Use of Long Half-Life Parenteral Cephalosporins in Ambulatory Practice

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Cefonicid (Monocid) and ceftriaxone (Rocephin) are long half-life cephalosporins that may be used for serious infections in the outpatient setting. They may be used as an extension of initial hospital treatment, or therapy can be initiated and completed in many cases with the patient remaining at home.

Sufficient clinical experience exists with both ceftriaxone and cefonicid to recommend these agents for selected patients having pyelonephritis, osteomyelitis, or soft tissue infections. Cefonicid, perhaps in combination with erythromycin, will provide excellent coverage for complicated community-acquired pneumonias. Ceftriaxone is effective as single-dose therapy for even complicated gonococcal infections. The use of long half-life cephalosporins in ambulatory practice may result in substantial cost savings for certain patients.

Clinicians are at times frustrated by prolonged hospitalizations of those who are not acutely ill simply to provide parenteral antibiotic therapy. Patients and their families may be equally disconcerted because of the high cost and disruption consequent to hospitalization. Nevertheless, the physician may wish to initiate parenteral antibiotic therapy for a particular illness, such as pyelonephritis or pneumonia, as the clinical circumstances can create apprehension about relying upon oral agents alone. Though the efficacy, safety, and financial advantages of outpatient intravenous antibiotic programs are well established,[1-3] such therapy is usually hampered by requisite multiple daily office or clinic visits and maintenance of venous access.

The availability of two new broad-spectrum, long half-life parenteral cephalosporins may, in some cases, obviate the need for hospitalization, and in others, significantly shorten hospital stay. In selected cases, parenteral antibiotic therapy may now be provided on a practical basis for serious infections, either in the physician's office or in the outpatient clinic. The pharmacology, spectra of activity, and clinical application of cefonicid and ceftriaxone in the ambulatory management of selected infections are herein reviewed.

Cefonicid (Monocid, Smith Kline & French) is a broad-spectrum cephalosporin that because of its spectrum of activity is typically grouped as a second-generation agent. Cefonicid is usually administered intravenously or intramuscularly in doses of 1 to 2 g, and because of its extended four-hour half-life, it can be given once every 24 hours (Table 1). Cefonicid is primarily excreted by the kidneys with over 90 percent of the drug being eliminated unchanged in the urine; therefore, dosing adjustments must be made in patients with renal failure. Although cefonicid's volume of distribution is small, reflecting high serum protein binding,[4] the agent attains good concentrations in sputum and bone within one hour following the initial dose.[5]

Ceftriaxone (Rocephin, Roche) has a half-life longer than any of the currently available cephalosporins. The mean half-life of 6.5 hours allows once daily dosing. Thirty to 60 percent of the drug is excreted by the kidneys, while the remainder is excreted in the bile.[6] Ceftriaxone readily penetrates the blood-brain barrier to achieve therapeutic concentrations, an attribute that has made it a preferred cephalosporin in the treatment of gram-negative meningitis, both in children and adults.[7]

The generations of cephalosporins and their related agents having a spectrum of activity that is therapeutically equivalent are displayed in Table 2.

Cefonicid's spectrum of activity is summarized in

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TABLE 1. REPRESENTATIVE CEPHALOSPORIN DOSING FOR SERIOUS INFECTIONS (EXCEPT MENINGITIS) IN PATIENTS WITH NORMAL RENAL FUNCTION

Cephalosporin*	Dosage
Cefazolin (Ancef, Kefzol)	500 mg to 1 g intravenously or intramuscularly, every 8 hours
Cefonicid (Monocid)	1 to 2 g intravenously or intramuscularly, once daily
Ceftriaxone (Rocephin)	1 or 2 g intravenously or intramuscularly, once daily

**These dosages are also appropriate for the clinically similar cephalosporins (Table 2)*

TABLE 2. REPRESENTATIVE CEPHALOSPORINS AND RELATED AGENTS HAVING A THERAPEUTICALLY EQUIVALENT ANTIBACTERIAL SPECTRUM OF ACTIVITY

Generation	Representative Cephalosporin	Clinically Similar Cephalosporin
First	Cefazolin (Ancef, Kefzol)	Cephalothin Cephapirin Cephradine
Second	Cefonicid* (Monocid)	Cefamandole* Cefuroxime Ceforanide
Third	Ceftriaxone (Rocephin)	Cefotaxime Ceftizoxime Cefmenoxime (investigational)

