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Short Research Communication

Prolonged Cefoxitin Infusion Using Mobile Elastomeric Infusors In Outpatients With Bone And Joint Infection

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Abstract

We reviewed all outpatients with bone and joint infection treated with cefoxitin in continuous intravenous infusion using mobile elastomeric infusors in our regional reference center between 2014 and 2017. The stability of cefoxitin provides an interesting and well-tolerated alternative for continuous infusion in outpatients with polymicrobial bone and joint infection.

Key words: cefoxitin, infusor, bone, joint

Introduction

Cefoxitin, a second-generation cephalosporin belonging to the cephamycin group, is classically used as prophylactic antibiotherapy in surgery (1). However, its characteristics can also enable therapeutic application in bone and joint infection (BJI), and a few studies published in the 1970s showed potential efficacy in this indication (2–4). As cefoxitin is not expensive, stable for 24h at 37°C, and has an interesting spectrum targeting *Staphylococcus aureus, Streptococci and Enterobacteriaceae* (5), it has been increasingly prescribed using mobile elastomeric infusors in some of our outpatients with BJI. The aim of the present study was to describe this emergent practice.

Methods

A retrospective observational cohort study included all BJI outpatients treated with cefoxitin in continuous intravenous infusion using mobile elastomeric infusors (LV10® pump, Baxter (Figure 1); DOSI-FUSER®, Asept Inmed; Easypump® II, Braun; or Accufuser®, Vygon) in our regional reference center (Hospices Civils de Lyon, France) between 2014 and 2017. Cefoxitin was quantified in serum by liquid chromatography associated to high-resolution mass spectrometry, routinely used in the laboratory; concentrations were evaluated at steady state and were expressed as mg/L. The study was approved by the institutional review board, based on French ethical rules: informed consent waiver was granted as all data were already available. Clinical and bacteriological data were retrospectively collected from electronic medical charts used and reported as means and percentages.

Results

Epidemiology

Thirty-three patients were included (26 male: 79%), with a mean age of 54.5±14.9 years. Fifteen (45.5%) had at least one or more underlying disease: paraplegia (n=5), obesity (n=5), diabetes (n=2), cancer

(n=2), immunosuppressive therapy (n=3) or chronic kidney disease (n=3).

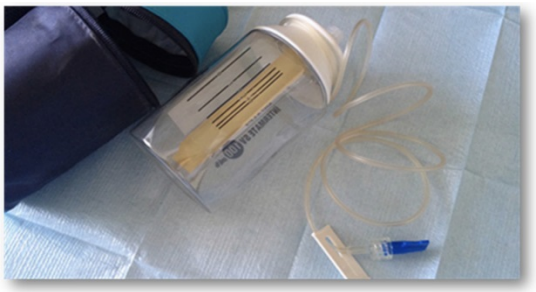

Figure 1. LV10® pump from Baxter

Clinical presentation

The BJI was localized in the lower limbs (n=16), the upper limbs (n=4), pelvis (n=6), spine (n=3), mandible (n=3) or skull (n=1) and consisted of medullary osteomyelitis (n=2), superficial osteomyelitis (n=14), localized osteomyelitis (n=4), diffuse osteomyelitis (n=7), prosthetic joint infection (n=3) or postoperative spine infection (n=3). Fifteen BJIs (45%) were orthopedic implant-related infections. The main BJI characteristics are summarized in Table 1. Bone was exposed in 8 of the 33 patients (24%). Infection mechanisms comprised direct inoculation (23/33: 70%), contiguity to another infection (4/33: 12%) and pressure ulcer-related osteomyelitis (6/33: 18%). Mean BJI progression was 8.3 ±13.7 years, with a median of 2 years and ranging from 1 month to 60 years. Twenty patients (64%) had undergone surgery for the BJI before treatment with cefoxitin.

Microbiology

Bacteriological identification was available for 32 patients (97%). BJI was polymicrobial in 23 patients (72%), with a mean 2.8±1.9 strains per patient and a median 3 strains: 24 (75%) *Staphylococcus* spp (12 *Staphylococcus aureus* and 15 coagulase negative staphylococci), 8 (25%) streptococci, 23 (72%) anaerobic bacteria, 3 (9%) enterococci and 13 (41%) *Enterobacteriaceae*. Cefoxitin susceptibility was determined by the antimicrobial susceptibility test and interpretation following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (6). It was not possible to perform cefoxitin minimal inhibitory concentration (MIC) measurement due to the retrospective study design, as no isolates were still available.

