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Dose Adjustment of Ciprofloxacin in Renal Failure: Reduce the Dose or Prolong the Administration Interval?

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Abstract
Background: Dose adjustments of antimicrobial drugs are necessary in renal failure. One method of dose adjustment is to reduce the dose and the other is to prolong the administration interval in proportion to the reduced drug clearance. Pharmacokinetically, both methods involve an identical drug exposure but pharmacodynamically there may be differences. It is not known which dose adjustment method is preferable in patients with renal failure.
Methods: We performed simulations using a published mechanism-based pharmacokinetic/ pharmacodynamic model of ciprofloxacin effects on growth and death of *Escherichia coli* bacteria. Ciprofloxacin 500 mg every 12 hrs was selected as the standard dose. In renal failure either the dose was reduced (250 mg every 12 hrs) or the administration interval was prolonged (500 mg every 24 hrs) in proportion to the reduced ciprofloxacin clearance. Simulations were done with use of a commercial software package.
Results: In normal renal function, using the standard dose, bacterial eradication was predicted on day 3. In renal failure, bacterial eradication was predicted on day 3 when using the interval prolongation scheme but only on day 6 when using the dose reduction scheme. The relationship between the efficacies of these 3 dosage schemes could have been predicted by AUC above MIC and AUIC, but not by AUC/MIC or time above MIC.
Conclusion: Prolongation of the administration interval may be the preferable dose adjustment method in renal failure with ciprofloxacin. We hypothesize that these results may be transferable to other so-called dose-dependent antimicrobial drugs.

Key words: Ciprofloxacin, antimicrobials, renal failure, dose adjustment, pharmacokinetics, pharmacodynamics, PK-PD, simulation, nephropharmacology

Introduction

Dose adjustments are necessary for many drugs in renal impairment. Failure to reduce the dose can lead to overdosing and adverse events secondary to drug accumulation [2, 10]. In contrast, reducing the dose too much can lead to underdosing and treatment failure.

Several dose adjustment methods exist. One method proposes reduction of the drug dose; another method proposes prolongation of the administration interval in proportion to the reduced drug clearance [2, 4]. Pharmacokinetically, both methods involve an identical drug exposure as measured by the area under the curve (*AUC*), but pharmacodynamically differences are possible. It is not known which dose adjustment method is preferable for antimicrobial drugs in patients with renal failure.

The use of pharmacodynamic principles can help distinguish between the dose adjustment methods. One could use pharmacokinetic-pharmacodynamic (PK-PD) indices [7, 13, 14], but there are multiple indices and these have not been evaluated for use in renal failure. Generally, a mechanism-based PK-PD model of drug effects should provide more reliable conclusions [9, 11]. PK-PD models of antimicrobial effects have been developed for several drugs [3, 6, 12].

The aims of the present study were (1) to determine whether dose reduction or prolongation of the administration interval of ciprofloxacin is preferable in renal failure and (2) to determine which PK-PD indices correlate with the effect of ciprofloxacin in renal failure. For these purposes, simulations with a published mechanism-based PK-PD model of ciprofloxain were performed.

Materials and Methods

We simulated the growth and killing of *Escherichia coli* due to ciprofloxacin using a published mathematical PK-PD model [12].

Pharmacokinetic-pharmacodynamic Model

The mechanism-based PK-PD model allows for modelling antimicrobial effects on the growth and death of microorganisms, and also allows for modelling of different microorganism subpopulations with different susceptibilities to the antimicrobial drug [12].

$$\frac{dN}{dt} = \frac{VG_{max}}{N_{50}+N} \bullet N - \left[1 + \frac{E_{max} \bullet (C/MIC)^H}{CE_{50}{}^H + (C/MIC)^H}\right] \bullet k_d \bullet N \quad (1)$$

The variables are N, the number of bacteria, and C, the concentration of the drug. The system parameters are VG_{max}, the maximal velocity of bacterial growth, N_{50}, the number of bacteria where half-maximal growth is present, and k_d, the natural death-rate constant of the bacteria. The *MIC* is the minimal inhibitory concentration as measured for the drug in-vitro. The pharmacodynamic parameters of the antimicrobial drug effect are E_{max}, the maximum effect, CE_{50}, the concentration where the half-maximal effect is present, and H, the sigmoidicity constant.