**Cefoxitin (Mefoxin) is not included in this listing because of its increased activity against Bacteroides fragilis and reduced activity against Hemophilis influenzae*

TABLE 3. IN VITRO ACTIVITY OF LONG-LASTING CEPHALOSPORINS

Infective Agents	Representative Cephalosporins*		
	Cefazolin	Cefonicid**	Ceftriaxone
Gram-positive bacteria			
Staphylococcus aureus	++	++	++
Staphylococcus epidermidis	++	+/++	++
Streptococcus (non-group D)	++	++	++
Enterococcus (group D streptococcus)	0	0	0
Gram-negative bacteria			
Escherichia coli	+	++	++
Klebsiella spp	+	++	++
Proteus mirabilis	++	++	++
Indole (+) Proteus spp	0	+	++
Enterobacter spp	0	+	++
Hemophilis influenzae	+	++	++
Serratia marcescens	0	0	++
Pseudomonas aeruginosa	0	0	+
Anaerobes			
Bacteroides fragilis	0	0	+
Miscellaneous anaerobic cocci and bacilli	++	++	++

**Clinically similar cephalosporins are shown in Table 2*
***Cefonicid may be slightly less active in vivo against staphylococci (especially Staphylococcus epidermidis) than clinically similar agents*
++ Highly susceptible (MIC 90 ≤ 8 μg/mL)
+ Marginally susceptible (MIC 90 = 16-32 μg/mL)
0 Resistant (MIC 90 > 32 μg/mL)

Table 3. Against most strains of Staphylococcus aureus, the minimal inhibitory concentration for 90 percent of clinical isolates (MIC 90) is less than 16 μg/mL. Though somewhat higher than other available second-generation cephalosporins, a MIC 90 of this order will allow successful treatment of most staphylococcal infections. Cefonicid shares good activity against Streptococcus species along with other cephalosporins in all classes. As do other cephalosporins, cefonicid has no activity against methicillin-resistant Staphylococcus aureus or against enterococcus species. Cefonicid's activity against Staphylococcus epidermidis is significantly less than other second-generation cephalosporins.

Ceftriaxone's spectrum of activity against gram-positive organisms is similar to that of cefonicid.

Against Staphylococcus aureus, ceftriaxone and cefonicid are equivalent clinically. Again, neither drug is efficacious against enterococcus.

With respect to gram-negative coverage, cefonicid is similar to that of cefoxitin, ceforanide, and cefamandole against Escherichia coli, Klebsiella pneumoniae, and indole-negative Proteus species. Cefonicid may be used therefore in many documented or suspected gram-negative infections for which a second-generation cephalosporin is indicated. There is excellent activity against Hemophilus influenzae including β-lactamase producers. Though effective against Neisseria gonorrhoeae, its activity is exceeded by ceftriaxone.

Cefonicid is inactive against Serratia marcescens, Pseudomonas aeruginosa, and Bacteroides fragilis. The only second-generation cephalosporins with Bacteroides fragilis activity are cefoxitin and cefotetan.

As summarized in Table 2, ceftriaxone's gram-negative coverage is superior to that of cefonicid with increased activity against the Enterobacter species, Escherichia coli, and Klebsiella, Proteus, and Serratia species. Ceftriaxone's anaerobic coverage is comparable to that of other third-generation cephalosporins. It has moderate activity against Pseudomonas aeruginosa in combination with an antipseudomonal aminoglycoside. Ceftriaxone has particularly good activity against the meningococcus and Neisseria gonorrhoeae (MIC 90 < 0.01 μg/mL). Ceftriaxone is ineffective against Listeria, Clostridium, Chlamydia, or Legionella species.[8]

Adverse effects reported with cefonicid include pain with intramuscular injection, which may be obviated by mixing the drug with 1 percent lidocaine. The pain upon intramuscular injection is not more than that caused by injection of procaine penicillin G. Many cephalosporins, including cefonicid, may cause transient elevation of hepatic transaminases. Hematologic and renal abnormalities occur rarely. Allergic reactions and flu-like syndromes have occurred in patients who are being treated with the agent for a prolonged period.[9]

