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Clinical Use of Ceftriaxone

A Pharmacokinetic-Pharmacodynamic Perspective on the Impact of Minimum Inhibitory Concentration and Serum Protein Binding

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Abstract

Ceftriaxone is a third-generation cephalosporin that is used for a variety of infections such as meningitis, gonorrhoea and community-acquired pneumonia. The most important aspects of its pharmacokinetics include a long half-life, excellent tissue penetration and saturable (dose-dependent) serum protein binding of the drug. A pharmacodynamic analysis [total area under the concentration-time curve (AUC)/minimum inhibitory concentration (MIC)] was performed in several populations (healthy volunteers, children, the elderly, and patients with renal and hepatic impairment) against various bacterial species (*Streptococcus pneumoniae*, the Enterobacteriacieae, methicillin-susceptible *Staphylococcus aureus*, and *Pseudomonas aeruginosa*). AUC/MIC [area under the inhibitory time curve (AUIC)] was chosen as the pharmacodynamic parameter for this analysis since ceftriaxone is a time-dependent killer and high peak concentrations are not needed. In addition, there is a significant correlation between AUIC, time when concentration exceeds the MIC (t > MIC) and time to eradication. Total and free AUICs (assuming a free fraction = 10%) were calculated since it is highly protein bound. It was postulated that a free AUIC of at least 125 would be required to achieve efficacy. From our analysis of these various populations, we were able to conclude that the free AUIC values support the use of 1g daily in infections where MIC values are below 2 mg/L. In addition, consistent with its reported good activity against CSF organisms with MICs ≤1.0 mg/L and marginal activity against organisms with MICs ≥2.0 mg/L, we also recommend the target free AUIC values of at least 125 for patients with severe infections such as meningitis. Patients with mild infections may recover with values below 125 but they may remain at risk of the development of resistant organisms. Furthermore, it is

essential to further validate these findings in patients who have received treatment, calculate AUICs and correlate these parameters with both clinical and microbiological outcomes.

Ceftriaxone is a third-generation cephalosporin that has been commercially available since 1985.[1] It manifests a broad spectrum of *in vitro* activity, including both Gram-positive and Gram-negative organisms as well as a few anaerobic bacteria. It is very active against most of the members of the Enterobacteriaceae [minimum inhibitory concentration against 90% of isolates (MIC_{90}) <1.0 mg/L], *Streptococcus pneumoniae* (MIC_{90} <0.5 mg/L), *S. pyogenes*, *S. agalactiae* and *S. viridans*. It is also very active in low concentrations against β-lactamase-positive and -negative isolates of *Haemophilus influenzae*, *Neissseria gonorrhoeae* and *N. meningitidis* (MIC_{90} <0.025 mg/L). Ceftriaxone has moderate activity against penicillin-susceptible and -resistant strains of *Staphylococcus aureus* (MIC_{90} 2 to 8 mg/L) but it should not be used to treat oxacillin-resistant strains of the species.[2,3] Organisms such as *Enterococcus* and *Pseudomonas aeruginosa* are usually resistant to ceftriaxone.[2,4] In addition, ceftriaxone distributes only into the extracellular space and does not enter cells. Intracellular pathogens such as *Mycoplasma*, *Rickettsia*, *Chlamydia* and *Legionella* are usually resistant *in vivo*, even if they appear to be susceptible *in vitro*.[3]

The past 15 years of clinical experience with this agent provide evidence that it is reliably active against organisms for which MIC is ≤1.0 mg/L, but fails with increasing frequency where MIC values are ≥2.0 mg/L. We decided to examine whether pharmacokinetic-pharmacodynamic calculations might enhance our understanding of these clinical observations. Consequently, the intent of this manuscript is to establish pharmacokinetic-pharmacodynamic understanding of this antibacterial. It is not intended to provide an exhaustive review of the pharmacokinetics of ceftriaxone, as this has been done previously.[3,5-7]

1. Pharmacokinetics

The 'highlights' of ceftriaxone pharmacokinetics include the long half-life, excellent penetration into the fluids surrounding cells, and saturable (dose-dependent) serum protein binding of the drug. Consensus pharmacokinetic parameters of ceftriaxone are provided in table I.

