MODELING THE INFLUENCE OF NON-ADHERENCE ON ANTIBIOTIC EFFICACY: APPLICATION TO CIPROFLOXACIN

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Abstract. Objective: To evaluate the consequences for antibiotic efficacy of different types of poor adherence to a short-term dosing regimen. Ciprofloxacin was taken as an example. Method. A simulation study on a two-compartment pharmacokinetic model and parameter estimates taken from the literature was performed. Two empirical efficacy measures as well as a specific pharmacodynamic model of the bacterial kill curve were used. Four patterns of non-adherence were investigated; dosage omission, irregular dosing intervals, delayed dosing and treatment discontinuation. Results: Errors in timing of doses with a standard deviation less than 2 hours had a minor effect on antibiotic efficacy. Dosage omission, in contrast, has a significant influence on the antibacterial effect of ciprofloxacin. Conclusions: Non-adherence patterns are difficult to measure experimentally, thus recommended dosing regimens should be sufficiently robust against most of the non-intentional disturbances.

KEY WORDS: non-adherence, ciprofloxacin, stochastic model, Monte-Carlo simulation.

INTRODUCTION

Poor adherence (compliance) to oral medication regimen is generally considered to be a major factor in the efficacy of antimicrobial therapy in ambulatory patients [Brixner 2005, Vrijens and Urquhart, 2005, Kardas 2002, Lipsitch and Levin 1997]. While the consequences of extreme non-adherence are readily apparent (e.g., omission of several doses), this does not hold for lesser degrees of poor adherence, as an inappropriate timing of doses. Thus, using a simulation approach, the aim of the present study is to reveal the relationship between various patterns of non-adherence and therapeutic efficacy of ciprofloxacin as an example. There is a lack of data on non-adherence patterns and thus we employ a wide range of different ones to show the possible effects.

Using stochastic models for drug administration, the computer simulations were based on the pharmacokinetics of ciprofloxacin in patients [Payen et al. 2003] and several pharmacodynamic measures [Corvaisier et al. 1998, MacGowan et al. 2000] and models [Regoes et al. 2004] of antibiotic effectiveness. Simulations were performed for multiple dosing, 250 mg every 12 hours, of orally applied ciprofloxacin over ten days. Finally, we compared some of the results with those obtained for an alternative dosing schedule of 500 mg every 24 hours. Since our aim was to demonstrate the effect of non-adherence, for clarity we neglected the influence of variability in pharmacokinetic parameters and therapeutic concentration range within the population.

MATERIALS AND METHODS

Pharmacokinetic model. Simulations were performed for the two-compartment disposition model with first order absorption used by [Payen et al. 2003]. Assuming a bioavailability of F = 0.85 [Payen et al. 2003], and an absorption rate constant of k_a = 0.6 h^{-1}, the following parameter values were calculated from the pharmacokinetic parameters estimated by [Meagher et al. 2004], for the 250 mg dose of ciprofloxacin: volume V = 55.765 liters, first-order elimination constant k_{2o} = 1.333 h^{-1}, intercompartmental rate constants k_{23} = 1.262 h^{-1} and k_{32} = 0.311 h^{-1}. Using these parameters, plasma concentration-time curves, $C(t)$, were simulated over 10 days assuming dosage schedules of 250 mg every 12 hours or 500 mg every 24 hours, respectively. Note that for a chronic administration of 500 mg/day, which implies a constant-rate infusion, the constant steady-state plasma concentration is 0.24 mg/liter. However, due to large fluctuations in $C(t)$, if the application is in regular intervals, the value of constant plasma concentration gives no direct information on the efficacy of ciprofloxacin dosing regimen. No diurnal variation in absorption or elimination pharmacokinetics was considered. The infectivity of pathogens is assumed to remain constant over time.

