Cefovecin: a new long-acting cephalosporin

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Cephalosporins belong to the class of beta-lactam antibiotics and are originally derived from Cephalosporin C, a substance isolated from the fungal species Cefalosporium acremonium. They are bactericidal and act by inhibiting the synthesis of the peptidoglycan layer of the bacterial cell wall through binding to the penicillin-binding proteins (PBPs) [20]. For reaching the PBPs, the antibiotics have to penetrate the bacterial cell wall [11]. This is easily done through the murein layer of gram-positive bacteria but the more complex cell wall of gram-negative bacteria with its outer layers consisting of lipopolysaccharides and lipoproteins can only be penetrated by positive loaded cephalosporins, using porins as canal [5].

Cephalosporins are traditionally grouped into different “generations” according to their antimicrobial properties [6,21]. The spectrum of the first generation, like cephalexin, cefadroxil and cefazolin is very similar to penicillin G and includes primarily gram-positive bacteria (e.g. Staphylococcus intermedius and Staph. aureus) whereas their effect against gram-negative bacteria is limited [21]. Resistances to these antibiotics led to the development of a second generation with better activity against gram-negative bacteria. This generation includes cefoxitin and cefotetan [6,13]. Both first and second generation cephalosporins can be administered either orally or parenterally [13]. Further developments led to the synthesis of the third generation, commonly known as “broad spectrum” cephalosporins. Members include ceftiofur, cefpodoxime and cefoperazone in veterinary medicine, as well as, among others, ceftriaxone, ceftazidime and cefotaxime in human medicine [6,13]. Their action against gram-negative bacteria was optimized with some members like ceftazidime or cefoperazone being active against P. aeruginosa [7] while retaining sufficient activity against gram-positive organisms [7,21]. This generation is also more resistant against beta-lactamases but can in most cases be hydrolyzed by extended spectrum beta-lactamases (ESBL) [8]. The next generation, the fourth, comprises substances like cefepime used in human medicine and cefquinome in veterinary medicine and presents an extended spectrum against gram-negative bacteria, especially Ps. aeruginosa and Enterobacteriaceae producing ESBLs as well as better bactericidal effect against gram-positive germs. The extension of the spectrum is mainly due to more rapid penetration of the outer membrane and better resistance to hydrolyzing beta-lactamases. As with all other cephalosporins, the fourth generation members are inactive against methicillin resistant Staph. aureus (MRSA) [39]. Due to its spectrum and its pattern of resistance to
beta-lactamases, cefovecin has been classified as a member of the third generation [2]. It was first granted a marketing authorisation for use in veterinary medicine in the European Union in June 2006 [3] and in the USA in June 2008 [12].

Cefovecin has been specifically developed for the veterinary medicine as a long-acting antibiotic, a characteristic it shares with ceftiofur, mostly used in food producing animals. The definition of a long-acting antibiotic is somewhat difficult and applies only to authorized species (use according to label). Among currently authorized veterinary antibiotics, “long-acting” may vary from 48 hours in some amoxicillin formulations in cattle or swine up to 158 hours (ceftiofur in swine) or 168 hours (ceftiofur in cattle), whereas in human medicine ceftriaxone has been described as long-acting with a t1/2 of 6-10 hours [7]. A long-acting formulation primarily requires the antibiotic to exert its action at the infection site for a long time. The mode of killing as well as the metabolism of the substance are therefore the most important factors besides physico-chemical parameters like formulation (suspension, slow-release systems) or route of application (very often subcutaneous). Beta-lactam antibiotics are particularly predestined for the development of long-acting formulations due to their mode of bactericidal killing being time dependent [10,18]. They require the maintenance of plasma concentrations over the MIC of the target germs during the whole treatment interval and an increase in peak concentration does not normally enhance their bactericidal effect [18]. In some third generation cephalosporins like ceftriaxone, long action has been attained by modification of the chemical structure at the C7 position [7]. This and additional factors help explain the prolonged therapeutic action of cefovecin. It is rapidly and nearly completely absorbed from the subcutaneous injection site, with a bioavailability of 99% in dogs and cats [2]. Another factor is the high plasma protein binding of 96-98.7% in dogs and cats [15] and more than 99% in cats [16]. A third, important factor is the fact that only the free drug is eliminated, primarily via the kidneys [2]. All of the latter concur to maintain therapeutic levels for approximately 10 to 14 days in dogs and 14 days in cats [2]. Very little data is available on the tissue distribution and metabolism of cefovecin. In cats and dogs, it is known not to undergo any hepatic metabolism and to be excreted as unchanged drug in the urine [12]. Further data on metabolism or distribution are currently unavailable. Third-generation cephalosporins are generally known to achieve therapeutic levels in most body fluids and tissues like blood, urine, bile, peritoneal fluid and skin blisters [7]. Ceftriaxone, a widely used antibiotic in human medicine distributes into bone, lung, prostate, uterine tissues, sputum, tears as well as pleural and synovial fluids. It crosses the placenta and the blood-brain barrier with enhanced penetration of the latter when meninges are inflamed [9]. Ceftiofur has been shown to present similar characteristics in swine [1].