For most protein-bound antibacterials, the percentage of protein binding remains relatively constant throughout the dose range. For ceftriaxone, there can be saturation of all available plasma protein binding sites within the normal dose range, with the expected result being an increase in the excreted amount. A study by Stoeckel[8] confirms this phenomenon. Intravenous doses of 150, 500 and 1500mg resulted in disproportionate increases in the total area under the concentration-time curve (AUC) and total concentrations of ceftriaxone. In fact, the free fraction increased from 4 to 17% as the serum concentrations varied between 0.5 and 300 mg/L. This is the range of plasma values after doses of 1 to 2g. The resulting higher concentrations of unbound drug in the plasma allow more rapid excretion and may also increase the free concentrations in the tissues. This occurs because the high extent of protein binding protects the drug from renal excretion, producing a longer plasma half-life.[3,8] The effect is theoretically greater if higher doses are given once daily as opposed to smaller doses given twice daily. Although the effect of an increase in free ceftriaxone on excretion is relatively easy to measure, it is much more difficult to show a change in antimicrobial activity that results from an increase in the unbound drug concentration, since antimicrobial testing is performed in protein-free broth media. It is also true that adding albumin to broth interferes with the action of ceftriaxone, particularly against Gram-positive organisms such as *S. aureus*.[9,10] Proving the existence of these differences *in vivo* has not yet been attempted.

Another parameter affected by the increase in free fraction is tissue fluid penetration. Ceftriaxone

is highly bound to albumin, and unbound drug is the active form. It should be pointed out that more than 50% of the body's total albumin concentration is in the extracellular fluid space, not circulating in the bloodstream. Ceftriaxone displays saturable protein binding, so once the available binding sites on albumin in the bloodstream are saturated, the free concentrations increase disproportionately and more free ceftriaxone can equilibrate by diffusing into tissue fluids, where binding to interstitial fluid proteins in organs and tissues can occur. But ceftriaxone has a higher affinity for binding to the penicillin-binding proteins of bacteria than it has to albumin, so the drug molecule can be stripped off the albumin binding site by contact with a bacterial pathogen. Once this occurs, a free ceftriaxone molecule in the bloodstream moves to the tissue space. Perhaps the bound fraction of this drug should be considered a reservoir, with the release of a constant supply of active drug for up to 24 hours.[3,6]

2. Pharmacodynamics

From concentrations greater than zero up to twice the MIC, all antibacterials kill bacteria more rapidly as concentrations increase. After 2 to 4 times MIC, the mechanisms of killing diverge. β-lactam agents, vancomycin, clindamycin and the macrolides kill bacteria in a time-dependent fashion. The aminoglycosides, fluoroquinolones and metronidazole are concentration-dependent killers.

Time-dependent killing is characterised by maximum efficacy of an antimicrobial at 2 to 4 times the MIC, an exposure profile achieved when 80 to 100% of the concentrations are above the MIC. This also coincides with an AUC_{24}/MIC ratio of 125 (where AUC_{24} is the AUC to 24 hours). Further increases in concentration above these values do not kill bacteria more rapidly.

For antimicrobials such as the aminoglycosides and fluoroquinolones, concentration-dependent killing mechanisms cause more rapid killing above an AUC/MIC ratio of 125, up to a maximum killing rate as the AUC/MIC ratio exceeds 250. For concentration-dependent killers, higher peaks translate into higher AUC/MIC ratios and longer times when concentration exceeds the MIC (t > MIC), both of which are correlates of increased rates of killing.[11]

Pharmacodynamic parameters used to assess efficacy in β-lactam antibacterials are t > MIC and area under the inhibitory time curve (AUIC), which is also known as AUC/MIC.[12] In a study conducted by our group, there was a significant correlation between AUIC, t > MIC and time to eradication.[13] Further analysis of the data revealed that an AUIC >125 also correlated with microbiological response. For long half-life antimicrobials such as vancomycin and ceftriaxone, there is a particularly close concordance between AUIC >125 and t > MIC of 80 to 100% of the dose administration interval.[14] A study by Highet et al.[15] confirmed earlier findings. They found that patients with culture-documented Gram-negative lower respiratory tract infections treated with β-lactam regimens had a better response to antimicrobial therapy if the AUIC was at least 125.[15]

