Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of a Once-Daily Treatment Using Ciprofloxacin in an Extended-Release Dosage Form*

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Abstract

Objective: To evaluate the suitability of a once-a-day dosing regimen of ciprofloxacin using a new extended-release dosage form based on PK/PD principles.

Methods: Ciprofloxacin's serum concentrations were measured after administration of 500 mg immediate-release twice-daily, and 1,000 mg extended-release once-daily to 19 healthy volunteers. Pharmacokinetic parameters were determined using non-compartmental and compartmental data analysis. Measured serum concentration profiles were linked to ciprofloxacin's effect against *Escherichia coli* (MIC 0.013 mg/l) from *in vitro* kill curve studies where the pharmacokinetics of ciprofloxacin were simulated and change in number of bacteria (CFU/ml) versus time was monitored. Resulting parameters were used to compare expected kill curves for the two dosing regimens based on measured ciprofloxacin concentrations.

Results: Fitting the data using an appropriate PK/PD model resulted in a set of mean pharmacodynamic parameters (bacterial growth rate constant, k_0, maximum kill rate constant, K_{max}, and EC_{50}). The model included a novel term to account for a change in kill rate after approximately 4 h when K_{max} decreased in concentration-dependent matter. The model allowed excellent curve fits of all ciprofloxacin concentrations investigated. Comparison of expected kill curves with the immediate-release versus extended-release treatments showed similar outcome. Both treatments resulted in a decrease in CFU/ml > 5 log units over 24 h.

Conclusion: Results indicate that once-a-day dosing of equal total daily doses with the new and more compliance-friendly extended-release dosing form will be therapeutically equivalent to once-a-day dosing with traditional immediate-release dosage forms for treatment of infections with this microorganism.

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Introduction

Pharmacokinetic/pharmacodynamic (PK/PD) modeling has become an important tool to streamline drug development [1–3]. With a good understanding of the dose-exposure relationship, or pharmacokinetics (PK), and the exposure-response relationship, or pharmacodynamics (PD), it may be possible to find a quantitative link between the dose and dosing regimen, on the one hand, and the desired and undesired drug effects, on the other hand. This information then can be used to make educated decisions about dose selection and the likelihood of success for clinical testing.

Antibiotics are normally evaluated on the basis of one of the following PK/PD indices, all of which are based on a direct comparison of serum concentrations of the antibiotic and the MIC of the respective bacteria: time above MIC (T > MIC), peak concentration/MIC ratio (C_{max}/MIC), and the 24 h area under the concentration versus time curve (AUC_{24})/MIC ratio. [4] For fluoroquinolones, the parameter that better correlates to therapeutic outcome is AUC_{24}/MIC ratio. The target is to achieve, for a given dosing regimen of fluoroquinolones, an AUC_{24}/MIC of at least 125 for the treatment of gram-negative bacteria causing respiratory tract infections (RTIs) in severely ill, elderly hospitalized patients [4, 5]. The target for gram-positive bacteria causing community-acquired RTIs is believed to be lower [6–12].

Another approach that has been successfully used to study the PD of antibiotics is time-kill analysis. This ap-

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proach is mathematically somewhat more complex but has been shown to offer certain advantages over MIC-based approaches [13–17]. In time kill experiments the *in vivo* half-life of the drug can be simulated and therefore the effects of fluctuating concentrations on bacterial growth and killing can be observed, as well as how bacteria respond when the concentrations fall below the MIC. The PD parameters derived from time kill experiments can then be combined with *in vivo* PK data in an integrated PK/PD model that describes the antibiotic's activity as a function of time and concentration.

Ciprofloxacin (CIP) is a broad-spectrum anti-infective of the fluoroquinolone class [18–20]. It is a well-known antimicrobial agent that has been available for the treatment of infections by both gram-negative and gram-positive bacteria for more than a decade. Oral CIP is available as conventional immediate release (IR) tablets of 100 mg, 250 mg, 500 mg, and 750 mg, which are administered two to three times a day. The PK parameters of CIP given orally are well characterized [21–24]. A new extended-release dosage form of CIP (Cipro XR) has been recently approved for treatment of acute uncomplicated and complicated urinary tract infections (UTIs), and uncomplicated pyelonephritis. The XR oral dosage form is available in 500 mg and 1,000 mg strength tablets.