Third generation cephalosporins have been specifically developed with enhanced spectrum against gram-negative bacteria [6]. Against isolates from dogs and cats, cefovecin
demonstrated good activity against gram-negative organisms like *E. coli*, *P. multocida*, *Proteus* spp., *Klebsiella* spp. (including *K. pneumoniae*) and *Enterobacter* [17]. In cats, cefovecin showed good activity against *Fusobacterium* spp., *Bacteroides* spp. and *Prevotella oralis* [2]. However, it is not active against *Ps. aeruginosa* [17]. Third generation cephalosporins are generally less active than members of the first or second generation against gram-positive organisms like streptococci or staphylococci [7], but cefovecin demonstrated good efficacy against *Staph. intermedius*, coagulase-negative Staphylococci and beta-hemolytic streptococci. No bactericidal activity was observed against *Enterococcus* spp., the combination amoxicillin-clavulanic acid offering a better alternative. Cefovecin is also active against anaerobic bacteria, including *Fusobacterium* spp., *Bacteroides* spp., *Prevotella* spp., *Corynebacterium* spp. and *Clostridium* spp. In the comparative study of Stegemann et al., there were no differences in the susceptibility of clinical isolates from dogs and cats from Europe or the United States [17]. In the United States, the marketed product is currently licensed for use against *Staph. intermedius* and *Sc. canis* in dogs and against *P. multocida* in cats [12]. The European authorization lists additional indications, such as infections with *E. coli*, beta-hemolytic Streptococci and *P. multocida* in dogs as well as *Fusobacterium* spp., *Bacteroides* spp. and *Prevotella oralis* in cats [3]. The potential for the development of resistances appears to be low at present time [2]: Among isolates from dogs and cats from Europe and the United States, 9 *E. coli* isolates were considered resistant to cefovecin and other beta-lactams like cephalaxin and amoxicillin-clavulanic acid. 3 *Staph. aureus* isolates, a subpopulation of *Enterobacter* spp. from Europe and 2.8% of anaerobic isolates also exhibited reduced sensitivity [17]. However, the use of third-generation cephalosporins is considered critical in relation to the development of resistances against similar antibiotics used in human medicine (e.g. ceftriaxone) [4]. The long-acting members even deserve more attention as the time when concentrations are close to the MIC of normal flora might be very long and therefore allow for longer selective pressure [14]. The main problems potentially arising from the use of such antibiotics are methicillin-resistant *Staph. aureus* (MRSA) and extended spectrum beta-lactamases (ESBL) in various gram-negative organisms. The emergence of MRSA is not solely related to cephalosporins of the third or fourth generations, but might be favored by all beta-lactam antibiotics [33]. In contrast, the use of cephalosporins of the third generation is a specific risk factor for ESBL colonization of human hospitalized patients and the use of ceftiofur in cattle and turkeys has been shown to have contributed to the spread of ESBL-producing *Salmonella* [29]. The link between resistance to ceftriaxone due to ESBLs and use of ceftiofur was similarly established for *E. coli* isolated from cattle [30,31] or pigs [32]. Even if exotic animals play no role in the food chain, they might have contact with humans in the zoo environment or even in home settings. Salmonella outbreaks following contact with reptiles have been described [34] and
in a study from Chen et al., 61% of the isolates were resistant to cephalothin [35]. The use of the newer cephalosporins should therefore be carefully evaluated under the point of view of resistance promotion.