Although no clinical studies of ceftriaxone have measured its AUIC or t > MIC values, or peak concentration : MIC ratio, it is highly likely that findings will be similar. This is especially true since the long half-life of ceftriaxone would allow for its concentrations to exceed the MIC for the desired

Table I. Pharmacokinetic parameters of ceftriaxone[1,6]

Parameter	Healthy adults	Children with meningitis
Elimination half-life (h)	5.8-8.7	4.3-4.6
Volume of distribution	5.78-13.5L	0.338-0.373 L/kg
Plasma clearance	0.58-1.45 L/h	0.049-0.060 L/h/kg
Fraction excreted unchanged in the urine (%)	33-67	
Protein binding	Concentration dependent	

Table II. Pharmacokinetic-pharmacodynamic parameters for ceftriaxone based on total concentrations. All AUCs are adjusted to 24 hours

Population and dose	AUC (mg·h/L)	AUIC			
		Streptococcus pneumoniae (MIC = 0.5-1 mg/L)	Enterobacteriaciae (MIC <1.0 mg/L)	MSSA (MIC = 2-8 mg/L)	*Pseudomonas aeruginosa* (MIC >64 mg/L)
Healthy adults					
500mg IV od[7]	610	610-1220	610	76.3-305	9.5
500mg IV q12h[7,17]	998	998-1996	998	124.8-499	15.6
500mg IM q12h[18]	823.8	823.8-1647.6	823.8	103-412	12.9
1g IV od[7]	1006	1006-2012	1006	125-1006	15.7
1g IM od[20]	901.44	901-1803	901	112.7-450.7	14.1
1g IV q12h[8,17]	863	863-1726	863	107.9-431.5	13.5
1g IM q12h[18]	1647	1647-3294	1647	205.9-823.5	51.5
2g IV od[1]	3084.0	3084-6168	3084	385.5-1542	48.2
2g IV q12h[8,17]	1441	1441-2882	1441	180.1-720.5	22.5
Children[22]					
Infants (average dose 462mg)	1223.9	1223.9-2447.8	1223.9	153-612	19.1
Young children (average dose 699mg)	1225.1	1225.1-2450.2	1225.1	153.1-612.6	19.1
Elderly[23]					
1g IV od	1289	1289-2578	1289	161-644.5	20.1
Renal impairment (1g IV od)[24]					
Dialysis (CL_{CR} <15 ml/min)	1858.7	1858.7-3717.4	1858.7	232.3-929.4	29
Severe impairment (CL_{CR} 5-15 ml/min)	1666.7	1666.7-3333	1666.7	208.3-833.4	26
Moderate impairment (CL_{CR} 16-30 ml/min)	1890.4	1890.4-3780.4	1890.4	236.3-945.2	29.5
Mild impairment (CL_{CR} 31-60 ml/min)	1418.4	1418.4-2836.8	1418.4	177.3-709.2	22.2
Hepatic impairment (1g IV od)[25]					
Alcoholic fatty liver	1234.6	1234.6-2469.2	1234.2	154.3-617.3	19.3
Cirrhosis without ascites	1048.2	1048.2-2096.4	1048.2	131-524.1	16.4
Cirrhosis with ascites	715.3	715.3-1430.6	715.3	89.4-357.7	11.2

AUC = area under the plasma concentration-time curve; **AUIC** = area under the inhibitory time curve; **CL_{CR}** = creatinine clearance; **IM** = intramuscular; **IV** = intravenous; **MIC** = minimum inhibitory concentration; **MSSA** = methicillin-susceptible *S. aureus*; **od** = once daily; **q12h** = every 12 hours.

period and an AUIC value of >125 is roughly equivalent to antimicrobial concentrations being above the MIC of an organism for approximately 80% of the dosage interval.[14] In addition, since ceftriaxone is a time-dependent killer, it is highly unlikely that peak : MIC is an adequate pharmacodynamic parameter to correlate with efficacy, since high peaks are not needed.[11,16]

The unknown effect on all of these calculations is that of saturable protein binding. Theoretically, this effect would minimise the differential impact of free versus total drug, and so we will evaluate this with consideration of free and total concentrations, realising that the final antimicrobial effect of this drug may be somewhere between these 2 extremes.

