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Pharmacological Properties of Parenteral Cephalosporins

Rationale for Ambulatory Use

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Abstract

Parenteral cephalosporins are among the most frequently used antibiotics in hospital therapy. They are characterised by an extended spectrum of activity against Gram-positive and Gram-negative bacteria, and some also have good activity against anaerobes. They kill proliferating bacterial cells rapidly, and generally show only a low tendency to select resistant mutants. However, there are cephalosporin compounds which induce cephalosporinases very rapidly in certain microorganisms. Together with other β-lactam antibiotics, parenteral cephalosporins interfere with bacterial cell wall synthesis by inhibiting peptidoglycan cross-linkage. Because of this specific target, they are nontoxic to mammalian cells, and have a very favourable adverse effect profile. The chemical stability of parenteral cephalosporins in aqueous solution is good. After intravenous injection, high concentrations of these agents are achieved in serum and tissue. Most cephalosporins are eliminated unchanged via the kidney, with a half-life of 1 to 2 hours. But there are also derivatives with a serum half-life of more than 2 and up to 8 hours, allowing 12- or 24-hour dosage intervals. Because of their reliable efficacy and low risk of adverse effects, the parenteral cephalosporins offer a high degree of tolerability even in the setting of outpatient antibiotic therapy. In particular, the derivatives of the third generation are characterised by unique pharmacological properties.

1. Antibacterial Activity of Parenteral Cephalosporins

Parenteral cephalosporins are among the most frequently used antibiotics in hospital therapy. They are active against a broad spectrum of bacterial pathogens, with the exception of enterococci and methicillin-resistant *Staphylococcus aureus* (MRSA), which are both resistant to all cephalosporins. Cephalosporins may be classified according to their pharmacodynamic (microbiological) and pharmacokinetic properties.[1-5] They were

Table I. Classification of cephalosporins according to generation[1-4,6]

Cephalosporin generation			
first	second	third	fourth
Cefalothin	Cefamandole	Cefotaxime	Cefepime
Cefazolin	Cefoxitin[a]	Ceftizoxime	Cefpirome
Cefaloridine	Cefuroxime	Cefmenoxime	
	Cefotiam	Ceftriaxone	
	Cefotetan[a]	Cefoperazone	
	Cefmetazole	Ceftazidime	
	Cefonicid	Latamoxef[b]	
		Flomoxef[b]	
		Cefodizime	

a Cephamycin.
b Oxacephem.

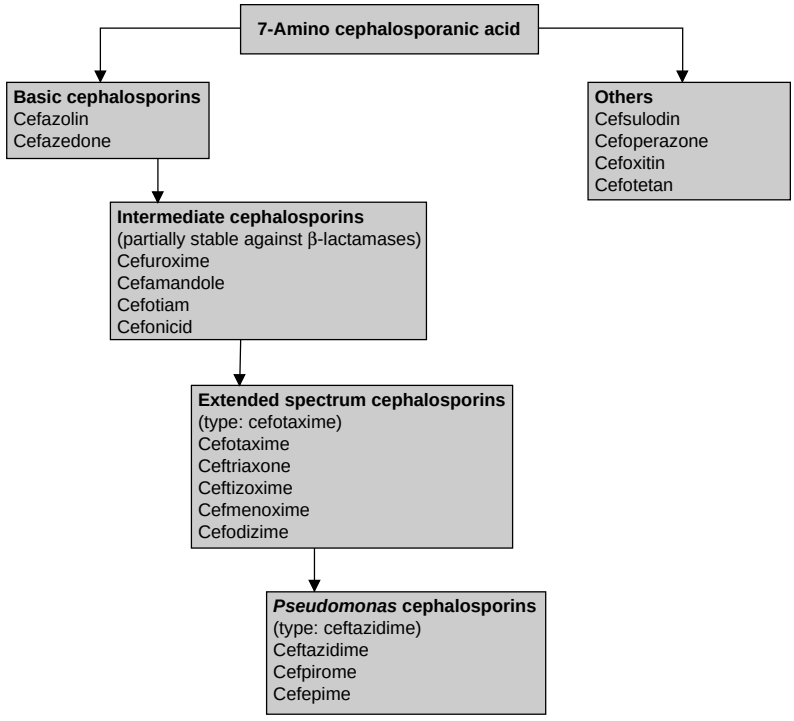


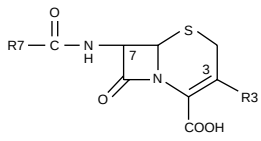
Fig. 1. Classification of clinically important parenteral cephalosporins based upon their chronological development, structure and microbiological features.[4]