Surgery

Thirty-two patients (97%) underwent surgery in addition to antibiotherapy: debridement (n=20), implant removal (n=10) including partial drop (n=1), negative pressure wound care (n=5), debridement with implant conservation (n=6), internal fixation (n=4), effusion drainage (n=5), bone graft (n=3), bone sequestrum removal (n=4), cement spacer implantation (n=2), one-step implant exchange (n=1), or skin flap (n=1). The surgery was considered optimal in 24 cases (73%). Eleven patients (33%) required a second procedure.

Antibiotherapy

For 27 patients (82%), other antimicrobials were already being used when cefoxitin was started. Cefoxitin was used for a mean 8.0±5.1 weeks, within a total mean duration of antibiotherapy of 18.2±6.1 weeks. Cefoxitin was chosen by the physician because of the polymicrobial character of infection or to avoid too many oral drugs with consequent risk of non-adherence, oral intake difficulties and/or cumulative toxicity. In all patients but one, cefoxitin was used in combination: with a fluoroquinolone (n=17), clindamycin (n=10), rifampicin (n=4), vancomycin (n=2), daptomycin (n=2), or metronidazole (n=3). The most common dose was 6g/day (n=18); 2 obese patients (98 and 75 kg) received 8g/day, 2 obese patients (115 and 105 kg) received 9g/day and 1 patient with low weight (45 kg) received 4g/day. For all patients, cefoxitin was administered continuously using a mobile elastomeric infusor connected to a PICC-line. Cefoxitin was stopped for oral relay in 21 patients (64%), end of antibiotherapy in 5 (15%), treatment failure in 6 (18%), and intolerance in 1 (3%). Mean steady-state cefoxitin plasma concentration was 13.2±6.1 mg/L, with a median of 11.7 mg/L, ranging from 4.6 to 34 mg/L, and always above the MIC of the targeted pathogen.

Tolerance

The tolerance was good for most patients (n=30; 91%). There were 2 minor adverse reactions; the only serious adverse event was a drug reaction with eosinophilia and systemic symptoms (DRESS), but implicating a fluoroquinolone introduced few weeks before. No patients experienced *C. difficile* infection.

Outcome

At the end of antibiotherapy, 23 patients (70%) were considered cured, including 1 under suppressive therapy. Three of the 10 treatment failures related to non-optimal surgery, 5 to superinfection by cefoxitin-resistant bacteria (with bone exposure in 4 cases), 1 to non-optimal antimicrobial chemotherapy because of multiple intolerance to oral molecules; the last patient counted as failure was lost to follow-up. In cured patients, mean follow-up was 5.8±5.7 months, with a median of 3 months. There was 1 relapse, due to a plurimicrobial osteomyelitis of the mandible 1 year after end of treatment.