3. Healthy Volunteers

By using the data from pharmacokinetic studies in healthy adult volunteers, one can derive AUC values and then calculate both free and total AUC.[2-8,17-21] The use of AUC is particularly appropriate because it provides an integrated measure of drug exposure and removes the need to rely on a single time point along a long half-life disposition curve to base conclusions. From AUC, both free and total, one can calculate predicted AUIC values

for target organisms. This exercise was performed for both total (table II) and free (table III) concentrations of ceftriaxone. Calculations were also performed for ceftriaxone blood concentrations reported from other populations, including children, the elderly and patients with renal or hepatic impairment (see sections 4, 5 and 6).

Table II shows the AUIC values (total drug) for different doses of ceftriaxone against 4 different pathogens arranged on the basis of ascending MICs. Ceftriaxone was highly active, using the AUIC > 125 criterion, against *S. pneumoniae* and the Enterobacteriaciae at all dosages, even at 500mg intravenously daily. This is of great importance, since the MICs used for *S. pneumoniae* are 0.5 mg/L (susceptible) and 1.0 mg/L (intermediate). So ceftriaxone can be used for intermediate strains even at lower dosages. The conclusion is that 1g of ceftriaxone either intramuscularly or intravenously can be safely used in the treatment of pneumococcal pneumonia to cover even an intermediately susceptible strain, at least if total concentrations are the marker for efficacy. Table II also confirms the current belief that ceftriaxone has little to no useful activity against *Pseudomonas*, since the MICs are much too high and the resulting AUICs are too low. The activity of ceftriaxone against methicillin-susceptible *S. aureus* is marginal in some cases, even using total AUIC, and outcomes against staphylococci are likely to be dose- and MIC-dependent.

Figure 1 depicts a simulated concentration-time curve for ceftriaxone 1g given intravenously. This figure shows both total serum concentrations and MIC values and establishes that the serum concentrations of this drug are above the MICs of 1.0 mg/L (*Escherichia coli* and *S. pneumoniae*) and 8.0 mg/L (methicillin-susceptible *S. aureus*) for most of the dosage interval, based on total drug concentrations. Again, AUIC correlates very well with t > MIC for total concentrations, as would be expected for a compound with a long half-life. At this dose of ceftriaxone, total AUICs ≥ 125 are achieved against MICs of 1.0 and 8.0 mg/L, and one could justify a laboratory breakpoint of 8.0 mg/L for this drug if outcome were based on total drug concentrations. This is the usual laboratory breakpoint for this drug in many countries. The figure also illustrates why ceftriaxone should not be used in the treatment of serious pseudomonal infections, since its AUIC is well below 125 against this organism, even using total concentrations, and total concentrations are below the MIC for most of the dosage interval.

The AUIC data for free drug in table III may be considered more important by some investigators, especially in the light of the high extent of protein binding of ceftriaxone. Free drug is responsible for activity *in vitro*, since *in vitro* testing systems are free of albumin. The other attributes attached to free concentrations are renal excretion and penetration into fluids surrounding infected tissues, such as the lung in the case of community-acquired pneumonia. Table III shows the AUIC values for free drug calculated from the available pharmacokinetic studies. 'Free' AUIC was subsequently calculated by assuming a free fraction of approximately 10%. The problem with analysing these data on the basis of AUIC or t > MIC is that there are no studies suggesting what a target free AUIC would be to achieve clinical success. Therefore, to continue the exercise, we shall postulate that a free AUIC of 125 is the target, since most of the drugs from which this value has been derived display insignificant plasma

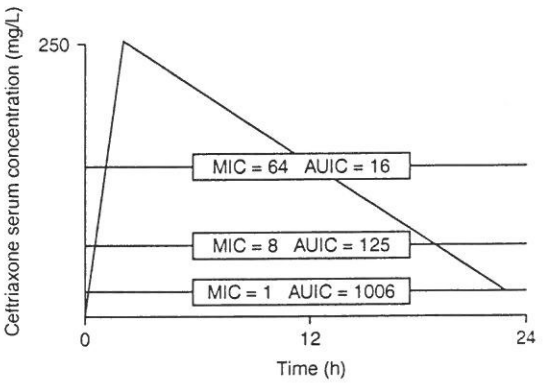

Fig. 1. Simulated serum total concentration-time curve for intravenous ceftriaxone 1 g/day showing effect of different MIC values on total AUIC. Area under the total concentration-time curve was assumed to be 1006 mg □h/L.[13] **AUIC** = area under the inhibitory time curve; **MIC** = minimum inhibitory concentration.