originally divided into 'generations' according to chronological development. This classification has been in common usage until now, although some derivatives developed in the 1980s have been assigned to the older second generation cephalosporins because of similar pharmacological properties (table I; figs 1 and 2).

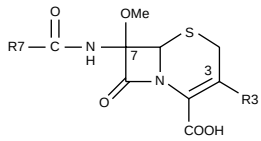
1.1 Cephalosporin Ring System

The cephalosporin ring system offers the possibility of a wide range of molecular modifications. Findings regarding the correlation of biological activity and specific modifications at the C-3 and C-7 atoms have made possible a kind of 'molecular modelling', thus enabling the development of derivatives with distinct pharmacodynamic properties, i.e. a distinct spectrum of activity and pharmacokinetic properties.[7,8] In addition, derivatives with considerably altered pharmacological properties have been obtained by the introduction of a methoxy group at C-6, or by the replacement of the sulphur in the dihydrothiazine ring by an oxygen or carbon atom.

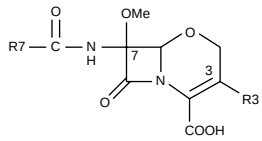
The first cephalosporins, cefalothin and cefaloridine, had the simple heteroaromatic thienyl ring at the C-7 acyl side chain, but no second substituent at the α-C atom in the side chain. These compounds were active against staphylococci and streptococci, but not against enterococci and important Gram-negative species, such as *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. Further enhancement of the lipophilicity of the acyl side chain was accompanied by a further reduction in activity against Gram-negative bacteria.



Cephalosporins



Cephamycins (CM)



7-Methoxy-Oxacephems (OC)

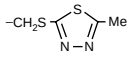
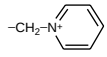
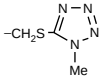
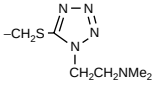
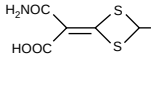
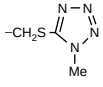
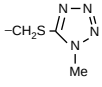
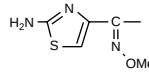
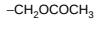
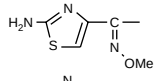
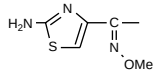
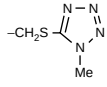
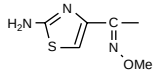
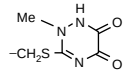
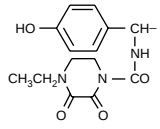
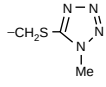
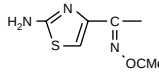
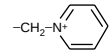
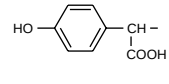
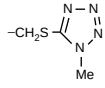
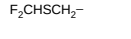
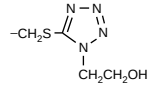
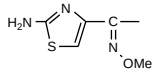
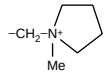
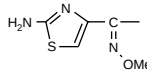
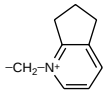
	R7	R3	R7	R3
Cephalosporin generation				
First				
Cefalothin				
Cefazolin				
Cefaloridine				
Second				
Cefamandole				
Cefoxitin (CM)				
Cefuroxime				
Cefotiam				
Cefotetan (CM)				
Cefmetazole (CM)				
Third				
Cefotaxime				
Ceftizoxime		H		
Cefmenoxime				
Ceftriaxone				
Cefoperazone				
Ceftazidime				
Latamoxef (OC)				
Flomoxef (OC)				
Fourth				
Cefepime				
Cefpirome				

Fig. 2. Structural formulae of cephalosporins according to generation.