Pharmacodynamic models. Various empirical pharmacodynamic measures proposed to evaluate the effectiveness antibiotic therapy on the basis of minimum inhibitory concentration (MIC) have been discussed with regard to their usefulness in optimizing fluoroquinolone dosing regimens [MacGowan et al. 2000]. Most of them are based on the concept of a MIC. For our simulation of ciprofloxacin concentration-time curves, MIC of 0.03 mg/l [Regoes et al. 2004], was considered. Among these measures are: (a) the time for which the plasma concentrations remain above MIC (t MIC) and (b) the area under the $C(t)$ curve (AUC) above MIC (AUC MIC). Accordingly, we used the following complementary measures for the assessment of the effect of non-adherence on drug exposure:

a) t MIC, the total time $C(t)$ spent below MIC.

b) AUC MIC, the total area between MIC and the concentration curve being below it. The complementary measure AUC MIC was used for example by [Corvaisier et al. 1998] when comparing different antimicrobial pharmacodynamic indices. While the area above MIC may reflect the positive effect of the antibiotic, the area below MIC is related to the lack of the effect. An obvious advantage of this measure over the measure t MIC is that AUC MIC reflects how deep the plasma concentration dwells under MIC. In this sense the measure is

closer to the simulated bacterial population (see below) which reacts gradually on the level of $C(t)$. Due to the fact that this measure is not commonly used, we illustrate its behavior.

Since the relationship between antibiotic concentration-time curve and effect is more complex than expressed by the above parameters, we also simulated the effect of treatment on the bacterial population, using the pharmacodynamic model [Wiuff et al. 2005]. The model assumes that the bacterial cells exist in two physiological states, sensitive and resistant, with densities X^S and X^T. When a new bacterial cell arises, the probability, f, that it will be resistant is independent of the state of the cell from which it came. In accordance with this model the mortality rate of the sensitive population, μ, is

$$\mu(t) = \frac{(\Psi_{\max}{}^{S} - \Psi_{\min}{}^{S})\frac{C(t)}{zMIC}}{\frac{C(t)}{zMIC} - \frac{\Psi_{\min}{}^{S}}{\Psi_{\max}{}^{S}}}, \qquad (1)$$

where constants $\Psi_{\min}{}^{S} = 6.5\ \mathrm{h}^{-1}$, $\Psi_{\max}{}^{S} = 0.88\ \mathrm{h}^{-1}$ and $zMIC = 0.017$ mg/liter were taken from [Regoes et al. 2004]. The constant $zMIC$ determines the concentration for which the net change of the bacterial concentration is zero. Function μ is in dependency on the antibiotic concentration of sigmoidal shape, constant $\Psi_{\max}{}^{S}$ determines the maximum growth rate of the bacterial population (in absence of the drug). On the other hand, constant $\Psi_{\min}{}^{S}$ reflects the death rate due to the saturation of the antibiotic concentration. The range for $\Psi_{\max}{}^{S} - \Psi_{\min}{}^{S}$ is wider than is likely to be the case *in vivo*, and thus all reasonable cases are encompassed in the model. Function (1) is in [Regoes et al. 2004] given in the form of a Hill function. It means that an additional parameter determines the slope of the sigmoid. Importance of the Hill coefficient for does adjustment is considered as an important issue [Czock 2006], however, [Regoes et al. 2004] reported the value of Hill coefficient for ciprofloxacin being equal to one. Thus the following equations are valid only for the case that the Hill coefficient is equal to one.

Then, the model for the density, $X = X^S + X^T$, of a bacterial population under treatment is given by differential equations

$$\frac{dX^S(t)}{dt} = (1-f)\left(\Psi_{\max}{}^{S} X^S(t) + \Psi_{\max}{}^{T} X^T(t)\right) - \mu(t) X^S(t), \qquad (2)$$

$$\frac{dX^T(t)}{dt} = f\left(\Psi_{\max}{}^S X^S(t) + \Psi_{\max}{}^T X^T(t)\right), \tag{3}$$