We used parameter values derived for growth and death of an intermediate susceptible strain of *Escherichia coli* (MIC 0.5 mg/L) from an in-vitro pharmacodynamic model [12]. Such intermediate susceptible strains should be the most relevant strains clinically as indicated by animal studies, with bacterial populations consisting of a susceptible and a partially resistant subpopulation [8]. Clinically, one third of serious ill patients had infections with pathogens with MICs of 0.5-1.0 mg/L [7]. The system parameters used for our simulation were VG_{max} = 4.56 • 10^7, N_{50} = 3.55 • 10^7, and kd = 0.274 h^{-1}. The pharmacodynamic parameters were E_{max} = 27.7, H = 2.31, CE_{50} = 0.099 mg/L for the susceptible subpopulation and CE_{50} = 1.79 mg/L for the partially resistant subpopulation. Initial numbers of microorganisms were 5.88 • 10^7 and 3.86 • 10^6 CFU/mL for the susceptible and the partially resistant subpopulation respectively.

The pharmacokinetic part of the model was a two-compartment model with first-order absorption and first-order elimination. Pharmacokinetic parameters used for our simulations were the central volume V_1/F = 56.4 L, the peripheral volume V_2/F = 213 L, the intercompartment clearance Cl_d/F = 58 L/h, the total clearance CL_{tot}/F = 63 L/h, the absorption delay T_{lag} = 0.708 h, and the absorption-rate constant k_a = 0.718 h^{-1}. For renal failure (glomerular filtration rate < 5 ml/min) the total clearance was set to CL_{tot}/F = 31.5 L/h.

Dose Selection

Ciprofloxacin 500 mg orally every 12 hrs was selected as the standard dose. The drug clearance of ciprofloxacin in renal failure averages 50% compared to normal renal function [1, 5]. Therefore, in renal failure, either the dose was reduced (250 mg every 12 hrs) or the administration interval was prolonged (500 mg every 24 hrs) in proportion to the reduced ciprofloxacin clearance.

Pharmacokinetic and Pharmacodynamic Indices

Calculated PK-PD indices were the time where the drug concentration is above the MIC (*T>MIC*) per 24 hours, the *AUC/MIC* per 24 hours, the *AUC* above *MIC* per 24 hours, as estimated by

$$AUC \text{ above } MIC = \int_{t_1}^{t_2} C - MIC \, dt \qquad (2)$$

and the so-called *AUIC* as estimated by

$$AUIC = \frac{\int_{t_1}^{t_2} C \, dt}{MIC} \qquad (3)$$

where t_1 is the point of time where the drug concentration reaches the MIC and t_2 is the point of time where drug concentration drops below the MIC again.

Steady-state values were used since the steady-state was reached after one day in all cases. The maximum concentration C_{max} or the ratio C_{max}/MIC was not useful in our study, as the impact of the administration interval had to be determined and an integrative measure for a 24 hour interval was needed.

Software

Simulations were done with the use of the software Trial Simulator 2.1.2 (Pharsight Corporation, Mountain View, California). Population aspects were not included in the present study. PK-PD indices were calculated with the use of WinNonlin professional 4.0.1 (Pharsight Corporation, Mountain View, California) and Excel 2000 (Microsoft Corporation, Washington).

Results

In normal renal function, using the standard dose, bacterial eradication was predicted on day 3 (Fig. 1A). In renal failure bacterial eradication was predicted on day