In contrast, the presence of a hydroxy group at the α-C atom in the acyl side chain (cefamandole) enhanced activity against Gram-negative species. Introduction of an α-methoximino group at this carbon atom (cefuroxime) increased stability in the presence of β-lactamases of Gram-negative bacteria, except for those of *Bacteroides*, *Pseudomonas* and *Enterobacter*. Cephalosporins containing the methoximino moiety vary in their tendency to induce cephalosporinases of *Citrobacter freundii*,

Table II. *In vitro* activity (minimum inhibitory concentration; mg/L) of cephalosporins of different generations[4,5,9,10]

	Staph. aureus[a]	*Strep. pyogenes*	*Strep. pneumoniae*	*Escherichia coli*	*Enterobacter*[b]	*Pseudomonas aeruginosa*	*Bacteroides fragilis*
Cefazolin	0.5-1	0.25	0.12	1-8	>128	>128	16
Cefuroxime	0.1-4	0.03	0.03	0.5-8	4-64	>128	16
Cefotetan	8	ND	ND	0.06-0.1	0.125-64	>128	4
Cefotaxime	1-2	0.06	0.02	<0.125	0.03-2	8-64	2
Ceftriaxone	2-8	0.012	0.025	<0.125	0.03-4	4-32	2
Ceftazidime	8-32	ND	ND	≥0.125	0.03-4	0.5-2	64
Cefpirome	2-4	0.008	0.03	0.125-0.25	0.03-4	1-16	16

a Penicillinase producing methicillin-sensitive strains.

b *Enterobacter*, indole-positive *Proteus, Morganella, Serratia* and *Citrobacter* species.

ND = no data; ***Staph.*** = *Staphylococcus*; ***Strep.*** = *Streptococcus*.

Enterobacter cloacae, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

A decisive factor with respect to intrinsic activity was the introduction of the 2-aminothiazolyl moiety into the acyl side chain, potentiating the affinity of cephalosporins for the pharmacological receptors – i.e. the penicillin-binding proteins (PBPs) – especially of Gram-negative bacteria.

Consequently, aminothiazolyl and methoximino moieties are typical components of the third and fourth generation cephalosporins (such as cefotaxime, ceftizoxime, ceftriaxone, cefepime and others).

Replacement of the methoximino group by an acid iminopropyl carboxy group (e.g. ceftazidime) has led to excellent activity against *P. aeruginosa*, *Burkholderia cepacia* (formerly *P. cepacia*), and *Acinetobacter*, but not against *Stenotrophomonas maltophilia* (*Xanthomonas maltophilia*). However, the activity against staphylococci unfortunately decreased.

In contrast, cefepime, which also has high activity against *Pseudomonas*, still has the methoximino group, and at C-3 a positively charged methylpyrrolidino moiety. It seems that the methoximino group is correlated with activity against staphylococci, while the pyrrolidino group enhances the ability of the drug to penetrate the outer membrane of Gram-negative organisms, especially of *P. aeruginosa*.

Cephalosporins with the thiomethyl tetrazole ring moiety at C-3 (cefamandole, cefotetan, cefoperazone, cefmenoxime and the oxacephem derivative latamoxef) have increased activity in general (table II). However, they also have adverse effects: they antagonise the effect of vitamin K and have disulfiram-like properties.[11]

In the oxacephems (latamoxef, flomoxef), the sulphur in the dihydrothiazine ring is replaced by oxygen. These agents are more active against Gram-negative bacteria including anaerobes, but only moderately active against aerobic β-lactamase–producing strains.

Cephalosporins containing a 7-α-methoxy group are called cephamycins, e.g. cefmetazole, cefoxitin and cefotetan. Comparison of the compounds demonstrates that cefotetan is more active against Gram-negative organisms, while cefoxitin is more active against Gram-positive bacteria. Cephamycins are very stable in the presence of β-lactamases, namely cephalosporinases, and also exhibit specific activity against *Bacteroides* species.[4,6,7]

Because of their extended spectrum of activity, the newer cephalosporins have been shown to induce alterations in the bacterial homeostasis of the physiological human flora. Superinfections by staphylococci (more frequently with administration of cefoperazone and ceftazidime, rarely with cefotaxime, and to a lesser extent with ceftriaxone), enterococci, and *P. aeruginosa* (rarely with cefotaxime, ceftriaxone and ceftizoxime, and scarcely with ceftazidime) may be observed.[12,13] The latest cephalosporins with the broadest spectrum of activity also favour superinfections by fungi, such as *Candida*.[11] However, there are very few good comparative data.