The adverse effects of ceftriaxone, which have been mild and relatively infrequent, include pain after intramuscular injection, rash, diarrhea, and colitis. Transient diarrhea, as well as oral or mucocutaneous candidiasis, has been reported in children.[10] As with cefonicid, elevated transaminases have been seen, and slight prolongation of the prothrombin time has been reported. Bleeding during ceftriaxone therapy appears to be rare. This agent does not have the methylthiotetrazole side chain, as do moxalactam and cefoperazone, that has been associated with clotting abnormalities.[8]

CLINICAL APPLICATIONS

The clinical applications of cefonicid and ceftriaxone most relevant to the ambulatory setting include treatment of pyelonephritis, osteomyelitis, community-acquired pneumonia, skin and soft tissue infections, and both complicated and uncomplicated gonococcal infections (Table 3). The decision to use parenteral agents on an ambulatory basis, rather than as inpatient treatment, represents a clinical judgment based upon a number of factors: the type and severity of infection, host resistance factors, and the opportunity for intensive short-term follow-up. For patients who have been discharged from the hospital early anticipating parenteral therapy on an ambulatory basis, there should have been demonstrated a satisfactory initial response to the long half-life cephalosporin.

The duration of parenteral antibiotic therapy in the ambulatory setting is determined by the same factors that govern the use of parenteral agents in the hospital: the specific type of infection and the patient's clinical response. These considerations also apply when deciding upon the most appropriate time to change from parenteral to oral therapy.

Pyelonephritis

Both cefonicid and ceftriaxone have good to excellent activity against those organisms most often implicated in outpatient-acquired pyelonephritis, ie, infections resulting from Escherichia coli and Klebsiella and Proteus species. High urinary levels and presumably renal parenchymal levels have been documented with both agents.[4,6] In selected cases of pyelonephritis, cefonicid may be used for empiric therapy when the urinalysis discloses bacilluria. Cefonicid has also been shown to be successful single-dose therapy for uncomplicated lower urinary tract infections in women.[11] Once-daily dosing may be prescribed in the nursing home setting, thereby obviating the need for transfer to an acute care hospital. In the more seriously ill or compromised patient, cefonicid or ceftriaxone may be used for specific therapy following initial hospitalization. In general, ceftriaxone would have the same applications as cefonicid for treatment of pyelonephritis; however, ceftriaxone should be reserved for those infections resistant to cefonicid. Ceftriaxone may be more appropriate for the treatment of catheter- or instrumentation-associated urinary tract infections in the hospitalized patient and, if necessary, ceftriaxone therapy should be continued on an ambulatory basis following discharge. The duration of therapy will vary but is commonly 10 to 14 days.

Osteomyelitis

Osteomyelitis is an attractive area for outpatient treatment because of the long duration of therapy required, typically six weeks or longer. Because of its activity against Staphylococcus aureus, the most common organism associated with osteomyelitis, cefonicid can be successfully employed in the ambula-

tory management of this illness.[9,12] Following diagnosis and initiation of treatment, the majority of patients may be discharged from the hospital and managed in the clinic or office.

Ceftriaxone has been more extensively studied in the ambulatory treatment of osteomyelitis and prosthesis-associated bone infections. Eron et al[13] reported their experience in treating 76 patients with bone infections. The majority of organisms cultured were Staphylococcus aureus or Staphyloccus epidermidis, but gram-negative organisms were isolated as well. The authors noted an 89 percent bacterial eradication rate in combination with surgical management. Many of the patients in this study had failed previous therapy, and several cases were complicated by vascular insufficiency. Seven of nine patients had cure or improvement in bone or joint infections in a study by Baumgartner and Glauser.[14] In these studies utilizing cefonicid and ceftriaxone, the majority of the patients were able to be treated for an extended period outside the hospital.

Pulmonary Infections

Some patients with community-acquired pneumonia, especially those debilitated by age, pulmonary disease, alcoholism, or diabetes, may be candidates for extended-spectrum parenteral antibiotic therapy. Cefonicid's excellent coverage against Streptococcus, Hemophilus, and Klebsiella species make it a good choice for empiric therapy. For hospitalized patients, cefonicid may be used as empiric therapy, and once the organism has been identified and sensitivities determined, the agent can be continued on an ambulatory basis. It is also a logical choice, perhaps in combination with erythromycin, for empiric antibiotic therapy in less severely ill patients who are appropriate candidates for management on an ambulatory basis. The use of ceftriaxone in the treatment of pulmonary infections would be reserved for the treatment of organisms resistant to cefonicid. For other pneumonias, such as those complicated by empyema or lung abscess, treatment may be continued out of the hospital as long as necessary once toxicity is resolving or drainage has been achieved.