Table III. Pharmacokinetic-pharmacodynamic parameters for ceftriaxone based on free concentrations. All AUCs are adjusted to 24 hours

Population and dose	AUC (mg □h/L)	AUIC			
		Streptococcus pneumoniae (MIC = 0.5-1 mg/L)	Enterobacteriaciae (MIC <1.0 mg/L)	MSSA (MIC = 2-8 mg/L)	*Pseudomonas aeruginosa* (MIC >64 mg/L)
Healthy adults					
500mg IV od[10]	610	61-122	61	7.63-30.5	0.95
500mg IV q12h[11]	998	99.8-199.6	99.8	12.48-49.9	1.56
500mg IM q12h[12]	823.8	82.38-164.8	82.4	10.3-41.2	1.29
1g IV od[13]	1006	100.6-201	100.6	12.6-100.6	1.6
1g IM od[14]	901.44	90.1-180.3	90.1	11.3-45.1	1.41
1g IV q12h[15]	863	86.3-172.6	86.3	10.8-43.2	1.35
1g IM q12h[12]	1647	164.7-329.4	164.7	20.59-82.4	5.15
2g IV od[11]	3084.0	308.4-616.8	308.4	38.55-154.2	4.82
2g IV q12h[15]	1441	144.1-288.2	144.1	18.0-72.1	2.25
Children[22]					
Infants (average dose 462mg)	1223.9	122.4-244.8	122.4	15.3-61.2	1.9
Young children (average dose 699mg)	1225.1	122.5-245.0	122.5	15.3-61.3	1.9
Elderly[23]					
1g IV od	1289	193.4-386.7	193.4	24.2-96.7	3.0
Renal impairment (1g IV od)[24]					
Dialysis (CL_{CR} <15 ml/min)	1858.7	185.9-371.2	185.9	23.3-92.9	2.9
Severe impairment (CL_{CR} 5-15 ml/min)	1666.7	166.7-333.3	166.7	20.8-83.3	2.6
Moderate impairment (CL_{CR} 16-30 ml/min)	1890.4	189.0-378.0	189.0	23.6-94.5	2.95
Mild impairment (CL_{CR} 31-60 ml/min)	1418.4	141.8-283.7	141.8	17.7-70.9	2.22
Hepatic impairment (1g IV od)[25]					
Alcoholic fatty liver	1234.6	123.5-247	123.4	15.4-61.7	1.93
Cirrhosis without ascites	1048.2	104.8-209.6	104.8	13.1-52.4	1.64
Cirrhosis with ascites	715.3	71.5-143.1	71.5	8.94-35.8	1.12

AUC = area under the plasma concentration-time curve; **AUIC** = area under the inhibitory time curve; **CL_{CR}** = creatinine clearance; **IM** = intramuscular; **IV** = intravenous; **MIC** = minimum inhibitory concentration; **MSSA** = methicillin-susceptible *S. aureus*; **od** = once daily; **q12h** = every 12 hours.

protein binding. Furthermore, at free AUICs of 125, free concentrations would be above the MIC for approximately 80% of the time.[26,27] We recognise that concentration-dependent protein binding could result in higher free AUIC than predicted from a multiplication factor applied to total AUC. Patients with diseases may experience variable protein binding, a phenomenon that we have described previously.[28]

The breakpoint of AUIC > 125 is a logical target for free concentrations of ceftriaxone. There is extensive evidence to support the use of ceftriaxone 1g either intramuscularly or intravenously daily to treat pneumococcal pneumonia.[1-3] Assuming a free fraction of approximately 10%, a 1g dose produces a free AUIC of approximately 100, and this would validate the usually good outcome of a dosage regimen of 1g daily against pneumococcal pneumonia and even meningitis. Unfortunately, MICs for ceftriaxone are rising against pneumococci, and there may soon be some failures, for example with MICs at 2.0 mg/L or higher. The remedy for this problem can be higher doses or more frequent administration.