2. Mechanism of Action of Cephalosporins

The pharmacological receptors for β-lactam antibiotics are the PBPs. In Gram-negative organisms, PBPs of types 1, 2, and 3 are essential for cell proliferation, whereas PBPs of types 4, 5 and 6 have less essential functions.[14,15] The sensitivity of bacteria to a specific cephalosporin depends on the affinity of the cephalosporin for one or more PBPs. The first generation cephalosporin cefalothin exhibits high affinity for the PBPs of Gram-positive bacteria, e.g. staphylococci. The aminothiazolyl cephalosporins (such as cefotaxime, ceftizoxime, ceftriaxone, ceftazidime etc.) demonstrate high affinity for the PBPs of Gram-negative strains, thereby dramatically enhancing activity against Gram-negative organisms.[7,15,16]

The PBPs are identical with the D-ala-D-ala trans-, carboxy-, and endopeptidases responsible for cross-linking of newly produced peptidoglycan. Cephalosporins bind mainly to D-ala-D-ala trans- and endopeptidases.[5] Because of the similar structure (of the D-alanyl-D-alanin bond of the peptidoglycan pentapeptide and β-lactams), the above-mentioned enzymes mistake cephalosporins for their normal biological substrates and react with them to yield chemically stable inactive esters. As a result, depending on which particular transpeptidases are inhibited, the cell may grow as a filament or as a spheroblast. Ultimately, lysis occurs because the deformed bacteria cannot withstand the osmotic pressure. In addition, cephalosporins may activate endogenous bacterial lysins, and in this way trigger autolysis of the cell.[16]

Nevertheless, bacteria are able to prevent the lethal effect of cephalosporins by different mechanisms of resistance (table III).[14] The different generations of cephalosporins vary in their ability to overcome these mechanisms of resistance: i.e. in their ability to penetrate the outer bacterial cell membrane to avoid inactivation by β-lactamases, and in the extent of their binding affinity for the PBPs. In addition, cephalosporins containing a methoximino group and cephamycins vary to an appreciable extent in their ability to induce cephalosporinases. The same is the case with carbapenems.

3. Pharmacokinetic Properties of Parenteral Cephalosporins in Relation to Effective Ambulatory Use

For ambulatory use, oral administration of a drug seems to be the route of choice. However, intravenous or intramuscular administration results in more predictable drug concentrations in blood and tissue and is also mandatory for some severe infections. In addition, parenteral administration of antibiotics results in higher serum and tissue concentrations than oral administration.[17-19] The broad spectrum cephalosporins exhibit time-dependent bactericidal activity and produce prolonged postantibiotic effects only with staphylococci. The duration of time that serum levels exceed the minimum inhibitory concentration (MIC) is the important pharmacodynamic parameter correlating with efficacy for these drugs. Maximal efficacy for cephalosporins in several animal infection models is approached when serum levels

Table III. Mechanisms of resistance to cephalosporin antibiotics[14]

Resistance resulting from target modification
Reduction in the affinity of penicillin-binding proteins (PBPs) for cephalosporins, e.g. in streptococci and Gram-negative organisms
PBP replacement
Autolysin deficiency (resulting in cephalosporin tolerance)
β-Lactamases as a cause of resistance, e.g. in *Staphylococcus aureus* and in Gram-negative bacteria
Chromosomal cephalosporinases
Plasmid-mediated β-lactamases (in Gram-negative aerobes)
Impermeability-mediated resistance
By permeability barriers
By outer membrane modifications
Interplay of above cellular defence mechanisms

Table IV. Pharmacokinetic parameters of clinically important cephalosporins.[22-27] Data are presented as mean values ± SD