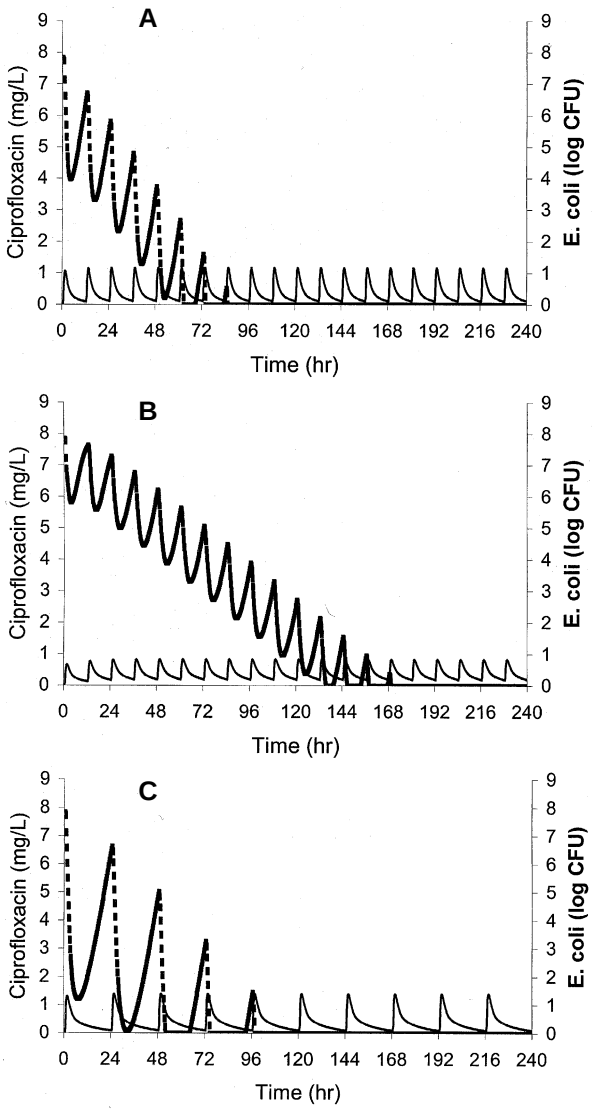

Fig. 1A, B, and C. Predictions of ciprofloxacin concentrations (thin continuous curves) and effects on Escherichia coli (thick broken curves) with normal renal function (1A: 500 mg twice daily) and with renal failure (1B: 250 mg twice daily; 1C: 500 mg once daily).

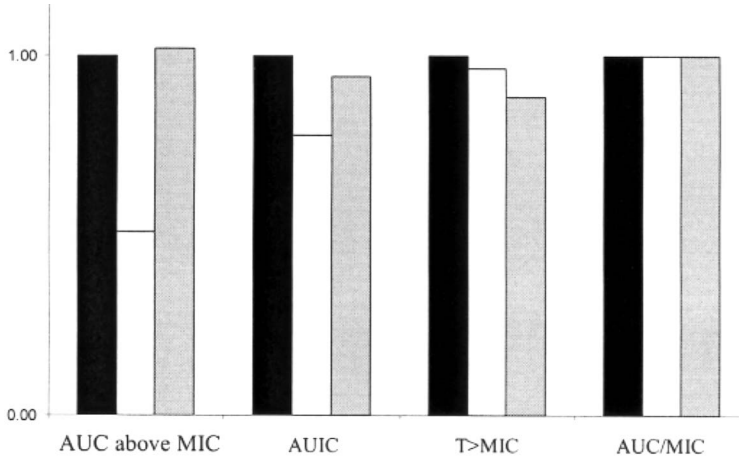

Fig. 2. Relative values of PK-PD indices derived from the predicted curves, where the value at normal renal function (500 mg twice daily; black column) was set at 1. Dose adjustment of ciprofloxacin in renal failure was either dose reduction (250 mg twice daily; white column) or prolongation of the administration interval (500 mg once daily; grey column). PK-PD indices were used as defined in the methods section.

3 when prolonging the administration interval, but only on day 6 when using dose reduction (Fig. 1B and C).

The PK-PD index values *AUC* above *MIC* and *AUIC* were lower with the dose reduction scheme, but unchanged with the administration interval prolongation scheme compared to the index value, in normal renal function. This coincides with the reduced efficacy and delayed bacterial eradication seen in our simulations with the dose reduction scheme. In contrast, the index values *AUC/MIC* and time above MIC were almost unchanged in all cases (Fig. 2).

Discussion

Dose adjustment in renal failure can be performed by reducing the dose or by prolonging the dose interval [2, 4]. There are no studies that compare these two dose adjustment methods either in-vivo or in-vitro. Pharmacokinetics alone are not sufficient to distinguish between the two methods. In fact, it is often assumed that both methods are equivalent and that dose reduction is adequate in most situations.

Our simulations with a mechanism-based pharmacokinetic-pharmacodynamic model of ciprofloxacin effects on *Escherichia coli* indicate that prolongation of the administration interval may be the better dose adjustment method in patients with renal failure. Dose reduction predictably leads to reduced effects and might even lead to treatment failure.

These results could have been predicted by the PK-PD index values *AUC* above *MIC* and *AUIC*. However, the differences between the values of *AUC* above *MIC* were more pronounced and there is a controversy on how to calculate the *AUIC*. Therefore we suggest that *AUC* above *MIC* might be used as a surrogate endpoint for dose adjustment of ciprofloxacin in renal failure. Interestingly, in contrast to *AUIC* the value *AUC/MIC*, which is often assumed to be identical with *AUIC*, was not predictive.

Limitations of our study are the dependence on published parameter values, which were derived from only one bacterial strain. In addition, these values were derived from in-vitro data, where no immunity is present. However, this can be assumed to be a worst-case scenario, similar to neutropenic patients. Furthermore, renal replacement therapy, which can remove the drug and, therefore, increases the risk of underdosing, was not considered.

We conclude, that prolongation of the administration interval may be the preferable dose adjustment method in renal failure in the case of ciprofloxacin. We hypothesize that these results may be transferable to other so-called dose-dependent antimicrobial drugs.

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