It was the purpose of this study to evaluate the suitability of a once-a-day dosing regimen of CIP using a new XR dosage form based on PK/PD principles. Specifically, it was the goal of this assessment to compare the expected performance of the 1,000 mg XR product given once a day to that of the traditional twice-a-day dosing of the same daily dose in an IR dosage form (500 mg IR).

Methods

Study Subjects

A total of 19 healthy male volunteers, aged between 23 and 49 years (median 36.5 years), participated in an open-label, single-center, randomized, non-controlled, multiple-dose, twofold crossover study to assess the single-dose and steady-state concentrations of 1,000 mg CIP in XR tablet in comparison to the 500 mg IR tablet twice daily. Both treatment phases were separated by at least 1 week. All subjects provided written consent prior to participating in the study. The study was conducted in the Department of Clinical Pharmacology of Bayer AG (Wuppertal, Germany), in accordance with the principles of the Declaration of Helsinki. The protocols were approved by the Ethics Committee of the North Rhine Medical Council (Düsseldorf, Germany).

Subjects received either treatment along with 180 ml of non-sparkling water in the morning after an overnight fast. PK profiles were determined on days 1 and 5 of the treatment. Blood was collected from the forearm vein at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, and 24 h post dose on days 1 and 5 and also at 30 h on day 5. During the administration of the 500 mg IR twice-daily regimen, samples were also collected at 13, 13.5, 15, and 15 h post dose.

Drug Assay

Concentrations of CIP in plasma and urine were determined by a validated high-pressure liquid chromatography (HPLC) method with fluorescence detection [25]. Ofloxacin was used as internal standard and the limit of quantification for CIP was 10 µg/l.

Pharmacokinetic Data Analysis

PK parameters were determined using standard PK methods [26]. Both non-compartmental and compartmental PK data analyses were performed with the software program Kinetica® (Innaphase, Philadelphia).

The primary non-compartmental PK parameters determined were the AUC, maximum concentration of the drug (C_{max}), time for C_{max} (T_{max}), and the elimination rate constant (k_e). AUC was calculated by the trapezoidal method (log-linear). Extrapolated AUC (AUC_{extra}) was determined as the calculated last concentration (C_{last})/k_e, and AUC_{tot} was calculated as AUC_{last} + AUC_{extra}, AUC_{last} being the AUC from zero to the last measured time point. Both C_{max} and T_{max} were obtained from the plots of serum concentration versus time. The k_e was obtained by linear regression of the terminal log linear phase of the concentration-time curve. The elimination half-life ($t_{1/2}$) was determined as 0.693/k_e.

CIP plasma concentrations were fitted to a one-compartment body model with first order absorption and elimination, according to the following equation:

$$C = \frac{F \cdot D \cdot k_a}{V \cdot (k_a - k_e)} \cdot \left(\frac{e^{-k_e t} \cdot (1 - e^{-nk_e \tau})}{(1 - e^{-k_e \tau})} - \frac{e^{-k_a t} \cdot (1 - e^{-nk_a \tau})}{(1 - e^{-k_a \tau})} \right)$$

where k_a is the absorption rate constant, k_e is the elimination rate constant from the central compartment, V is the volume of distribution, F is the fraction absorbed, D is the dose, n is the number of doses and τ is the dosing interval. Furthermore, a lag time (t_{lag}) was employed.

From the parameters obtained by curve fitting, CL and $t_{1/2}$ were calculated as CL/F = k_e*V/F, and $t_{1/2}$ = 0.693/k_e. Adequacy of fit was based on the Aikaike Information Criterion (AIC) as well as the visual inspection of the fitted curves.