where $X(0) = 10^6$ was taken, [Regoes et al. 2004] and it was proportionally with respect to f divided between sensitive and resistant population. Obviously, the sensitive population decreases or increases in dependency on the value of the function $\mu(t)$ given by equation (1) and the constant *zMIC* may also reflect the innate killing rate. The resistant population following model (3) only increases, unless an innate capability to contribute to bacterial kill is included. For the sake of comparison with [Wiuff et al. 2005], we have not included the spontaneous bacterial kill, except in one case to illustrate its effect. The size of bacterial population was calculated numerically by using equations (2) and (3) from the simulated concentration-time curve $C(t)$. The constant $f=0$, unless stated otherwise.

Non-adherence models. Poor adherence is a very complex phenomenon in its causes and manifestation. Nevertheless, some reliable data on adherence are quite rare. Normal spontaneous behavior of a patient is changed by application of an electronic device to monitor dosing assessment. On the other hand, patient diary or retrospective questionnaires are not very reliable way to judge real non-adherence patterns.

We selected the following models of dose taking and dose timing, which may shed light on some of the underlying behaviors. Of course, as any models, also these considered here, are idealization of reality. Detailed description of stochastic non-adherence models can be found in [Wang and Ouyang 1998].

a) Dosage omission. Dosage omission is the most common cause of poor adherence [Kardas 2002]. At each occasion when the dose should be administered it is skipped with fixed probability *p*. It means that in each cycle there is a probability *p* to forget to take the dose and with probability $1-p$ the dose is taken. Then, the distribution of the time for the next dose is

$$g(t) = \sum_{i=0}^{\infty} (1-p)p^i \delta(t-(i+1)\Delta), t > \Delta, \tag{4}$$

where $\delta(.)$ is the Dirac delta function, and Δ the exact dosing interval. This model of non-adherence resulting in the geometric distribution was successfully fitted in [Wong et al. 2003] to pill-count data. Equation (4) for $p = 0$ defines so called Dirac comb.

b) Irregular dosing intervals. Here it is assumed that the time instant, S_k, of *k*-th dose is

$$S_k = k\Delta + \varepsilon_k , \tag{5}$$

where, as previously, Δ is the exact dosing interval and ε_k is the error. The time interval between two consecutive doses in model (5) is equal to Δ "corrected" by the difference of two dosing errors, $T_k = S_{k+1} - S_k = \Delta + \varepsilon_{k+1} - \varepsilon_k$. We slightly simplify model (5), which originally results in pair-wise dependent inter-dose intervals, and we assume that T_k are independent and identically distributed random variables. In our simulation this is done by proposing a probability distribution of the random time, *T*, between two consecutive doses. Thus, the correlation structure of model (5) is neglected assuming that two errors in timing are separated at least by one correctly taken dose. The occasion when the last dose was administered is taken as "time zero".

For *T* we selected a distribution which is asymmetrical and centered around Δ, which is the length of regular dosing interval. We imposed the condition E(*T*)= Δ, it is, that the mean inter-dose interval is equal to the regular dosing interval and intervals shorter than Δ may appear. It means that the dose is taken in advance. The Gamma distribution with parameters *a* and *b*

$$g(t) = \frac{t^{a-1}\exp(-t/b)}{\Gamma(a)b^a} , \tag{6}$$

where $a = E(T)^2 / Var(T)$, $b = Var(T) / E(T)$ was applied, $\Gamma(a) = \int_0^\infty t^{a-1}\exp(-t)$ is the gamma function, see e.g. [Tuckwell 1995].As said before, we use E(*T*) = 12 h, and for small Var(*T*), the shape of the distribution is close to Gaussian. Under this scenario the patient often takes the drug before the scheduled interval but with small deviations. On the other hand if the administration is delayed then the delay is relatively large.

