less effective[25]. To date, there are no published data on cefoxitin PK/PD in intensive care unit patients, where the need to spare carbapenem is of utmost importance, and increased distribution volume in severe septic patients presents a challenge to achieving effective cefoxitin concentration. Continuous infusion may well be an optimal mode of administration in this setting.

Polymicrobial Bone and Joint Infections (BJI)

There are few studies about the use of cefoxitin in BJI. In a study by Webb et al.[43] including 30 patients with various infections treated with cefoxitin, there were three cases of osteomyelitis: one mandibular BJI due to *Bacteroides fragilis* and *Streptococcus* treated with 8 g of cefoxitin over 26 days in conjunction with incision and debridement; another mandibular BJI due to several *Bacteroides* species treated with 8 g of cefoxitin over 16 days along with incision and debridement; and one gangrene of toe with osteomyelitis of the phalanx due to *Bacteroides corrodens* and *Proteus vulgaris* treated by 8 g of cefoxitin over 17 days with toe resection. Of the 30 patients, clinical failure occurred only in the two patients with mandibular osteomyelitis. Perkins et al.[44] presented 27 skin and soft tissue infections, including three diabetics with foot ulcers and contiguous osteomyelitis. Organisms isolated from these patients were *S. aureus, Streptococcus, Staphylococcus epidermidis* and *Peptococcus* species in one patient, *Peptococcus* species, *Fusobacterium nucleatum* and *S. epidermidis* in the second, and *E. coli, B. fragilis*, and *Peptococcus* species in the third. They were treated with cefoxitin for 21-40 days. Two patients received follow-up therapy, one with oral cephalexin and one with oral penicillin V, and one required repeated drainage; all three patients with osteomyelitis were cured[44]. Schurman and Dillingham[45] presented a study of 47 patients treated by cefoxitin in an orthopedic ward: there were three orthopedic implant-related infections (all with removal of the prosthesis), five joint infections (with local debridement or joint aspiration) and nine bone infections. Doses ranged from 6 to 10 g per day and the mean treatment duration ranged from 13.8±4.5 days for acute joint infection to 20.7±11.5 days for acute bone infection. The cure rate for the 15 BJI evaluated was 73%. With regards to diabetic foot, a review identified a clinical trial with 18 patients with diabetic foot infection treated by cefoxitin (including 28% with osteomyelitis) compared to 18 patients treated by ampicillin-sulbactam (including 44% with osteomyelitis), and the cure rate was significantly higher with cefoxitin (39%) than with ampicillin-sulbactam (6%)[46].

The results obtained with cefoxitin are similar to those obtained with the cephamycin-related moxalactam. Fitzgerald[47] showed a good penetration of moxalactam in normal and osteomyelitic bone in dog, with calculated concentrations of moxalactam in the interstitial fluid space equivalent to simultaneously obtained serum concentrations. In a study of 3358 patients treated with moxalactam, there were 122 BJI (including 92 osteomyelitis and 19 septic arthritis): bacterial agents were *S. aureus* (38), *Pseudomonas* spp. (24), *Serratia* spp. (16), *Proteus* spp. (14), *E. coli* (10), *Enterobacter* spp.[13]. The patients were treated with 1-2 g moxalactam every eight hours for four-six weeks and the cure rate was 90%[48].

When used in an antibiotic-releasing implant coating, there is a negative effect on osteoblast-like cells compared to other antibiotics in various families[49].

Skin and Soft Tissue Infection

The study of 27 skin and soft tissue infections showed that cefoxitin provided a cure rate of 93%[44]. In a clinical trial including 63 patients with skin and soft tissue abscess, cefoxitin was shown to be equivalent to ampicillin-sulbactam, with cure or improvement rates of 93.6% vs. 89.8%, respectively[50].

Other Infections

Cefoxitin is used in the treatment of intraabdominal infections and showed various results in clinical trials. For the treatment of pelvic inflammatory disease, cefoxitin was equivalent to ampicillin-sulbactam in one study (93 women with cure and improvement rates of 68% and 24% for cefoxitin versus 67% and 30% for ampicillin-sulbactam, respectively)[51] and bacteriologically inferior but clinically equivalent in another (76 women with cure rate of 79% for cefoxitin versus 87% for ampicillin-sulbactam but persistence of the causative organism in 12% and 3%, respectively)[52]. Cefoxitin was inferior to ampicillin-sulbactam in the treatment of intraabdominal infections in a study of 197 patients that showed approximately 9% greater frequency of failure with cefoxitin relative to ampicillin-sulbactam[53].

Cefoxitin is also part of multitherapy used in the treatment of infection due to *Mycobacterium abscessus*, especially in lung disease of cystic fibrosis. A study of 65 patients treated by cefoxitin in association with clarithromycin, ciprofloxacin,

doxycycline, and amikacin showed treatment response rates of 83% for symptoms and 74% for high-resolution computed tomography, but a very high rate of side effects (with 60% cefoxitin discontinuation) due to high posology of cefoxitin, up to 12 g per day[54]. Cefoxitin is also used for treatment of prosthetic joint infection due to *M. abscessus*[55].

In children, cefoxitin showed good efficacy in cellulitis, pneumonia, BJI, abscess, and bacteremia due to *S. aureus*, *Haemophilus influenza,* and *Streptococcus pneumoniae*[56,57].

Prophylaxis

Cefoxitin is one of the recommended antibiotics for prophylaxis during surgery, in particular for biliary tract, small intestine, colorectal, or gynecological surgery[11]. A prospective and randomized quality control study in 422 patients showed that cefoxitin was equivalent to ampicillin-sulbactam and piperacillin-metronidazole in elective colorectal surgery[58].

Adverse Effects

Adverse effects during cefoxitin treatment are rare. Cross-reactivity has been described between cephamycins and others beta-lactam antibiotics but allergic reactions seem uncommon and mild in severity[59]. Other described adverse events are local reaction (thrombophlebitis, pain, local induration), allergic reaction (rash, itching, fever), gastrointestinal disorder (nausea, vomiting, pseudomembranous colitis), hematologic disorder (eosinophilia, leucopenia, anemia), hepatic disorder, and renal disorder[12]. The seminal study published in 1977 on 143 patients identified the following rates of adverse events: eruption 1.4%, hepatic toxicity 2%, leucopenia 2%, eosinophilia 2.5%, and thrombophlebitis at injection site 5%[8]. Another study of cefoxitin administered at doses of up to 12 g per day in cystic fibrosis patients infected by *M. abscessus* identified a 60% rate of treatment interruption with 51% of patients having neutropenia, 6% thrombopenia, and 15% hepatic toxicity[54].

As cephalosporins, cefoxitin can be responsible for *Clostridium difficile*-associated disease[60].

There is no study concerning pregnancy but there are no known teratogenic effects of cefoxitin. Of note, cefoxitin is excreted in breast milk[12].

Conclusion

Cefoxitin is an old and inexpensive intravenous beta-lactam, up to now neglected but with interesting properties, even if it is not available in all countries. Its broad spectrum is interesting, specifically in BJI or skin and soft tissue infections. Considering the emergence of E-ESBL infections, cefoxitin is an alternative to carbapenems, although efficacy data in patients with bacteremia are lacking. Moreover, cefoxitin stability allows its use in continuous infusion, including in elastomeric diffusers in the outpatient setting. Finally, cefoxitin appears extremely well tolerated.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.F., J.C.R., C.D., Concept: T.F., Design: T.F., Data Collection or Processing: Z.C., F.D., Analysis or Interpretation: J.C.R., C.D., Literature Search: Z.C., F.D., Writing: Z.C., F.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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