Table 1. Main characteristics of the 33 BJI

PATIENT	CEFOXITINE DURATION (WEEKS)	CEFOXITIN DAILY DOSE	IMPLANT	TYPES OF BJI	SURGERY	MICROBIOLOGY	ADDITIONAL MOLECULE TO IV CEFOXITIN	OUTCOME
1	10	9g	yes	post-operative spine infection	collection drainage, partial implant removal	*Finegoldia, E. coli*	Ciprofloxacin Daptomycin	cure
2	4	6g	no	superficial osteomyelitis	none	*S. epidermidis, Peptostreptococcus*	Ciprofloxacin	failure
3	4	6g	yes	diffuse osteomyelitis	implant removal, debridement	*S. aureus, S. lugdunensis, Peptostreptococcus*	Clindamycin	cure
4	5	6g	yes	diffuse osteomyelitis	debridement, implant removal, osteosynthesis, bone graft	*S. capitis*	Ofloxacin	failure
5	12	8g	yes	prosthetic joint infection	collection drainage, debridement and implant retention	*Streptococcus mitis/oralis*	Levofloxacin	failure
6	2	6g	no	superficial osteomyelitis	debridement, negative pressure wound care establishment	*S. aureus*	Ofloxacin	failure
7	6	6g	no	localized osteomyelitis	debridement, bone sequestrum removal	*S. aureus, Streptococcus constellatus, Bacteroides, Citrobacter*	Ofloxacin Metronidazole	cure
8	4	6g	yes	superficial osteomyelitis	debridement, implant removal, negative pressure wound care establishment	*S. aureus, S. lugdunensis, Corynebacterium, E. coli*	Ofloxacin	failure
9	2	6g	yes	post-operative spine infection	debridement and implant retention	*S. capitis, Propionibacterium, E. coli, Proteus*	Ofloxacin	cure
10	8	6g	yes	superficial osteomyelitis	implant removal, negative pressure wound care establishment	*S. aureus, Enterococcus avium, Helcococcus, Proteus, E. coli*	Teicoplanin	cure
11	8	6g	yes	diffuse osteomyelitis	implant removal, osteosynthesis, bone graft	*S. capitis, Streptococcus mitis/parasanguinis*	Ofloxacin	cure
12	6	6g	no	superficial osteomyelitis	debridement, bone sequestrum removal	*S. aureus, Prevotella, Haemophilus*	Clindamycin	cure
13	6	6g	no	localized osteomyelitis	debridement	*Streptococcus parasanguinis/mitis/salivarius, Veilonella, Citrobacter*	Levofloxacin Metronidazole	cure
14	6	9g	no	superficial osteomyelitis	debridement	*Propionibacterium, Gemella, Fusobacterium, Finegoldia*	Metronidazole	cure
15	23	6g	yes	superficial osteomyelitis	debridement and implant retention, skin flap	*S. aureus, S. lugdunensis, Streptococcus mitis, Peptinophilus, Finegoldia*	Clindamycin	cure
16	3	6g	no	superficial osteomyelitis	debridement	*S. aureus*	Clindamycin	cure
17	12	6g	yes	superficial osteomyelitis	debridement and implant retention	*S. aureus, Streptococcus agalactiae*	Ofloxacin Rifampicin	cure
18	12	4g	no	diffuse osteomyelitis	debridement, bone graft, osteosynthesis	*sterile*	Ciprofloxacin	cure
19	24	6g	yes	superficial osteomyelitis	debridement, debridement and implant retention	*Enterococcus faecalis, Prevotella, Peptinophilus, Porphyromonas, E. coli*	Daptomycin Ciprofloxacin	cure
20	12	6g	no	superficial osteomyelitis	collection drainage, debridement	*S. aureus, Streptococcus anginosus/constellatus /interm, Bacteroides, Actinomyces, Corynebacterium, Finegoldia, E. coli*	Clindamycin	failure
21	6	6g	no	medullary osteomyelitis	collection drainage, debridement	*S. aureus*	Rifampicin	cure
22	12	6g	yes	diffuse osteomyelitis	implant removal, debridement	*S. aureus*	Clindamycin	failure
23	8	6g	no	superficial osteomyelitis	debridment, negative pressure wound care establishment	*S. capitis, Propionibacterium, Proteus*	Moxifloxacin	failure
24	8	6g	yes	prosthetic joint infection	debridement and partial implant retention, partial	*S. lugdunensis, S. caprae, S. capitis*	Ofloxacin	cure

PATIENT	CEFOXITINE DURATION (WEEKS)	CEFOXITIN DAILY DOSE	IMPLANT	TYPES OF BJI	SURGERY	MICROBIOLOGY	ADDITIONAL MOLECULE TO IV CEFOXITIN	OUTCOME
					implant one-stage exchange			
25	6	6g	no	superficial osteomyelitis	debridement	*S. aureus, Actinomyces*	Clindamycin	cure
26	3	6g	no	localized osteomyelitis	debridement, bone sequestrum removal	*Streptococcus gordoni/mitis/constellatus/intermedius, Actinomyces, Haemophilus*	no	cure
27	6	6g	no	localized osteomyelitis	debridement	*Veilonella*	Clindamycin	cure
28	6	6g	yes	diffuse osteomyelitis	implant removal, debridement	*S. aureus, Propionibacterium*	Clindamycin	cure
29	8	6g	yes	medullary osteomyelitis	collection drainage, implant removal, negative pressure wound care establishment	*S. epidermidis, Corynebacterium*	Rifampicin	failure
30	12	6g	no	superficial osteomyelitis	debridement	*S. aureus, Streptococcus equismilis, Corynebacterium, Proteus*	Vancomycin Ofloxacine	cure
31	3	6g	no	post-operative spine infection	debridement	*S. epidermidis*	Clindamycin	cure
32	8	8g	yes	prosthetic joint infection	implant removal, cement spacer establishment	*Proteus*	Ofloxacin	cure
33	8	6g	no	diffuse osteomyelitis	debridement, cement spacer establishment, osteosynthesis	*S. capitis, S. epidermidis, Propionibacterium*	Rifampicin	failure