Studies about the therapeutic use of cefovecin have been conducted on cats, dogs, hens, green iguanas and ferrets [15-17,19,23-28]. Besides, brief elimination studies have been performed in 4 species of ruminants, 2 species of primates, 3 species of exotic felids, ring tailed lemurs and in the domestic pig [40]. In cats, cefovecin is approved for use at a single subcutaneous injection of 8 mg/kg with a 14 days dosing interval if clinically indicated [16]. Mean peak plasma concentrations of 141±12 μg/ml have been achieved within 2 hours after subcutaneous injection and plasma concentrations 14 days after injection still exceeded 15 μg/ml, well above the MIC₉₀ for P. multocida (0.06 μg/ml) [15]. A study by Six et al. [22] used cefovecin as a treatment for abscesses and infected wounds in cats. In this study, a single injection of 8 mg/kg was considered safe for the treatment of skin infections and as effective as oral cefadroxil at 22 mg/kg once daily for a time period of 14 days. Only few patients showed minimal adverse effects after medication, most commonly gastrointestinal disturbances. An older study by Stegemann et al. [23] had already established, that a single subcutaneous injection of cefovecin at the same dose of 8 mg/kg bodyweight repeated at 14 day intervals if clinically indicated was as effective as the twice-daily oral application of the combination amoxicillin/clavulanic acid for the treatment of feline abscesses and infected wounds [23]. Finally, the treatment of feline urinary tract infections by a single subcutaneous administration of cefovecin at 8 mg/kg favorably compared to a twice daily oral application of cephalaxin [27].

In dogs, the dosage of cefovecin is similar to cats, with 8 mg/kg body weight [15,24-26]. Mean peak plasma concentrations of 121 μg/ml have been achieved after a single subcutaneous injection and mean peak concentrations of free cefovecin remained above 0.25 μg/ml for 19 days [15]. As in cats, injections of cefovecin at 14 days intervals was determined to be a safe and effective treatment for canine superficial or deep pyoderma, as well as for infected wounds and abscesses. Moreover, it was non-inferior to the well established combination of amoxicillin/clavulanic acid given orally for 2 weeks [24]. The same dosage applied at the same interval compared favorably with twice-daily oral cefadroxil for the treatment of bacterial folliculitis, abscesses and infected wounds in dogs [25]. Some gastrointestinal adverse effects like vomiting or diarrhea were observed in a few patients. As in cats, urinary tract infections were successfully treated in dogs with the same dose of 8 mg/kg applied subcutaneously every 14 days. The treatment demonstrated non-inferiority compared to cephalexin orally administered twice daily over the same period [26].