	$t_{1/2}$ (h)	Vd (% bodyweight)	Protein binding rate (%)	CL_R (% of dosage)
Cefazolin	1.8 ± 0.4	0.14 ± 0.04	89 ± 2	80 ± 16
Cefamandole	0.8 ± 0.1	0.16 ± 0.05	74	96 ± 3
Cefuroxime	1.7 ± 0.6	0.20 ± 0.04	33 ± 6	96 ± 10
Cefotiam	0.8 ± 0.2	0.39 ± 0.05	40 ± 3	50-70
Cefonicid	4.4 ± 0.8	0.11 ± 0.01	98	88 ± 6
Cefotetan	3.6 ± 1.0	0.14 ± 0.03	85 ± 4	67 ± 11
Cefoxitin	0.8 ± 0.1	0.25 ± 0.10	73	79 ± 5
Cefoperazone	2.2 ± 0.3	0.14 ± 0.03	89 ± 4	29 ± 4
Cefotaxime	1.1 ± 0.3	0.23 ± 0.06	36 ± 3	55 ± 10
Ceftizoxime	1.8 ± 0.7	0.36 ± 0.19	28 ± 5	93 ± 8
Cefodizime	2.5	0.20	88	67 ± 12
Ceftriaxone	7.3 ± 1.6	0.16 ± 0.03	84-95	49 ± 13
Ceftazidime	1.6 ± 0.1	0.23 ± 0.02	21 ± 6	84 ± 4
Cefepime	2.0 ± 0.1	0.25 ± 0.05	20 ± 2	97 ± 3

CL_R = renal clearance; **SD** = standard deviation; **$t_{1/2}$** = serum half-life; **Vd** = volume of distribution.

are above the MIC for 60 to 70% of the dosage interval for Enterobacteriaceae and streptococci, and for 40 to 50% of the dosage interval for *S. aureus*. Based on MIC_{90} values of 0.5 mg/L for enteric bacilli and 4 mg/L for *S. aureus*, these times above MIC goals can be easily met in infected and/or elderly patients after 1 to 2g of cefotaxime (e.g. at 12-hour intervals).[19]

3.1 Absorption

Parenteral administration is mandatory when oral formulations are not available, e.g. with vancomycin, the carbapenem imipenem and aminoglycosides, or when poor gastrointestinal absorption is likely, e.g. in cases of diarrhoea, nausea and vomiting, and immediately after surgery. Normally, parenteral antibiotics are administered by intravenous infusion to achieve the highest concentrations in the body. Intramuscular administration may be considered as follow-up therapy after initial intravenous infusion, and as a possible alternative in children.[20,21]

Because of limited absorption from the gastrointestinal tract, most cephalosporins – especially all the most active – are for parenteral use only. They are usually administered by a short intravenous infusion. Typically, peak serum concentrations of 40 to 150 mg/L are observed at the end of a 1g infusion,[15] and are 10 times greater than after oral administration of cephalosporins. Consequently, tissue concentrations are also higher following parenteral administration. Therefore, compared with oral administration, parenteral administration of cephalosporins has distinct advantages with regard to efficacy and compliance in outpatient therapy.

3.2 Distribution

The volume of distribution of all β-lactam antibiotics is restricted to the extracellular space. For parenteral cephalosporins, it varies between 15 and 40% of bodyweight[22,23] (table IV), being low for highly protein bound cephalosporins (ceftriaxone) and high for cephalosporins with low protein binding. However, protein binding has no major effect on the tissue penetration of cephalosporins.

With respect to penetration into the cerebrospinal fluid, the newer cephalosporins apparently behave similarly.[17,18,28,29] The common pathogens of meningitis – *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *E. coli* and, rarely, *Klebsiella* – are susceptible to third generation cephalosporins. Meningitis caused by *P. aeruginosa* should be treated with ceftazidime or cefepime. Most available clinical results relate to the use of cefotaxime and ceftriaxone, and ceftazidime in meningitis caused

by *Pseudomonas*.[9,17,24] However, it should be stressed that meningitis is not treated on an outpatient basis, except in children.[21]

3.3 Excretion

Together with all β-lactam antibiotics, parenteral cephalosporins are polar, water-soluble compounds, which are mainly excreted unchanged in the urine. Up to 40% of ceftriaxone is eliminated in the bile, while for cefoperazone this value can be as great as 70%. Of the newer compounds, only cefotaxime is metabolised to an appreciable extent by nonspecific esterases to desacetyl cefotaxime, which is somewhat less active than the parent compound. Synergism with the parent compound has been observed *in vitro*.[15]

For economic and practical reasons, a low frequency of administration is of key importance in the outpatient use of parenteral drugs. The dosage intervals are based on serum half-life, MICs against target organisms and the clinical situation of the patient.

