

# A Retrospective Analysis of Pharmacokinetic-Pharmacodynamic Parameters as Indicators of the Clinical Efficacy of Ceftizoxime

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## Abstract

**Objective:** To analyse the relationship between a series of estimated pharmacokinetic-pharmacodynamic parameters and the reported efficacy of ceftizoxime.

**Design:** Retrospective literature search and analysis using different correlation models.

**Methods:** The following parameters were calculated for each group of patients included in the study from the simulated plasma concentration curves corresponding to the dosage regimen administered: (i) peak concentration at steady state divided by the minimum inhibitory concentration ( $C_{\max}^{ss}/MIC$ ); (ii) the time that the plasma drug concentration exceeded the MIC scaled to 24 hours at steady state [ $(t^{ss})_{24h} > MIC$ ]; (iii) the total area under the concentration-time curve over 24 hours at steady state divided by the MIC [ $(AUC^{ss})_{24h}/MIC$ ]; and (iv) the AUC at steady state for the period of time that the concentration is above the MIC over a period of 24 hours divided by the MIC [ $(AUC^{ss})_{24h}$ ]. A univariate correlation analysis was performed considering efficacy [rate (%) of clinical cure or bacterial eradication] as the dependent variable and the pharmacokinetic-pharmacodynamic parameter as the independent variable, using linear and nonlinear models.

**Results:**  $(t^{ss})_{24h} > MIC$  was the only parameter that was statistically correlated with efficacy, the linear model being the best choice among the 4 relationship approaches tested. A biased frequency distribution of reported efficacy data constrains the correlation analysis to a narrow range of efficacy and hinders interpretation of the results.

**Conclusions:** The reporting of cases with low efficacy rates as well as those with high efficacy rates, including information on patient idiosyncrasies and the infecting organisms, would be of great help in performing retrospective analyses of the use of antimicrobial agents, leading to the optimisation of therapy with this type of drug in clinical practice.

Antibacterial agents belong to a very heterogeneous group of drugs used in clinical practice with the common aim of preventing bacterial growth in human hosts. The outcomes of patients with infec-

tious diseases receiving antibacterial treatment depend on the interactions among the 3 elements involved in the final response:<sup>[1]</sup> patient, drug and pathogen. The patient with the infection interacts

with the drug, producing a plasma concentration profile dependent upon the absorption, distribution and elimination rates, and also interacts with the infecting bacterium, leading to a destruction rate that depends on the immune response. The antibacterial agent interacts with the pathogen to produce a growth inhibition rate that depends on its potency, its mechanism of action and the time or intensity of exposure (which is in turn determined by the plasma curve). The clinical outcome for infectious pathologies is conditioned by the pharmacokinetics and pharmacodynamics of the drug, as also happens for any other type of illness; nevertheless, in the latter case both depend only on the patient, while in the former case the pharmacokinetics are influenced by patient characteristics and the pharmacodynamics by the type of infecting bacterium.

This type of dual dependence hinders the establishment of the correct dosage pattern for antimicrobial agents. This was first considered by Schentag et al.<sup>[1,2]</sup> and later by many other authors.<sup>[3-5]</sup> In recent years, considerable efforts have been directed at finding a suitable methodology that considers both the pharmacokinetic and pharmacodynamic variability of drugs with a view to optimising antimicrobial treatment in clinical practice.<sup>[6,7]</sup> As a consequence, several so-called efficacy indices, pharmacokinetic-pharmacodynamic parameters, or surrogate markers, have been defined as indicators of the potential efficacy of antibacterial treatments. Such indicators consider a pharmacokinetic parameter together with the minimum inhibitory concentration (MIC) value.

Despite the limitations of the MIC as an indicator of the *in vivo* antibacterial activity of a drug, until now it has been the pharmacodynamic parameter universally considered for this purpose. Regarding pharmacokinetics, 3 different parameters have been involved in the definition of efficacy indices: the maximum drug plasma concentration ( $C_{max}$ ), the elimination half-life of the drug ( $t_{1/2\beta}$ ) and the area under the plasma concentration-time curve (AUC). The definitions of, and differences among, the several indices can be found in the literature.<sup>[2,7]</sup>