Pharmacodynamic Study Design: Time Kill Curves of CIP

In an *in vitro* system *Escherichia coli* 11775 (clinical isolate, MIC = 0.013 mg/l) was exposed to changing concentrations of CIP, simulating a half-life of 4 h [27, 28]. Concentrations were changed by means of a pump providing a continuous flow of broth to dilute the CIP concentrations. The following initial concentrations of CIP were investigated:

- 0.03 mg/l, equivalent to an AUC/MIC of 14
- 0.06 mg/l, equivalent to an AUC/MIC of 27
- 0.13 mg/l, equivalent to an AUC/MIC of 59
- 0.25 mg/l, equivalent to an AUC/MIC of 113
- 0.5 mg/l, equivalent to an AUC/MIC of 226

Samples were taken at predetermined time points up to 32 h. Two to three 10-fold serial dilutions were plated in duplicates in proper agar plates and incubated overnight at 37 ºC. The number of colony forming units (CFU) were counted and averaged. Time kill curves were constructed by plotting the number of CFU/ml against time for each initial concentration tested.

Pharmacodynamic Data Analysis

Time kill analysis and mathematical modeling of the time kill data was performed with the non-linear regression software program Scientist (Micromath, Salt Lake City, UT). Model selection was

based on the model selection criterion (MSC) provided by the program, as well as visual inspection of the fitted curves.

PK/PD Simulations and Comparisons of Outcome

Comparisons of outcome between the two treatments were based on AUC_{24}/MIC ratios and simulated time kill profiles with both regimens. The AUC_{24} for both treatments were obtained by adjusting the $AUC_{0\text{-}t}$ for the total daily dose of each regimen. The resulting AUC_{24} were then used to calculate the respective AUC_{24}/MIC ratios of the 1,000 mg XR once-daily and the 500 mg IR twice-daily regimens. Simulations of the time kill profiles of CIP were performed with the software program Scientist. The PK profiles for both treatments were independently connected to a newly developed PK/PD model and multiple-dose regimens with both dosage forms were simulated. Comparison of outcome between the two dosing regimens was based on the visual inspection of the simulated time kill curves.

Results

Pharmacokinetic Analysis

Table 1 shows the results of the non-compartmental PK analysis performed with the software Kinetica. The PK parameters obtained for both the 500 mg IR and 1,000 mg XR tablets were similar, indicating a small effect of the *in vivo* release process on the PK of CIP. The 2-h T_{max} obtained with the IR formulation is consistent with the values reported in the literature, while the value found for the XR formulation, 2.5 h, is slightly above the range [18]. Comparisons between the other parameters also suggest an increase in absorption time with the XR formulation, although the differences between the two regimens are small. The terminal half-life after administration of the XR tablet is slightly longer compared to the one obtained with the IR tablet (4.9 vs 4.0 h). The mean residence time (MRT) of the XR dosage form is also slightly longer (7.0 vs 6.0 h) compared to the one for the IR tablets. If a constant systemic MRT is assumed, then the results suggest that the mean absorption time of CIP after administration of the XR product is prolonged by approximately 1 h.

The AUC values indicate a linear PK in the dose range studied, and seem to be independent of the dosage form. The AUC_{24} obtained with both formulations are almost identical, 14.2 µg/ml*h for the XR dosage form and 14.8 µg/ml*h for the IR dosage form, when adjusted for total daily dose. This observation indicates that the extent of absorption is not changed with the new XR dosage and is in accordance with previous reports [29].

Values for CL were almost identical for both formulations (67.6 l/h for IR tablet, 70.6 l/h for the XR tablet), which is to be expected since both regimens resulted in similar AUCs. Values for volume of distribution were slightly different (504 vs 394 l for XR and IR, respectively for Vz and 493 vs 406 l for Vss). However, the differences observed between the volumes of distribution of the two formulations are most likely artifacts caused by the differences in absorption rate and terminal half-life. Vz is calculated as CL/k_e, so a longer terminal elimination half-life will result in a larger volume of distribution. Vss is calculated from the product of CL and mean residence time. These values obtained for clearance and volume of distribution for both formulations may be slightly higher than the ones reported in the literature if a bioavailability (F) of 0.6-0.85 is assumed for the calculations [19, 30, 31].