If AUIC > 125 is the target exposure, a clinician could make an argument against using ceftriaxone to treat a serious infection caused by methicillin-susceptible *S. aureus*, especially when their MICs exceed 2.0 mg/L. Figure 2 shows the free drug

concentration-time curve for a 1g dose of ceftriaxone given intravenously, and calculates the free AUIC values for the target MICs. If the target free AUIC value is to be approximately 100, a 1g dose is obviously too low. On further inspection of figure 2, one can also conclude that the free drug concentration is above an MIC of 1.0 mg/L for most of the dosage interval, whereas at an MIC of 8.0 mg/L the concentration clearly does not exceed the MIC for most of the dosage interval. This may be increasingly important, as resistance selection is a growing problem with third generation cephalosporins, and low AUICs predict the selection of resistant microbes.[29] Clearly, clinical trials are justified to establish a target value for free AUICs. Nevertheless, there is already general clinical support for the interpretation of ceftriaxone outcomes using free AUICs, and these calculations may be useful along with locally measured MICs in the practice of antibacterial selection. Alternatively, the data in tables II and III suggest that ceftriaxone may best be considered effective in relation to total drug rather than free drug concentrations, since the total drug concentrations and AUICs appear high enough to achieve efficacy against marginal organisms such as *S. aureus*. As many clinicians realise, they should not select a low dose of ceftriaxone for treatment of a severe methicillin-susceptible *S. aureus* infection in preference to oxacillin, even though the bacterium is reported as being susceptible to ceftriaxone at an MIC of 8.0 mg/L.[17-21]

4. Children

Schaad and Stoeckel[22] studied single dose pharmacokinetics of ceftriaxone in 5 infants and 5 young children. On clinical grounds, they concluded that 50 mg/kg as a single daily dose was sufficient to treat childhood meningitis caused by *S. pneumoniae*, *H. influenzae* and *N. meningitidis*. This dose produces an AUC (total drug) of 1225 (table II). The total AUIC value would be 1225 against an organism with an MIC of 1.0 mg/L, a very high total AUIC value and one consistent with 100% t > MIC against *S. pneumoniae*, which has the highest MIC values of the 3 organisms. The free AUIC of this regimen (assuming approximately 10% free fraction) would be approximately 125, illustrating that an MIC of 1.0 mg/L is actually borderline if the free concentrations are predictive of the outcome. An MIC of 2.0 mg/L would produce an AUIC well below 100, with potential for resistance development and even clinical failure in serious infections. On this basis, it is reasonable to designate organisms with MIC values of 2.0 mg/L as intermediate. One potential solution to this borderline exposure profile is to double the dosage to 2g daily.

The free AUIC may indeed be most important, especially since only free drug can pass the blood-brain barrier. The free fraction for both groups of patients in this study was approximately 16%, allowing us to calculate a free AUIC value of 184 against an intermediately susceptible strain of pneumococcus with an MIC of 1.0 mg/L. This would be too low for the treatment of an organism with an MIC of 2.0 mg/L. Even more importantly, it should be noted that ceftriaxone penetration into CSF results in concentrations that are between 5 and 15% of total serum concentrations in the CSF. Assuming that the dose is 1g, the free AUIC data would also support the use of once daily administration in paediatric meningitis caused by organisms with MIC values ≤1.0 mg/L.[22]

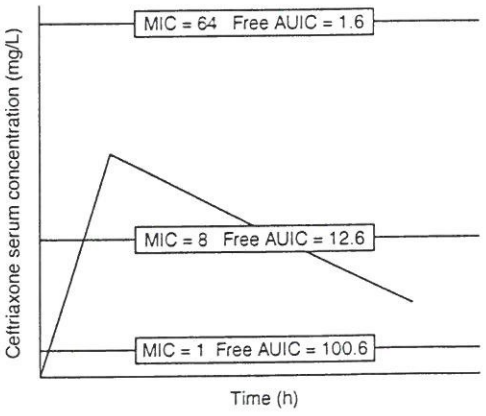

Fig. 2. Simulated serum free concentration-time curve for intravenous ceftriaxone 1 g/day showing effect of different MIC values on free AUIC. Area under the free concentration-time curve was assumed to be 100.6 mg □h/L.[13] **AUIC** = area under the inhibitory time curve; **MIC** = minimum inhibitory concentration.