Antibacterial agents can be divided into different groups on the basis of their patterns of bactericidal activity.<sup>[8]</sup> One pattern is characterised by concentration-dependent killing over a wide range of concentrations, as happens with the aminoglycosides or fluoroquinolones and with metronidazole for anaerobic bacteria.<sup>[9]</sup> Another pattern is characterised by a limited killing rate when the concentration surpasses the MIC value by 3- to 4-fold, and this is observed with the  $\beta$ -lactam antibacterials, vancomycin, clindamycin and macrolides.<sup>[9]</sup> The peak value at steady state ( $C_{max}^{ss}$ )/MIC ratio seems to be the parameter best related to efficacy for drugs with concentration-dependent bactericidal activity, and the time that the plasma drug concentration exceeds the MIC scaled to 24 hours at steady state [ $(t^{ss})_{24h} > MIC$ ] has been proposed as the best predictor for the other group. Despite this, the total AUC over 24 hours at steady state divided by the MIC [ $(AUC^{ss})_{24h}/MIC$ ] and the AUC at steady state for the period of time that the concentration is above the MIC over a period of 24 hours divided by the MIC [ $(AUC^{ss})_{24h}$ ] have been reported as good predictors of clinical outcomes for several drugs belonging to both groups, particularly the fluoroquinolones.<sup>[2]</sup> Moreover, recent publications<sup>[10,11]</sup> have pointed to  $(t^{ss})_{24h} > MIC$  as the pharmacokinetic-pharmacodynamic parameter best related to efficacy for any group of these drugs.

As previously reported,<sup>[2,10,12]</sup> there may not be any single efficacy index to predict patient outcome after treatment with a particular antimicrobial agent for all clinical situations, but the optimum pharmacokinetic-pharmacodynamic predictor might be dependent on clinical features.

Analysis of the correlation between the values taken by these parameters and the observed clinical efficacy of treatments may help to find the efficacy index to be considered for antimicrobial dosage optimisation. With this in mind, we were prompted to conduct a retrospective study to establish the relationship between the values achieved by different efficacy indices and the corresponding efficacy of treatment observed with the  $\beta$ -lactam drug ceftizoxime. The aim of this study was to evaluate

the validity of the above-mentioned parameters in the prediction of clinical outcomes with this anti-bacterial administered under different dosage schedules for different clinical environments, using the data reported in the literature.

## Patients and Methods

The methodology followed to carry out this work has been described previously in *Clinical Pharmacokinetics*<sup>[7]</sup> and was recently applied to ciprofloxacin.<sup>[10]</sup> Briefly, it consists of the following steps: acquisition of data, selection of data, estimation of efficacy indices and correlation analysis.

### Data Acquisition

WINSPIRS (which includes MEDLINE, IPA and LIFE-SCIENCES) and Iowa Drug Information Service (IDIS) computer systems were used for the bibliographical search to collect information about the clinical efficacy of ceftizoxime, published within the period 1980 to 1997. Other biomedical journals not included in these databases were also reviewed.

### Selection of Data

First, all publications including data about the clinical efficacy of treatments with ceftizoxime were collected. Following this, the following exclusion criteria were applied to the data thus acquired: (i) infectious processes caused by more than one pathogen; (ii) infections produced by an unidentified micro-organism; (iii) incomplete description of the treatment applied; (iv) paediatric patients; (v) renally impaired patients; (vi) multiple antibacterial treatments; and (vii) studies with less than 5 patients.

We define a 'clinical case' as a group of 5 or more patients infected at the same site with the same species of bacteria. After applying these criteria, the data were reduced to 60 different clinical cases<sup>[13-19]</sup> corresponding to infections caused by 24 different bacteria; these bacteria are shown in table I.<sup>[20-27]</sup>

### Estimation of Efficacy Indices

The following indices were calculated for each clinical case:  $C_{\max}^{ss}/MIC$ ,  $(t^{ss})_{24h} > MIC$ ,<sup>[6]</sup>  $(AUC^{ss})_{24h}/MIC$  and  $(AUC^{ss})_{24h}$ .

A mean MIC value calculated from the data found in the literature was used to estimate the different indices. Table I shows the range of reported MIC values for the pathogens responsible for the infections in the clinical cases considered.