The half-life of most parenteral cephalosporins varies between 1 and 2 hours, resulting in a 3-times-daily dosage regimen. 24-hour dosage intervals are appropriate only for ceftriaxone.[30,31] Because of their low MICs against relevant pathogens, twice-daily administration of other parenteral third and fourth generation cephalosporins with shorter half-lives (e.g. ceftazidime, cefepime and ceftizoxime) has been clinically effective.[20,21] In addition, intramuscular injection of parenteral cephalosporins, which prolongs the residence time of the drug in the body, is an option and enables longer dosage intervals.[32,33]

3.4 Pharmacokinetics Relevant to Special Patient Groups

3.4.1 Renal Impairment

Most cephalosporins are eliminated via the kidney. The half-life of ceftazidime, ceftizoxime, cefmenoxime, cefsulodin and cefepime increases proportionally to renal impairment and deterioration in creatinine clearance.[34] The serum half-life of these compounds is prolonged by a factor of 4 when the creatinine clearance is less than 30 ml/min, and may increase to between 10 and 20 hours in renal failure. Therefore, in patients with renal insufficiency, in addition to dose reduction, dosage intervals may be prolonged to between 12 and 24 hours for cephalosporins with half-lives of less than 2 hours.

30 to 50% of the administered dose of third generation cephalosporins is removed within 4 hours via haemodialysis, except for the highly protein bound cefoperazone[35] and ceftriaxone.[36-38] Therefore, a supplementary dose should be administered after finishing haemodialysis. However, only 10% of the administered dose is eliminated by peritoneal dialysis; thus, no supplementary dose is required.[35]

In situations where kidney function may be impaired, but not yet diagnosed, cefoperazone and ceftriaxone represent a lower risk to the patient. However, in patients with a certified grade of renal insufficiency, the dosage interval of renally excreted cephalosporins can be easily adjusted.[19,39]

3.4.2 Hepatic Disease

The distribution and elimination of third generation cephalosporins are not influenced by liver disease, with the exception of cefotaxime (reduced desacetylation), and cefoperazone and ceftriaxone (reduced biliary excretion). In liver disease, the half-life of cefoperazone increases by a factor of 2 to 4, but at a dosage of 1g twice daily no significant accumulation is observed. In simultaneous liver and renal insufficiency, dose reduction is recommended for these compounds.

3.4.3 Elderly Patients

In geriatric patients, because of the physiological decrease in kidney function associated with aging, the serum half-lives of renally excreted cephalosporins (e.g. cefuroxime, ceftazidime, ceftizoxime and cefmenoxime) are doubled, but not those of cefoperazone and ceftriaxone, which are also excreted via the bile. Considering the reduced kidney and liver function in many geriatric patients, cephalosporins with low toxicity should be the first-line drugs.[11,13,24]

Because many geriatric patients may be taking several drugs concomitantly, antibiotics associated with possible drug interactions should be avoided. In this respect, all cephalosporins are low risk drugs.[39] Interactions with other highly protein bound drugs, e.g. coumarins, should not be expected, since cephalosporins normally exhibit protein binding rates of less than 90%, and none are bound to the extent that clinically relevant drug interactions caused by displacement from protein binding are observed.[24,35]

Naturally, in ambulatory use, cephalosporins associated with alcohol intolerance (thiomethyl tetrazole moiety at C-3) as an adverse effect, namely cefamandole, cefoperazone and moxalactam, are not as highly recommended. Also, antibiotics causing more frequent diarrhoea, i.e. broad spectrum antibiotics with a high biliary excretion rate (e.g. cefoperazone), should be administered with care in outpatient therapy.[11]

3.4.4 Paediatric Patients

Pharmacokinetic parameters in paediatric patients are more complex because of the dynamic physiological changes occurring with maturation and growth. Neonates have a higher percentage of extracellular volume, lower body fat, lower protein binding and limited liver and kidney function. In neonates, the dosage regimen should be adjusted, so that longer dosage intervals result.[35]