Table 1
Results of the non-compartmental pharmacokinetic data analysis performed with Kinetica.

Parameter (units)	Dosage form	
	1,000 mg XR	500 mg IR
C_{max} (µg/ml)	2.12	1.24
t_{max} (h)	2.5	2.0
$AUC_{0\text{-}t}$ (µg/ml*h)	13.7	6.46
AUC_{extra} (µg/ml*h)	0.46	0.93
AUC_{tot} (µg/ml*h)	14.2	7.39
$\%AUC_{extra}$	3.25	12.6
ke (h^{-1})	0.14	0.17
$t_{1/2}$ (h)	4.9	4.0
MRT (h)	7.0	6.0
CL/F (l/h)	70.6	67.6
Vz/F (l)	504.1	393.9
Vss/F (l)	493.3	405.9

Figure 1 shows the curve fits obtained with the one-compartment model for both dosing regimens. It can be seen that the model is able to describe the PK profile of both treatments very well. Although some of the last data points were slightly missed by the fitted curve, the estimates of half-life in both scenarios are in good agreement with the values obtained from the non-compartmental analysis (Table 1) and are well within the range reported in the literature. A two-compartment body model was also attempted but did not provide a better AIC for the fit. In addition, the correlation matrix generated in the output report by Kinetica indicated a strong correlation between several parameters when a two-compartment model was attempted. This is an indication for overparametrization and, therefore, the simpler one-compartment model was chosen to explain the data.

PK parameters resulting from the curve fitting of both regimens and are shown in table 2. The values obtained by compartmental analysis are in agreement with the values reported by previous studies, as well as with the ones obtained with the non-compartmental PK analysis [19, 30, 31]. It can be seen that fitting the concentration versus time profiles of both the 1,000 mg XR once daily or 500 mg IR twice daily to a one-compartmental model produced very similar PK parameters for both formulations. The values obtained for the absorption rate constant (k_a) were 1.17 h^{-1} and 1.04 h^{-1} for the 500 mg IR tablet and the 1,000 mg XR tablet, respectively. For k_e, the values obtained were 0.19 and 0.20 for the 500 mg IR tablet and the 1,000 mg XR tablet, respectively, which resulted in similar half-lifes for

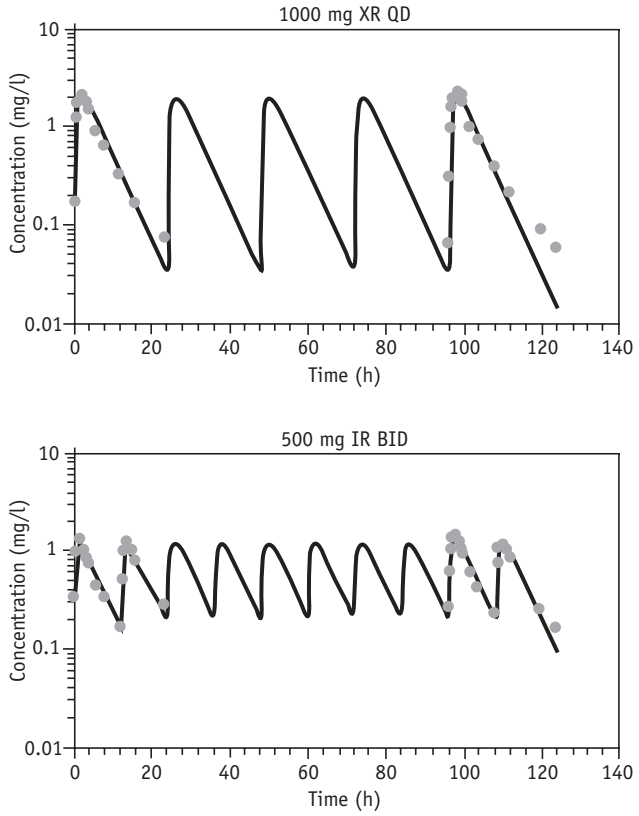

Figure 1. Fitted CIP plasma concentrations (geometric means) using a one-compartment body model with Kinetica (semi-logarithmic plots) for 1,000 mg XR formulation once a day (top) and 500 mg IR tablet twice a day (bottom). Symbols represent the experimental data; the line represents the fit obtained by the one-compartment model. QD: once-a-day dosing; BID: twice-a-day dosing.