$C_{\max}^{ss}/MIC$ ,  $(t^{ss})_{24h} > MIC$ ,  $(AUC^{ss})_{24h}/MIC$  and  $(AUC^{ss})_{24h}$  were obtained from the simulated plasma concentration curves corresponding to the reported dosage regimens of ceftizoxime administered. As happens with other drugs, the administration route determines the optimum pharmacokinetic model to be used. The parameters defining the 1- and 2-compartment models were taken from the literature.<sup>[28-38]</sup> A 2-compartment model was used

**Table I.** 90% minimum inhibitory concentration (MIC<sub>90</sub>) of ceftizoxime for the pathogens responsible for the infections in the clinical cases considered for correlation analysis

Pathogen	MIC <sub>90</sub> (mg/L)	References
<b>Gram-negative</b>		
<i>Escherichia coli</i>	0.03-0.5	20- 24
<i>Klebsiella pneumoniae</i>	0.03-0.5	20, 21, 24
<i>Klebsiella oxytoca</i>	0.12	27
<i>Klebsiella</i> spp.	0.003-0.125	20, 23
<i>Enterobacter cloacae</i>	0.25-32	20, 21
<i>Enterobacter</i> spp.	0.12-100	20, 22-24
<i>Proteus mirabilis</i>	0.006-0.5	20, 24
<i>Proteus</i> spp.	0.06	22
<i>Citrobacter freundii</i>	1-32	20, 23
<i>Citrobacter</i> spp.	1	20, 22
<i>Serratia</i> spp.	0.125-8	20, 22-24
<i>Pseudomonas aeruginosa</i>	6.3-100	21, 22-25
<i>Neisseria gonorrhoeae</i>	0.002-0.125	20-23
<i>Haemophilus influenzae</i>	0.0015-1.6	20-22
<i>Bacteroides fragilis</i>	4-128	21, 22
<b>Gram-positive</b>		
<i>Staphylococcus aureus</i>	3.1-64	20-24
<i>Streptococcus pneumoniae</i>	0.015-0.39	21, 22, 24
<i>Streptococcus viridans</i>	0.4-8	20, 21
<i>Streptococcus pyogenes</i>	0.1-0.25	22- 23
<i>Streptococcus</i> spp.	0.5	27
<i>Enterococcus</i> spp.	16-256	20- 24
<i>Peptococcus</i> spp.	0.25-64	26

**Table II.** Values of estimated pharmacokinetic-pharmacodynamic indices and corresponding reported efficacy of ceftizoxime

Efficacy (%)	$C_{\max}^{SS}/MIC$	$(t^{SS})_{24h} > MIC$ (h)	$(AUC^{SS})_{24h}/MIC$ (h)	$(AUC^{SS})_{24h}$ (h)	Reference
100	201.3	24	1789	2060	13
100	43.9	24	390.4	449.4	13
100	96.6	24	859	988.7	13
100	3.22	12.6	28.6	26.4	13
100	1.66	6.3	14.8	8.9	13
100	259.2	24	718.3	819.9	14
100	2246	24	6225	7192	14
100	46.3	24	560.2	643.3	15
100	0.83	0	5.6	0	16
100	84.3	21.8	373.5	429.9	16
100	200.7	24	889.2	1027	16
100	148.5	20.8	373.5	429.1	16
100	605	24	2918	3367	16
100	0.37	0	1.8	0	16
100	645.8	24	3112	3592	16
100	0.76	0	3.73	0	16
100	1.48	9	16.7	9.03	17
100	99.5	24	1120	1289	17
100	829.2	24	9336	10742	17
100	99.5	24	1120	1289	17
100	95.7	24	1077	1239	17
100	1.48	9	16.7	9.03	17
100	1.24	0.5	8.40	0.71	17
100	314.4	24	2100	2424	18
99	46.5	24	413	475.3	13
97	351.2	24	1556	1798	16
96	74.2	17.5	186.8	212.2	16
96	48.3	24	429.5	494.4	13
95	0.72	0	6.41	0	13
95	270	24	747	863.1	14
94	402.6	24	3579	4120	13
94	81.06	21.6	359.1	413.2	16
94	1.25	0.83	5.6	1.72	16
94	18.6	11	46.7	49.05	16
93	580	24	1459	1686	16
93	72.5	24	484.8	559.4	18
92	1.16	0.33	5.60	0.45	16
91.5	658.6	24	2918	3372	16
90.6	56	24	373.4	430.8	16
90	437	24	2917	3365	16
90	605.5	24	2918	3367	16
90	1.16	0.33	5.60	0.445	16
89	0.23	0	2.06	0	13
87.5	77.5	24	373.5	431.1	16
87.5	77.5	24	375.5	431.1	16
87.5	0.6	0	2.92	0	16
86	115	24	1022	1177	13
85.7	1.27	0.66	8.5	1.72	16
83	5.75	18	51.1	54.5	13