In conclusion, the tolerability of most parenteral cephalosporins has been proven for more than 10 years, and these agents seem ideally suited for outpatient therapy, without the need for close surveillance by physicians and nurses in the hospital.[3]

4. Rationale for Ambulatory Use of Parenteral Third Generation Cephalosporins versus Other Cephalosporins

The dosage interval, ideally 24 hours, is a crucial consideration in ambulatory parenteral antibiotic therapy. Antibiotics that comply with this requirement are as follows: teicoplanin; aminoglycosides; some quinolones (e.g. fleroxacin and pefloxacin); and, of the cephalosporins, only ceftriaxone.[15,40-42] The drug may be administered via heparin-coated indwelling catheters, which normally remain patent for the duration of therapy, e.g. by pump, if the drug is physically stable for at least 12 hours.[21] Ceftriaxone, for example, is often given by an initial intramuscular injection. Of all the above-mentioned antibiotics, ceftriaxone offers the most appropriate pharmacokinetic ambulatory therapy. In addition, once-daily administration of this cephalosporin results in clear cost benefits in outpatient therapy. Compared with hospital therapy, intravenous ceftriaxone once daily in the familiar home environment reduced overall costs by $US3100 monthly, while cefazolin or ceftazidime twice daily saved $US1800.[20,21] Fortunately, ceftriaxone is stable at room temperature for 72 hours, whereas, for example, imipenem-cilastatin is stable for only 4 hours under these conditions.[20]

The spectrum of pathogens in an outpatient setting differs from that in the hospital situation. It typically contains streptococci, staphylococci, *E. coli*, *Klebsiella*, *Proteus*, and only rarely *P. aeruginosa*, *Bacteroides* and other infrequently occurring pathogens. Because of their extended spectrum of antibacterial activity and high stability in the presence of β-lactamases, third and fourth generation cephalosporins should be given in preference to older derivatives when the pathogens have not yet been identified.[3,4,9,15,16,18]

MRSA and enterococci, being resistant to cephalosporins, are rare in community-acquired infections. An increase in β-lactamase producing anaerobic cocci (e.g. *Bacteroides* spp.), which are only moderately susceptible to cephalosporins, should not be expected in the familiar home environment, which is also the situation with *B. cepacia* or *Stenotrophomonas* spp.[20,21]

The physician will select drugs such as ceftazidime or cefepime at the initiation of therapy, if *P. aeruginosa* is the probable pathogen.[9] In some instances, a combination with penicillins active against *Pseudomonas* (e.g. piperacillin), aminoglycosides (e.g. gentamicin) or quinolones (e.g. ciprofloxacin)[40,42,43] may be chosen. Only when *P. aeruginosa* has been identified as the sole

causative organism can cefsulodin be considered for therapy.

5. Conclusion

It can be concluded – because of their reliable bactericidal action and low tendency to favour the emergence of resistant mutants[6] – that the third generation cephalosporins appear to be the first-line drugs in the setting of ambulatory antibiotic therapy.

In addition, cephalosporins are well tolerated and should be preferred to other antibiotics,[20,21] e.g. quinolones and aminoglycosides, which favour the development of resistant strains or which carry the risk of oto- and nephrotoxicity, respectively.[40]

The pharmacological properties of modern broad spectrum, long-acting cephalosporins enable the use of these drugs for common indications in outpatient therapy. These conditions include cellulitis, osteomyelitis, endocarditis, pneumonia, chronic lung infections, bacterial meningitis (especially in children), pelvic inflammatory diseases and uncomplicated pyelonephritis.[20,21,32,44-46]

However, it has to be stressed that some severe community-acquired infections (e.g. meningitis) require hospitalisation, whereas some hospital-acquired infections may be treated on an outpatient basis at a later stage. In particular, because outpatient therapy is associated with a lower risk of nosocomial infections in neonates and children, e.g. rotavirus or respiratory syncytial virus, it should be preferred whenever possible in the paediatric area. In addition, children are less exposed to emotional stress at home, since many hospital-related painful treatments are avoided.[20,21,32,45]

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