Discussion

BJI is difficult to manage, often requiring surgery and prolonged antibiotherapy, sometimes with several drugs that may be poorly tolerated. Cefoxitin is an old antibiotic developed in the early 1970s, but not available in all countries; it is mostly used in prophylactic treatment, but has specific features that allow increasing use in curative treatment of BJI (7).

Few studies of cefoxitin in BJI have been published. Bone diffusion is similar to that of other cephalosporins, reaching 20% of serum level in bone and synovial fluid 1 hour after administration (8,9). Perkins *et al*. reported 27 skin and soft tissue infections treated by cefoxitin, with 93% success, including 3 with contiguous osteomyelitis (4). More interestingly, Schurman *et al*. reported 31 patients with acute or chronic infections of bone, joint or muscle and tendon, with an 84% cure rate (2).

Cefoxitin is a broad-spectrum molecule, including gram-positive cocci (methicillin-susceptible staphylococci, streptococci), Gram-negative bacilli (including extended-spectrum beta-lactamases [ESBL] producing *Enterobacteriaceae*) and anaerobic bacteria (5). In comparison, ceftriaxone exhibits sub-optimal in-vitro activity against MSSA isolates and is not active on anaerobes, unlike cefoxitin, which is usually active on *Bacteroides fragilis* (10). In the present study, cefoxitin was chosen mainly because of the nature of the BJI, so as to avoid using 3 or 4 oral antibiotics, with potentially higher risk of cumulative toxicity.

A maximum time above 2-3 target bacterium MIC is generally considered a suitable pharmacologic goal. Considering that, for susceptible isolates, the maximum MIC of cefoxitin is 8 mg/L for Gram-negative bacilli, 4 mg/L for *S. aureus* and *S. lugdunensis* and 8 mg/L for *S. saprophyticus* (6), the present mean steady-state level of 13.2 mg/L reached this therapeutic target. These concentrations were obtained with a mean dose of 6g/day, adjusted for patients with extreme weights.

Cefoxitin is also a time-dependent antibiotic, stable at room temperature (11,12) and at 37°C (13). Consequently, continuous infusion administered at home with elastometric diffusors is a very interesting means of reducing hospital stay. Elastomeric infusors in silicone are preferable than polyisoprene for constant stable infusion (14). Cefoxitin stability in elastometric diffusors was evaluated by Baxter, but only up to 8°C (manufacturer's data). However, the mean pharmacological dose at equilibrium was adequate in the present patients.

Finally, adverse effects of cefoxitin are rare. Cross-reactivity between cephamycins and other beta-lactams was reported, but incidence of allergic reaction was low and any reactions were mild (15). Other possible adverse events comprise: local reactions, and gastro-intestinal, hematologic, hepatic or renal disorders (5). The seminal study published in 1977, with 143 patients, found a 1.4% rate of eruption, 2% cytolysis, 2% leucopenia, 2.5% eosinophilia and 5% thrombophlebitis (16). In the present study, global tolerance was good, with only 1 severe adverse event, which was likely not related to cefoxitin but to another antibiotic used concomitantly.

Conclusion

Cefoxitin can be a useful outpatient parenteral alternative in the treatment of BJI. Its spectrum is interesting in case of polymicrobial infection, its potential stability enables continuous infusion with elastomeric infusors, and tolerance is generally good. A prospective study with homogeneous infusor management (type of diffusor, dilution, stability analysis) in patients with BJI and with blood pharmacokinetic/ pharmacodynamic analysis is needed to confirm these results.

Competing Interests

The authors have declared that no competing interest exists.

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