Table II. Contd

Efficacy (%)	$C_{\max}^{ss}/MIC$	$(t^{ss})_{24h} > MIC$ (h)	$(AUC^{ss})_{24h}/MIC$ (h)	$(AUC^{ss})_{24h}$ (h)	Reference
82	8.84	7.5	22.2	20.9	16
82	82.5	18	207.5	236.4	16
81	0.74	0	1.87	0	16
80	0.34	0	3.90	0	19
80	761.9	24	8753	9989	19
80	0.84	0	3.73	0	16
75	1.45	3	16.7	4.99	19
71	97.5	24	1120	1278	19
71	77.5	24	373.5	431	16
35	0.36	0	0.90	0	16
33.3	0.40	0	1.80	0	16

$(AUC^{ss})_{24h}/MIC$  = total area under the concentration-time curve over 24 hours at steady state divided by the MIC;  $(AUC^{ss})_{24h}$  = AUC at steady state for the period of time that the concentration is above the MIC over a period of 24 hours divided by the MIC;  $C_{\max}^{ss}/MIC$  = peak concentration at steady state divided by the MIC; MIC = minimum inhibitory concentration;  $(t^{ss})_{24h} > MIC$  = time that the plasma drug concentration exceeded the MIC scaled to 24 hours at steady state.

for the simulation of drug curves for intravenous administration with the following pharmacokinetic parameter values: distribution volume of the central compartment ( $V_c$ ) = 0.27 L/kg; plasma clearance ( $CL_p$ ) = 0.15 L/h/kg; transfer rate constant from the central to the peripheral compartment ( $k_{12}$ ) = 3.17 h<sup>-1</sup> and transfer rate constant from the peripheral to the central compartment ( $k_{21}$ ) = 2.11 h<sup>-1</sup>.

When ceftizoxime was administered intramuscularly, simulation of plasma curves was carried out using a 1-compartment model with the following parameters: volume of distribution ( $V_d$ ) = 0.34 L/kg;  $CL_p$  = 0.15 L/h/kg and absorption rate constant ( $K_a$ ) = 1.87 h<sup>-1</sup>.

Dosages, administration intervals and the total number of doses received by the patients described in the literature searched, and selected according to the above-mentioned exclusion criteria, were considered for curve simulation.  $C_{\max}^{ss}$  and  $(t^{ss})_{24h} > MIC$  were obtained directly from simulated curves. Additionally, the simulated curves provide the time-concentration data necessary to calculate  $(AUC^{ss})_{24h}$  and  $(AUC^{ss})_{24h}/MIC$  by numerical integration,<sup>[39]</sup> as previously described.<sup>[7]</sup>

Simulation of the plasma concentration curves was carried out using the PKS Pharmacokinetic Computer System (Abbot Laboratories Diagnostic Division, Abbot Park, IL, USA).

## Correlation Analysis

A univariate correlation analysis<sup>[40]</sup> was performed with the percentage of reported efficacy and the calculated indices as the dependent and independent variables, respectively. Linear and nonlinear conventional response models<sup>[41]</sup> were used for the correlation analysis. The equations defining these models are:

Linear models:

$$E = a + b \times I$$

$$E = a' + b' \times \log I$$

where  $a$ ,  $a'$  and  $b$ ,  $b'$  are the intercept and the slope values of the regression straight lines, respectively,  $I$  represents the calculated index [ $C_{\max}^{ss}/MIC$ ,  $(t^{ss})_{24h} > MIC$ ,  $(AUC^{ss})_{24h}/MIC$  or  $(AUC^{ss})_{24h}$ ] and  $E$  is the observed efficacy expressed as the percentage of either clinical cure or bacterial eradication.  $E_{\max}$  model:

$$E = E_0 + \frac{(E_{\max} - E_0) \times I^n}{I_{50}^n + I^n}$$

where  $E_{\max}$  and  $E_0$  represent the maximum and intrinsic responses, respectively,  $I_{50}$  is the value of the index for a response of 50% of  $E_{\max}$ , and  $n$  is the Hill coefficient related to the curve profile,

leading to the asymptotic and sigmoid  $E_{\max}$  models when  $n = 1$  and  $n \neq 1$ , respectively.