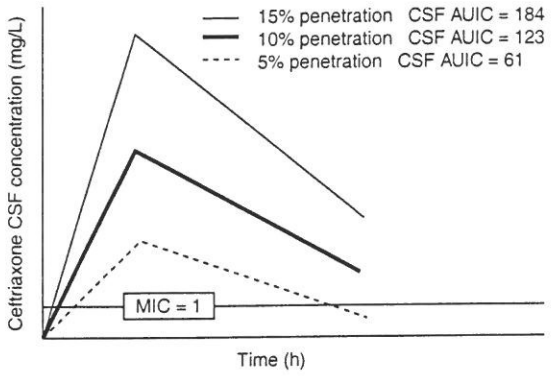

Fig. 3. Simulated cerebrospinal fluid (CSF) concentration-time curves for intravenous ceftriaxone 50 mg/kg/day in children, showing effect of different extents of CSF penetration on AUIC in CSF. Area under the total serum concentration-time curve was assumed to be 1225 mg □h/L.[22] **AUIC** = area under the inhibitory time curve; **MIC** = minimum inhibitory concentration.

These conclusions are supported by the AUIC analysis of figure 3. A 5% penetration of ceftriaxone into CSF results in AUIC values of approximately 61 against an intermediately susceptible strain of pneumococci with an MIC value of 1.0 mg/L. Assuming 10 or 15% penetration into CSF, the resulting AUICs would be 123 or 184, respectively, against this same organism. These CSF AUICs are (realistically) free AUICs. The efficacy of this drug in paediatric meningitis can be supported by AUIC values, given that the MIC value is 1.0 mg/L or lower. t > MIC would be in agreement with AUICs, but also show high dependence on the actual MIC of the treated pathogen. A pneumococcal organism with an MIC value of ≥2.0 mg/L would necessitate either a higher dose or possibly the addition of a second active agent such as vancomycin. The total AUIC value for a combination of ceftriaxone plus vancomycin would be the sum of the individual AUICs of each drug against the respective pathogen, as AUIC values *in vitro* for these 2 agents show additivity.[12]

5. The Elderly

Luderer et al.[23] derived the single dose pharmacokinetic parameters of ceftriaxone in 8 healthy elderly individuals by giving 1g doses intravenously. On the basis of half-life, they concluded that no dosage adjustments are needed in the geriatric population, except in patients who are debilitated or malnourished, or who have marked renal impairment. Analysis of their AUC data reveals that no substantial alterations to the conclusions derived in section 3 for younger adults are necessary for geriatric patients, except for the free AUIC being higher in these patients because of a modest increase in the free fraction of about 15% as compared with their younger counterparts (about 11%). The free AUCs in the geriatric patients were disproportionately higher than in the younger individuals because of the effects of aging on plasma protein binding and also the effect of reduced creatinine clearance in the elderly, lowering the ability to excrete free drug.

As overall AUC was higher (not lower) in the geriatric patients, the effect of lower renal function appears to be more important than the effect of aging on the amount of free ceftriaxone. If the free fraction and protein binding effects were predominant, the drug could be cleared more rapidly and have a shorter half-life than otherwise expected, and the overall AUC of this drug would be lower in the geriatric patients, because drug displaced would be cleared more rapidly. The data in tables II and III argue that this was not the case.