There is currently only very little data available on the use of cefovecin in exotic animals. In a recent study [19], the main pharmacokinetic parameters were investigated in juvenile green
Iguanas (*Iguana iguana*) and female Lohmann hens (*Gallus gallus domesticus*). In the first and second part of this study, cefovecin was administered subcutaneously as a single injection of 10 mg/kg body weight under the skin of the shoulder in the Lohmann hens and under the skin of the flank in the juvenile green iguanas. The results were in great contrast to parameters known from dogs and cats with much shorter half-life in hens (0.9 h vs. 5.5 days in dogs) and green iguanas (3.9 h vs. 6.9 days in dogs). Plasma protein binding in these species might explain the difference. It was not determined in hens and iguanas, but the much higher volume of distribution calculated in these species compared to dogs is an indicator for lower plasma protein binding. In preliminary studies, the authors determined the use of cefovecin as a single subcutaneous injection of 10 mg/kg in additional bird species, including two scarlet ibis (*Eudocimus ruber*), one African grey parrot (*Psittacus erithacus*), two blue-fronted amazons (*Amazona aestiva*) and reptiles, including one Russian tortoise (*Testudo horsfieldii*), one Spur-thighed tortoise (*Testudo graeca*), two Russian ratsnakes (*Elaphe schrenckii*), one Boa constrictor (*Boa constrictor*) and one central bearded dragon (*Pogona vitticeps*). Cefovecin could be detected in the first blood sample taken shortly after administration in all of these species, but at 2h after injection, the antibiotic could only be detected in scarlet ibis (6.5 ± 0.2 µg/ml), Russian ratsnake, boa constrictor (both 6.6 µg/ml) and central bearded dragon (16 µg/ml). In all other species, no cefovecin was detectable in the blood 2 hours after injection. The much shorter half-life in all investigated species makes a dosing scheme similar to dogs and cats impossible and cefovecin would have to be applied with intervals of 1 hour in birds and 2 hours to 2 days in reptiles, thereby offering no alternative to substances currently used in exotic animal medicine like ceftazidime, a third generation cephalosporin from human medicine. A study from Montesinos [28] determined the pharmacokinetics of cefovecin after subcutaneous injection of 8 mg/kg bodyweight in healthy, adult ferrets. Plasma concentrations were measured at different times prior and after subcutaneous injection. Peak plasma concentrations remained above the MIC$_{90}$ for *Staphylococcus intermedius* and *E.coli* for at least 2 days [28]. During this study, no adverse effects could be detected. A study from Bertelsen [40] showed that cefovecin may be a possible alternative for long dosing interval treatment in exotic feline species, lemurs and pigs. Finally, in two case reports, cefovecin was used as an antibiotic for treating a captive, juvenile chimpanzee (*Pan troglodytes*) and an orangutan (*Pongo pygmaeus pygmaeus*) [37,38]. To the knowledge of the reporting authors, no pharmacokinetic or pharmacodynamic studies have been conducted in these species yet and dosages seem to be empirical and extrapolated from canine and feline medicine. Cephalosporins as a class are relatively safe antimicrobial agents. Adverse effects are usually not serious and occur at relatively low frequency. Most importantly, the use of most cephalosporins, including cefovecin is contraindicated in small herbivores, including rabbits.
and guinea pigs because of the destruction of their natural gut flora [2]. Hypersensitivity unrelated to the dose applied is among the most frequent reactions. It can manifest as rash, fever, eosinophilia, lymphadenopathy or anaphylaxis [13]. The use of cephalosporins in patients allergic to penicillin is controversial. In humans, the risk of cross-reactions between penicillin and cephalosporins of the second and third generations has been estimated to be very low, near 0.5% [36], but the incidence in veterinary medicine is unknown [13]. Anorexia, vomiting and diarrhea are well known adverse effects observed after oral administration [13] but might also occur following parenteral application of cephalosporins undergoing hepatic metabolism and elimination through the bile (e.g. ceftriaxone or cefoperazone in humans) [7]. Emesis and diarrhea are also reported following use of cefovecin in cats and dogs [3,12]. Additional adverse reactions like phlebitis, pain at injection site have been reported for third-generation cephalosporins like cefotaxime [7]. Manifestations of neurotoxicity like convulsions or encephalopathy have been described after high doses of cephalosporins and other beta-lactam antibiotics in humans, but so far no such clinical signs have been observed in animals after cefovecin administration. Specifically, no adverse effects have been observed after treatments with up to 7.5 times the recommended dose in dogs or cats. In fact, cefovecin was well tolerated in these species up to a single subcutaneous dose of 180 mg/kg, representing 22.5 times the recommended dose. Only mild swelling and discomfort at injection site were noted. Overdosage did not produce abnormalities in haematology, clinical chemistry and histopathology [2]. Due to lack of specific studies, the use of cefovecin during pregnancy and lactation is contraindicated. However and as no teratological effects have been described for cephalosporins, reproductive toxicity is not to be expected. Finally, cefovecin is not thought to be carcinogenic or mutagenic [2].

Diseases like deep pyoderma or urinary tract infections require antibiotic treatment over a long time. In companion animals like dogs or cats, this is very often done by twice daily oral administration. However, the development of newer antimicrobials like ceftiofur or cefovecin, maintaining therapeutic levels in target tissues over many days opens new possibilities when owners are unable to pill their pets. Exotic pets are more susceptible to stress from handling for medication and therefore, longer dosing intervals for treatments would be beneficial to minimize risks related to stress [19]. However, the concept of long-acting substances can only apply to species in which the formulation was tested, as shown here for cefovecin. The therapeutic action of the latter is very short in birds and short to moderately long in reptiles. By contrast, its use in ferrets at dosing intervals of 2 to 3 days seems to be more promising. Despite having the potential to offer some decisive advantage for the treatment of exotic animals, antimicrobials like cefovecin should only be used when data are specifically available for the species to be treated. Therefore it is hoped that more specific studies and case reports will generate the required knowledge in the future.