Model fitting was carried out using the PCNonlin 4.2 program (Scientific Consulting, Inc., Apex, NC, USA), which optimises the model parameters by nonlinear regression techniques according to statistical criteria such as the standard deviation of parameters and minimum Akaike's information criterion (AIC).<sup>[42]</sup>

An analysis of variation (ANOVA) of the regression<sup>[40]</sup> was performed to establish the statistical significance of the slope for the linear models ( $p < 0.05$ ).

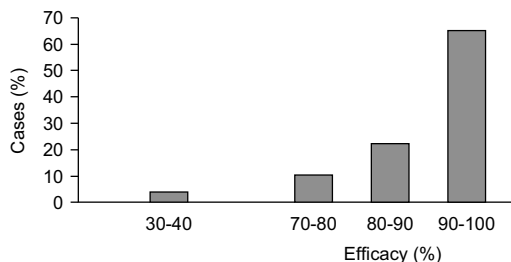
## Results

Table II shows the values of  $C_{\max}^{ss}/MIC$ ,  $(t^{ss})_{24h} > MIC$ ,  $(AUC^{ss})_{24h}/MIC$  and  $(AUC^{ss})_{24h}$  calculated and their corresponding reported percentages of efficacy for ceftizoxime. Most data are for high efficacy rates, as shown by the biased frequency distribution histogram for reported efficacy in figure 1, which constrains the range to 71 to 100% efficacy and restricts the correlation analysis. A high dispersion of the index values for the same percentage of efficacy reported is observed, with mean values of  $286.90 \pm 505.22$ ,  $19.81 \pm 7.39h$ ,  $1573.63 \pm 2304.11h$  and  $1811.21 \pm 2656.43h$  for  $C_{\max}^{ss}/MIC$ ,  $(t^{ss})_{24h} > MIC$ ,  $(AUC^{ss})_{24h}/MIC$  and  $(AUC^{ss})_{24h}$ , respectively, when 100% efficacy is recorded. The cases in table II with zero values for the calculated indices were not considered for the correlation analysis.

Tables III and IV show the parameters corresponding to the linear and the asymptotic  $E_{\max}$  models respectively, together with the statistics of the correlation analysis. No correlation was found when the log-linear or the sigmoid  $E_{\max}$  approaches were used.

## Discussion

As seen in table II, several cases of high efficacy with very low index values (even zero) were found. Scrutiny of these cases reveals that these correspond to infections caused by *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterobacter* spp. and



**Fig. 1.** Frequency distribution histogram of ceftizoxime efficacy data used to perform the pharmacokinetic-pharmacodynamic analysis. A 'clinical case' is a group of 5 or more patients infected at the same site with the same species of bacteria.

*Bacteroides* for which MIC ranges of 6.3 to 100, 3.1 to 64, 0.12 to 100 and 4 to 128 mg/L, respectively, are reported for ceftizoxime. It should be noted that a mean MIC value was used to calculate the indices; the mean value is considered to be a good estimator of a particular value for normally distributed, low dispersed data, but it may differ strongly from any particular value for highly dispersed sample data.<sup>[10]</sup>

It is likely that the mean MIC literature values used to estimate these efficacy indices are not representative of the actual MIC value in such cases. This contradictory finding of some cases with maximum efficacy accompanied by low index values is not new for ceftizoxime, but rather had appeared previously when performing a similar study with ciprofloxacin,<sup>[10]</sup> although this happened in fewer cases for the quinolone. It is evident that the high variability in the literature MIC values seriously restricts the above-described methodology, since a true value of this parameter is essential for the correct calculation of the indices. This high variability in the reported MIC values also compromises the efficacy of antimicrobial treatments in such cases when the drug is empirically selected on the basis of the suspected pathogen and its reported MIC value, as for community-acquired infections or acute phases of hospital infections. Fortunately, growing concern about this problem has arisen among microbiologists and specialists in infectious disease and specific actions, such as the Alexander Project,<sup>[43,44]</sup> are being carried out to examine the

antimicrobial susceptibilities of bacterial isolates from all over the world. There is a fair degree of consensus about the importance of greater surveillance of susceptibility and standardised test methods among laboratories, and recently very interesting results have been reported by Livermore et al.<sup>[45]</sup> highlighting the significance of these problems.