Table 2
Results of the compartmental pharmacokinetic data analysis obtained in Kinetica with a one-compartment body model with first-order absorption and elimination.

Dosing regimen	V/F[a] (L)	k_a (h^{-1})	k_e (h^{-1})	t_{lag} (h)	$t_{1/2}$[b] (h)	CL/F[c] (l/h)
500 mg IR BID	345.9	1.17	0.19	0.30	3.65	69.2
1000 mg XR QD	345.4	1.04	0.20	0.44	3.47	69.1

[a] F: fraction of dose absorbed; [b] calculated as $t_{1/2} = 0.693/k_e$; [c] calculated as $CL/F = k_e*V/F$; BID: twice-a-day dosing, QD: once-a-day dosing

both treatments (3.65 h for the IR tablet and 3.47 h for the XR tablet). However, care should be taken in the interpretation of the rate constants. The identification of rate constants in both the one- and two-compartment body models with first order absorption is extremely difficult and can only be done reliably when intravenous data are available in the same subjects [32]. Nonetheless, the constants still allow a good curve fit independent of their interpretation.

Pharmacodynamic Analysis – The New Adaptive E_{max} Model

Time kill curves for CIP exhibited a biphasic killing profile, in accordance with what has been observed with other quinolone antibiotics [33]. After an initial phase of very rapid killing, there is rapid development of an adaptive resistance slowing down the killing rate to a lower rate than initially. A novel PK/PD model has been developed to describe the time kill profiles of CIP against *E. coli* [34]. The model included a term to account for the change in the killing rate of CIP after approximately 4 h. The new adaptive E_{max} model is presented below:

$$\frac{dN}{dt} = \left(k - \frac{\left(k_1 \cdot \left(1 - \frac{C_r}{IC_{50} + C_r}\right) + k_2\right) \cdot C}{EC_{50} + C} \right) \cdot N \cdot (1 - e^{-z \cdot t})$$

where N is the number of bacteria (CFU), k is the growth rate constant in absence of the antibiotic, k_1 is the initial fast contribution to the maximum kill rate constant, k_2 is the permanent maximum kill rate constant, C_r is the drug concentration inducing adaptive resistance, C is the active drug concentration, and z is an adjustment factor at the beginning of the experiment accounting for the fact that the bacteria are not instantaneously in their logarithmic growth phase.

C_r, the concentration inducing the adaptive resistance, builds up with an initial lag-time (t_{lag}) and declines at a rate depending on an additional rate constant k_{ecr}:

$$C_r = C_0 \cdot (e^{-k_e \cdot (t - t_{lag})} - e^{-k_{ecr} \cdot (t - t_{lag})})$$

where C_0 is the initial CIP concentration in the experiment, k_e is the simulated elimination rate constant (0.17 h^{-1}, equivalent to a half-life of 4 h) and k_{ecr} is the fitted rate constant describing the decline of the adaptive resistance.

CIP's effects against *E. coli* can be successfully described by the novel adaptive E_{max} model accounting for the change in maximum kill rate under treatment. The model described above allowed simultaneous curve fits of a number of doses with the same set of parameters over a wide range of investigated concentrations. These simultaneous curve fits are presented in figure 2. Table 3 shows the respective PD parameters generated by curve fitting with the new adaptive E_{max} model.

PK/PD Simulations and Comparison of Outcome

500 mg IR and 1,000 mg XR produced almost identical AUC_{24} values and, consequently, identical AUC_{24}/MIC ratios of 1,100. Therefore, both regimens would be expected to be equivalent based on the traditional non-compartmental MIC-based approach.