Skin and Soft Tissue Infections

Cellulitis and lymphangitis, most commonly caused by streptococcal and staphylococcal organisms, are among the most common infections seen in ambulatory practice. Many of these infections are potentially serious or are serious at the time of initial evaluation. For those patients requiring parenteral antibiotic therapy, in whom it is felt hospitalization is not an absolute requirement, empiric therapy with cefonicid can be undertaken. Either ceftriaxone or cefonicid may be used in the treatment of these infections once cultures and sensitivities have been obtained. Ceftriaxone would generally be reserved for those organisms that are resistant to cefonicid and sensitive to ceftriaxone.

Gonococcal Infections

Both cefonicid and ceftriaxone are effective in the treatment of gonorrhea. Cefonicid has been studied in uncomplicated gonococcal urethritis produced by penicillinase-producing Neisseria gonorrhoeae and can be used in most patients with good results.[15] Cefonicid is probably not efficacious in the treatment of pharyngeal gonorrhea.[16] Ceftriaxone, however, is superior to spectinomycin for the treatment of pharyngeal infections with Neisseria gonorrhoeae in both men and women.[16] A single intramuscular dose of ceftriaxone, 125 mg, cured 52 homosexual men with anorectal gonococcal infections.[16] Ceftriaxone is also very active against penicillinase-producing Neisseria gonorrhoeae and can be used in most patients with a history of penicillin allergy. As with other cephalosporins, neither cefonicid nor ceftriaxone eradicates coexisting chlamydia.

Important exclusions for these drugs correspond to their lack of activity against enterococcal infections and Bacteroides fragilis. These drugs should not be used alone for treatment of infections from Pseudomonas species. Ceftriaxone has modest activity against Pseudomonas aeruginosa in combination with an antipseudomonal aminoglycoside. Both of these agents are inactive against methicillin-resistant Staphylococcus aureus. Cefonicid has been studied in the treatment of staphylococcal endocarditis and has been found to be ineffective.[17] Cefonicid should not be used for treatment of meningitis because of its poor penetration into the cerebrospinal fluid. Ceftriaxone has excellent penetration into cerebrospinal fluid and is effective in the treatment of hospitalized patients with meningitis.

COST CONSIDERATIONS

Numerous studies[12,14,18,20] have documented cost savings with ambulatory treatment of infections. These cost savings are quite substantial and involve a number of factors: (1) reduced cost of administration (the cost of 1 g of cefonicid is approximately $15 and 1 g of ceftriaxone is approximately $28,[21] (2) reduction of hospital stay, and (3) recovery of potentially lost income for patients who are able to return to work while receiving parenteral antibiotic therapy. Other less easily measured factors include increased patient comfort in the home environment and the psychosocial benefits of a lessened financial burden.

Pharmacies should make these drugs available outside the hospital, and there must be provision for monitoring of intravenous catheters should they be

necessary. In large programs, ambulatory parenteral antibiotic therapy can be performed by a team approach that can be supported from the consequent cost savings.[1-3,18,19]

Both cefonicid and ceftriaxone are long half-life cephalosporins that may be conveniently and effectively prescribed for serious infections in the outpatient setting, either as an extension of initial hospital treatment or as therapy initiated and completed, in many cases, with the patient remaining at home or in a nursing institution. Common clinical settings include the treatment of osteomyelitis, skin and soft tissue infections, pulmonary infections, and urinary tract infections for which parenteral therapy is indicated. Successful outcome requires that these agents be used in an appropriate clinical setting, keeping in mind their limitations and areas of highest efficacy. Cultures, where appropriate, may be collected at the time of initiating empiric therapy. There needs to be careful monitoring for drug toxicity and resolution of the infection. Numerous studies document substantial cost savings and effective clinical application of the long-acting cephalosporins in the treatment of difficult infections. Further study of these agents in outpatient settings will be helpful in increasing knowledge regarding other indications and efficacy.

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