Despite the above limitations of using literature MIC values, the correlation analysis was performed by rejecting those cases with zero values for the indices. Although a poor correlation was found between the values of the estimated indices and the efficacy reported for ceftizoxime, a linear relationship between  $(t^{ss})_{24h} > MIC$  and efficacy was established (Pearson coefficient value of 0.402, and statistical significance of the slope of  $1.9 \times 10^{-3}$  [ $p = 0.0019$ ]). For the rest of the indices, the slope did not show statistical significance ( $p > 0.05$ ).

The asymptotic  $E_{max}$  model managed to fit the data for  $C_{max}^{ss}/MIC$ ,  $(t^{ss})_{24h} > MIC$  and  $(AUC^{ss})_{24h}/MIC$ , but not for  $(AUC^{ss})_{24h}$ . According to the statistical criteria of model selection, this model is not a better choice since the AIC values do not decrease in comparison with the simplest linear model. Moreover, a lower degree of precision of the estimated parameters is observed with the asymptotic  $E_{max}$  model. Regarding the log-linear model and the sigmoid  $E_{max}$  model, both failed to fit the data. Accordingly, the time that the plasma concentrations are above the MIC value is the pharmacokinetic-pharmacodynamic parameter best related to efficacy for ceftizoxime under the conditions used in this study, which included a broad spectrum of in-

fecting bacteria and a wide range of clinical circumstances.

In comparison with results recently obtained with ciprofloxacin in a very similar study,<sup>[10]</sup> these point to analogies and differences that merit comment. First,  $(t^{ss})_{24h} > MIC$  is the index best correlated with efficacy for both antibacterials, but in the case of ciprofloxacin not only this parameter but also the other 3 proved to have a statistical correlation, all of them being indicators of efficacy. Another difference is that the asymptotic  $E_{max}$  ( $n = 1$ ) model constitutes a good alternative for correlation analysis with the quinolone, whereas it is not a good choice for ceftizoxime. The better goodness of data fitting observed for ciprofloxacin may be because of the wider efficacy range (100% to 24%) reported for this drug, since the remaining factors involved in the study were very similar for both cases.

Regarding the finding of  $(t^{ss})_{24h} > MIC$  as the best predictor of efficacy, according to previous information on the pharmacodynamics of  $\beta$ -lactam antibacterials this is in total agreement with the expectations for ceftizoxime; nevertheless, it is not expected for antibacterial agents that show concentration-dependent bactericidal activity, such as the fluoroquinolones, which should theoretically show the best correlation between the  $C_{max}^{ss}/MIC$  ratio and treatment efficacy. Despite the large body of information confirming higher bacterial killing rates with higher concentrations for fluoroquinolones or aminoglycosides, several studies carried out with this type of drug have disclosed that the  $C_{max}^{ss}/MIC$  ratio is not the pharmacokinetic-

**Table III.** Parameters defining the linear relationship between the reported efficacy and estimated indices of ceftizoxime

Parameter	a ± SD	b ± SD	r	AIC	p-Value
$C_{max}^{ss}/MIC$	89.81 ± 1.94	0.0065 ± 0.005	0.17	557.7	NS
$(t^{ss})_{24h} > MIC$	84.75 ± 2.92	0.41 ± 0.16	0.402	552.88	0.0019
$(AUC^{ss})_{24h}/MIC$	90.1 ± 1.97	0.0009 ± 0.0009	0.127	558.45	NS
$(AUC^{ss})_{24h}$	90.06 ± 1.97	0.00078 ± 0.0007	0.128	558.43	NS

**a/b** = intercept and slope of the regression model described in the Methods section; **AIC** = Akaike's information criterion; **(AUC<sup>ss</sup>)<sub>24h</sub>/MIC** = total area under the concentration-time curve over 24 hours at steady state divided by the MIC; **(AUC<sup>ss</sup>)<sub>24h</sub>** = AUC at steady state for the period of time that the concentration is above the MIC over a period of 24 hours divided by the MIC; **C<sub>max</sub><sup>ss</sup>/MIC** = peak concentration at steady state divided by the MIC; **MIC** = minimum inhibitory concentration; **NS** = not significant; **r** = Pearson correlation coefficient; **SD** = standard deviation; **(t<sup>ss</sup>)<sub>24h</sub> > MIC** = time that the plasma drug concentration exceeded the MIC scaled to 24 hours at steady state.