Figure 3 shows the simulated plasma concentrations and bacterial counts for both the 500 mg IR twice-a-day

and the 1,000 mg XR once-a-day regimens against *E. coli*. According to the simulated time-kill profiles, both 500 mg IR twice a day and 1,000 mg XR once a day would be equally effective against *E. coli*, resulting in a decrease in CFU/ml > 5 log units over 24 h.

Discussion

According to the FDA guidance document "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" from 1997, "In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form from a previously studied immediate-release dosage form" [35]. Because the PK patterns of controlled-release and IR dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, i.e. effect on the bacterial population, to extrapolate to the new dosage form. Since pharmacokinetic studies have been performed with the XR product and CIP concentration profiles are known, and furthermore, the concentration-effect relationship of CIP has been studied, it should be possible to establish reasonable expectations about the performance of the new XR product with a once-a-day dosing regimen.

In this study, we have applied principles of PK/PD to the evaluation of a new dosage form of CIP and the suitability of using this new dosage form in once-daily dosing regimens against *E. coli*. We have used two different PK/PD approaches to evaluate the new XR dosage form in comparison to the IR dosage form, the traditional non-compartmental MIC-based approach, and time kill analysis, also known as compartmental PK/PD. Both approaches indicate that 1,000 mg XR once a day is as effective as 500 mg IR twice a day against *E. coli*, which is in accordance with previous studies [36, 37].

The new CIP XR formulation has been designed to release 35% of the dose according to an immediate release process and the remaining 65% within 3–4 h prior to the tablet reaching the distal region of the small intestine, where CIP absorption is decreased [29]. Results from our study show that, despite a small trend towards a longer absorption time with the XR tablet, the release kinetics from the XR formulation did not affect the extent of the absorption of CIP and both regimens provide the same drug exposure. This observation has been previously reported [29]. In fact, little difference was observed between the other PK parameters obtained with the two formulations. Since the total daily exposure of CIP obtained for the two dosing regimens, measured as the AUC_{24}, is almost identical both treatments will produce the same AUC_{24}/MIC ratio (1,100 h for this indicator organism), and therefore, the same pharmacological activity should be expected against *E. coli* according to the MIC-based approach.

Nevertheless, the XR tablet might have a potential pharmacodynamic advantage over the traditional 500 mg IR tablet. The therapeutic efficacy of fluoroquinolone has

Table 3
PD parameters of CIP against *E. coli* (11775) MIC = 0.013 mg/l.

Parameter	*E. coli* (11775)
k_0 (h^{-1})	7.76
k_1 (h^{-1})	10.8
k_2 (h_{-1})	8.40
EC_{50} (mg/l)	0.0035
IC_{50} (mg/l)	0.00047
k_{ecr} (h^{-1})	0.01
t_{lag} (h)	4.0
z (h^{-1})	0.09

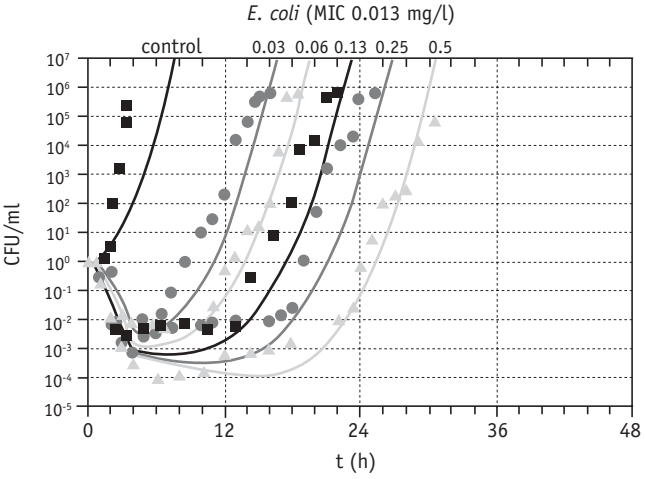

Figure 2. Simultaneous curve fittings as a function of time and initial concentration (mg/l) for: *E. coli* (MIC = 0.013 mg/l). The points were experimentally determined CFU values, the curves are simultaneously fitted with the same set of parameters for all doses. Numbers on top represent the initial concentrations (mg/l) tested.