As might be expected from the AUIC values, ceftriaxone remains highly active against pneumococci and the Enterobacteriaceae in elderly patients at MICs ≤1.0 mg/L, even without reliance on increased concentrations associated with decreased renal function. Unreliable ceftriaxone activity is the rule against *Pseudomonas*, and variable activity is possible against methicillin-susceptible *S. aureus*, as in younger patients, because the somewhat higher AUC in the elderly does not seem likely to force the AUIC high enough to improve the chances of eradicating these marginal organisms.[30]

6. Patients with Renal and Hepatic Impairment

Patel et al.[24] reported ceftriaxone pharmacokinetic parameters in patients with varying degrees of renal dysfunction. The AUC of ceftriaxone in-

creased as renal function decreased (tables II and III). This is because the free drug is cleared renally by glomerular filtration. The increases in AUC are more modest than would be seen with most third generation cephalosporins, because the clearance of ceftriaxone also occurs via the biliary route into the gastrointestinal tract, and there is no enterohepatic cycling because the drug is not absorbed in the gastrointestinal tract. The authors used these data to conclude that dosage adjustments were not needed as long as the daily dose was less than 2g. As with most of the third generation cephalosporins, ceftriaxone is not appreciably removed by dialysis, and a supplemental dose following haemodialysis was not recommended.[24]

Stoeckel and Koup[25] reported the effects of hepatic disease on ceftriaxone pharmacokinetics. Cirrhotic patients without ascites had free AUCs that were about the same as those of normal volunteers, but the AUCs were one-third lower than those of normal volunteers if the patient had cirrhosis. This is presumed to be the effect of lower serum protein concentrations causing an increased free fraction, which is cleared renally. The authors concluded that it was not appropriate to reduce the dosage in hepatically impaired patients with normal renal function. In these patients, there was more free drug, which increased the amount excreted renally. The renal elimination pathway was clearly more important for this drug.

Clearly, anephric patients with major liver impairment would require dosage adjustments, because they are unable to excrete the drug renally, offsetting the effect of a higher free fraction and the consequent ability to clear drug more rapidly. In addition, the authors concluded that the dosage of ceftriaxone should not exceed 2 g/day in patients with either hepatic or renal impairment, because of decreased plasma protein binding and higher free AUC values; such a restriction of dosage would be cost saving.[25]

7. Conclusion

It is essential to further validate these findings by measuring total and free ceftriaxone concentrations in treated patients and calculating AUICs, correlating these pharmacokinetic-pharmacodynamic measurements with both clinical and microbiological outcomes. Doing so would undoubtedly shed further light on the phenomenon of lower AUC and AUIC in patients with normal renal function and low albumin levels (see section 6). In the case of older patients treated with ceftriaxone, the potential for lower protein binding to increase excretion and lower AUC is largely offset by the tendency of their decreasing renal function to raise the AUC, and thus few patients risk concentrations more than 3 times normal. This extends the 'accidental spectrum of action' of this antibacterial to organisms having MIC values as high as 2.0 mg/L.

According to the calculated AUICs, ceftriaxone is an active antimicrobial for infections caused by most *S. pneumoniae*, *N. meningitidis*, *N. gonorrhoeae*, *H. influenzae* and Enterobacteriaceae. It is not reliably active against *P. aeruginosa*. It has variable activity against methicillin-susceptible *S. aureus*, which is dependent on the actual MIC of the infecting organism and the dose used. Ceftriaxone may soon begin to display variable reliability against penicillin-resistant *S. pneumoniae*, particularly as the MIC values of these organisms rise above 2.0 mg/L and approach 4.0 or even 8.0 mg/L. Anecdotal reports indicate that this is occurring, and the calculated AUICs for the free drug (fig. 3) explain why. These infections include community-acquired pneumonia and bacterial meningitis.

The AUIC values calculated here support the use of ceftriaxone 1g daily in infections where MIC values are below 2.0 mg/L, because in these conditions the free AUIC will be ≥125. This analysis leads us to conclude that the clinical experiences with ceftriaxone are in good concordance with its pharmacokinetics and pharmacodynamics, both when total and free concentrations are considered. Consistent with its reported good activity against CSF organisms with MIC ≤1.0 mg/L, and marginal activity against organisms with MIC values ≥2.0 mg/L,[22] we recommend the perspective of free AUICs when prescribing this drug, with the target for free AUIC being 125. This is the mathematical

equivalent of the free concentration being above an MIC of 1.0 mg/L for 80 to 100% of the dosage interval, and we advocate that this target be used for patients with serious infections. Patients with mild infections may recover with free AUICs below 125, but they may remain at increased risk of acquiring or spreading resistant organisms.[29]

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