**Table IV.** Parameters defining the asymptotic relationship between the reported efficacy and estimated indices of ceftizoxime

Parameter	$E_{\max} \pm SD$	$E_0 \pm SD$	$I_{50} \pm SD$	AIC
$C_{\max}^{ss}/MIC$	108.11 $\pm$ 37.2	89 $\pm$ 2.4	1123.01 $\pm$ 3729.1	558.82
$(t^{ss})_{24h} > MIC$	100.6 $\pm$ 40.11	34.66 $\pm$ 8.54	10.64 $\pm$ 19.96	665.7
$(AUC^{ss})_{24h}/MIC$	104.22 $\pm$ 27.35	89 $\pm$ 2.5	4667.4 $\pm$ 15868.1	559.1

**AIC** = Akaike's information criterion;  **$(AUC^{ss})_{24h}/MIC$**  = total area under the concentration-time curve over 24 hours at steady state divided by the MIC;  **$C_{\max}^{ss}/MIC$**  = peak concentration at steady state divided by the MIC;  **$E_{\max}$** ,  **$E_0$** ,  **$I_{50}$**  = parameters of the maximum response model described in the Methods section; **MIC** = minimum inhibitory concentration; **SD** = standard deviation; **MIC** = minimum inhibitory concentration;  **$(t^{ss})_{24h} > MIC$**  = time that the plasma drug concentration exceeded the MIC scaled to 24 hours at steady state.

pharmacodynamic parameter best correlated to efficacy in clinical practice. Instead, other parameters depending on the AUC seem to be better predictors of efficacy for these antibacterials.<sup>[46,47]</sup> Since AUC is a pharmacokinetic parameter depending on  $t_{1/2\beta}$ , there is covariance between both types of index and, therefore, if one is related to clinical response the other should also be related to it. This proves that the clinical efficacy of these drugs is also governed by the time that their concentrations remain above the MIC. This hypothesis is supported by the results from Bouvier et al.,<sup>[11]</sup> who integrated the kinetic behaviour of the drug and the fate of the bacterial population in a pharmacokinetic-pharmacodynamic model, and concluded that for concentration-independent as well as for concentration-dependent antimicrobial agents the longer the  $(t^{ss})_{24h} > MIC$  the higher the efficacy.

Additional studies of the correlation between pharmacokinetic-pharmacodynamic parameters and efficacy observed in clinical practice would be of great interest in clarifying the type of relationship between both variables and also in establishing the influence of certain clinical factors, such as the infecting organism or site of infection. In this context, it has recently been reported that the type of infecting bacteria is a relevant factor to be considered for the optimisation of administration of fluoroquinolones; an  $(AUC^{ss})_{24h}/MIC$  ratio of 125 to 250h has been reported to be related to clinical efficacy for Gram-negative infections, but values of 30 to 55h are sufficient for aerobic Gram-positive pathogens.<sup>[47]</sup> This is an interesting finding and should be taken into account when analysing the relationship between the efficacy of antibacterial agents and pharmacokinetic-pharmacodynamic in-

indices. It is possible that the type of infecting bacteria could strongly determine the efficacy index to be considered as well as the type of antibacterial. The infection site may also be another factor. This might explain the lack of agreement in the data reported in the literature about the efficacy index that best predicts clinical outcome for a particular antibacterial. Further investigations in this field are necessary to confirm or reject such a hypothesis.

## Conclusions

According to our results with ceftizoxime, the time that the plasma concentrations remain above the MIC is the only pharmacokinetic-pharmacodynamic index correlated with efficacy, although the biased efficacy range reported for this drug and used to perform the correlation analysis may influence this finding. If more information about the use of antimicrobial agents in clinical practice (including failures as well as successes) were available, a more accurate retrospective correlation analysis could be performed to determine the factors influencing clinical outcome. In this sense, maximum information about the patients' idiosyncrasies and the infecting organism(s), together with the widest efficacy range observed, should be provided in the literature to facilitate the pharmacokinetic-pharmacodynamic interpretation of the results reported.

Prospective studies designed to provide all the necessary information (the aetiology of the infection with the actual MIC value, together with a complete description of patients, the treatment administered and the response obtained) would be the best alternative to investigate the pharmacokinetic-pharmacodynamic relationship for antimicrobial



agents in order to optimise such type of pharmacotherapy in clinical practice.

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