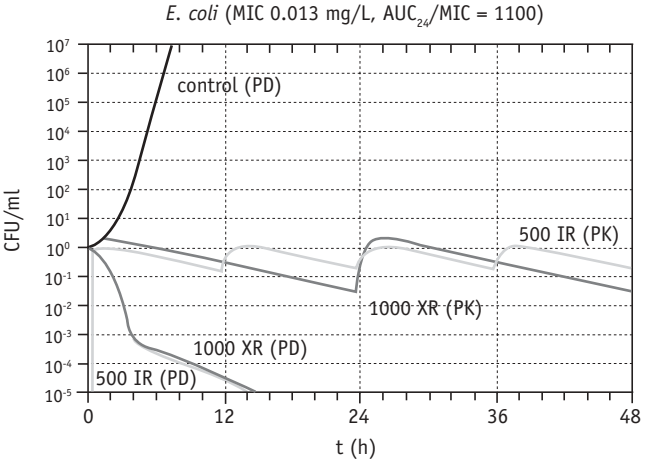

Figure 3. Simulation of the plasma concentrations (PK) and bacterial counts of *E. coli* (PD) after administration of 1000 mg XR once a day and 500 mg IR twice a day, respectively. The resulting AUC_{24}/MIC ratio is shown for comparison.

also been shown to relate to some extent to the ratio of the peak concentration (C_{max}) and the MIC (C_{max}/MIC ratio) [4, 13, 38]. The XR dosage form is proposed to be given in once-daily dosing regimens of the same total daily dose as the traditional IR formulation. Consequently, even though the AUC_{24} was shown to be identical for both treatments, the C_{max} obtained with the XR tablet is higher, resulting in a higher C_{max}/MIC ratio. These higher initial concentrations could result in an increased bactericidal effect during the initial hours after each dose, which is important in order to prevent the selection of resistant mutants in the bacterial population [19, 39].

The beneficial effects of higher initial concentrations and C_{max} with the XR dosing regimen were not observed in this study because the *E. coli* strain tested is extremely sensitive to CIP (MIC = 0.013 mg/l). In this case, the concentrations obtained from the traditional 500 mg IR twice-a-day dosing regimen were already high enough to promote maximum killing so that no benefits were observed with the higher C_{max} from the 1,000 mg XR tablet. This is reflected in the time kill curves that we simulated, showing the same effect with both regimens. However, for bacteria that are less sensitive to CIP, the beneficial effect of the higher C_{max} obtained with the XR tablet can be observed [40].

The more elaborated compartmental approach, based on the new adaptive E_{max} model confirms the therapeutic equivalence of both treatments against *E. coli*. Simulated time kill curves show that both regimens are predicted to produce an equally rapid killing, with a decrease in CFU/ml > 5 log units over the first 24 h. It should be stressed, however, that the resulting simulations are valid only for expected outcome in the *in vitro* system but do not necessarily reflect therapeutic outcome *in vivo* for the same concentrations. However, assuming that all non-*in vitro* influences (e.g. the immune system) are the same for both treatments, these simulations allow a sensitive comparison of the two treatments, indicating their equivalence.

In conclusion, this study showed that the XR formulation provides the same extent of bioavailability as the conventional dosage form, so that there is no change in the resulting AUC values. 1,000 mg XR once a day results in the same AUC_{24}/MIC ratio as 500 mg IR twice a day and therefore, both regimens should be therapeutically equivalent against *E. coli*. Simulated time kill profiles with the new adaptive E_{max} model confirmed the equivalence of both treatments. This study strongly suggests that the CIP 1,000 mg XR tablets are a beneficial contribution for improving therapy of infections sensitive to CIP since once-a-day regimens vastly improve patient compliance.

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