c) Delayed dosing. This is probably most common type of poor adherence to timing of doses. It is a special case of model (5) in which the error can be only in a positive direction, $\varepsilon_k > 0$. We selected the exponential distribution as a simple example of delay in taking the drug

$$g(t) = \frac{1}{\mu}\exp(-(t-\Delta)/\mu), t > \Delta \tag{7}$$

This means that after the scheduled time of the dose application at time Δ the dose is taken completely randomly with the mean delay μ.

d) Discontinuation of the treatment. This is a common type of poor adherence to antibiotics. Simply, in some moment, usually close to the end of the treatment, the remaing doses are skipped. In this sense, the model is a special case of "dosage omission" with p=1 for a given time. In contrast with remaining non-adherence patterns, this one is, most probably, intentional. The effect is straightforward and shown only on the size of bacterial population.
The investigated types of noncompliance are illustrated in Figure 1.

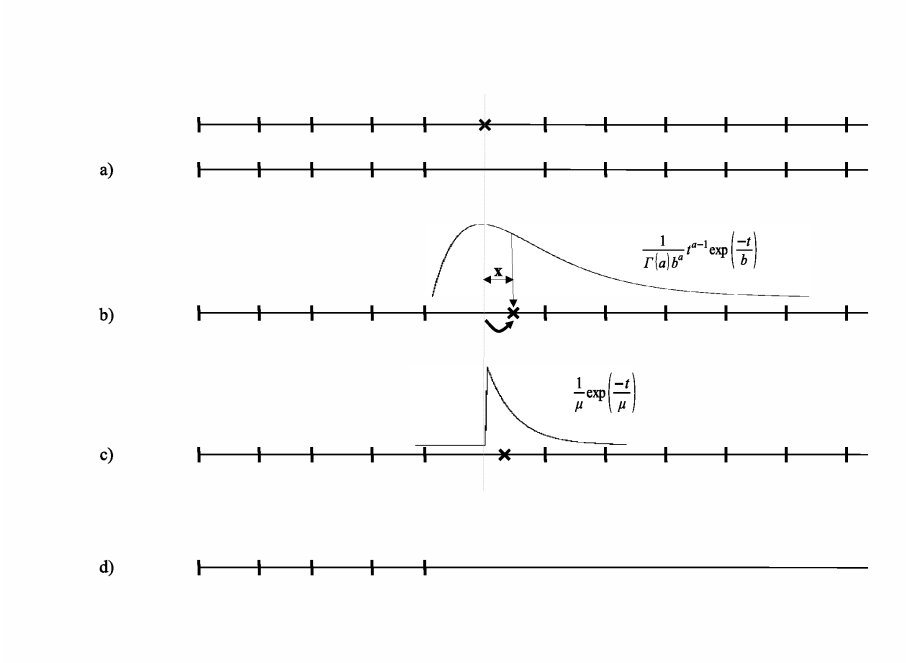

Figure 1. Schematic representation of the regular dosing and investigated types on non-compliance, where ticks denote dosing instants, the crosses denote the current dose time which is delivered with four types of error. Upper line shows regular dosing, (a) omission of a dose, (b) irregular dosing, (c) delayed dosing and (d) discontinuation of the treatment.

Numerical simulations. The differential equations describing the pharmacokinetic model were solved numerically. Monte-Carlo methods were used to generate irregular inter-dose intervals. One thousand of treatments were simulated for each selected set of parameters and then were statistically evaluated. Unless stated otherwise, simulations were made for a dosing regimen of 250 mg ciprofloxacin every 12 hours over 10 days.

RESULTS

Figure 2. shows three examples of concentration-time curves of ciprofloxacin simulated over 96 hours following start of multiple dosing (250 mg/12 h) for regular dosing and two types of poor adherence, namely, irregular dosing and dosage omission. Due to the short half life, the steady state is reached very quickly. This authorizes our assumption that the dosing errors are

mutually independent. It is apparent from Figure 2. that not only the maximal value of the plasma concentration, but also its minimal value, under regular dosing are far above MIC. If the doses would be lower, these extreme values of plasma concentration would decrease and the effects of non-adherence would be more expressive.

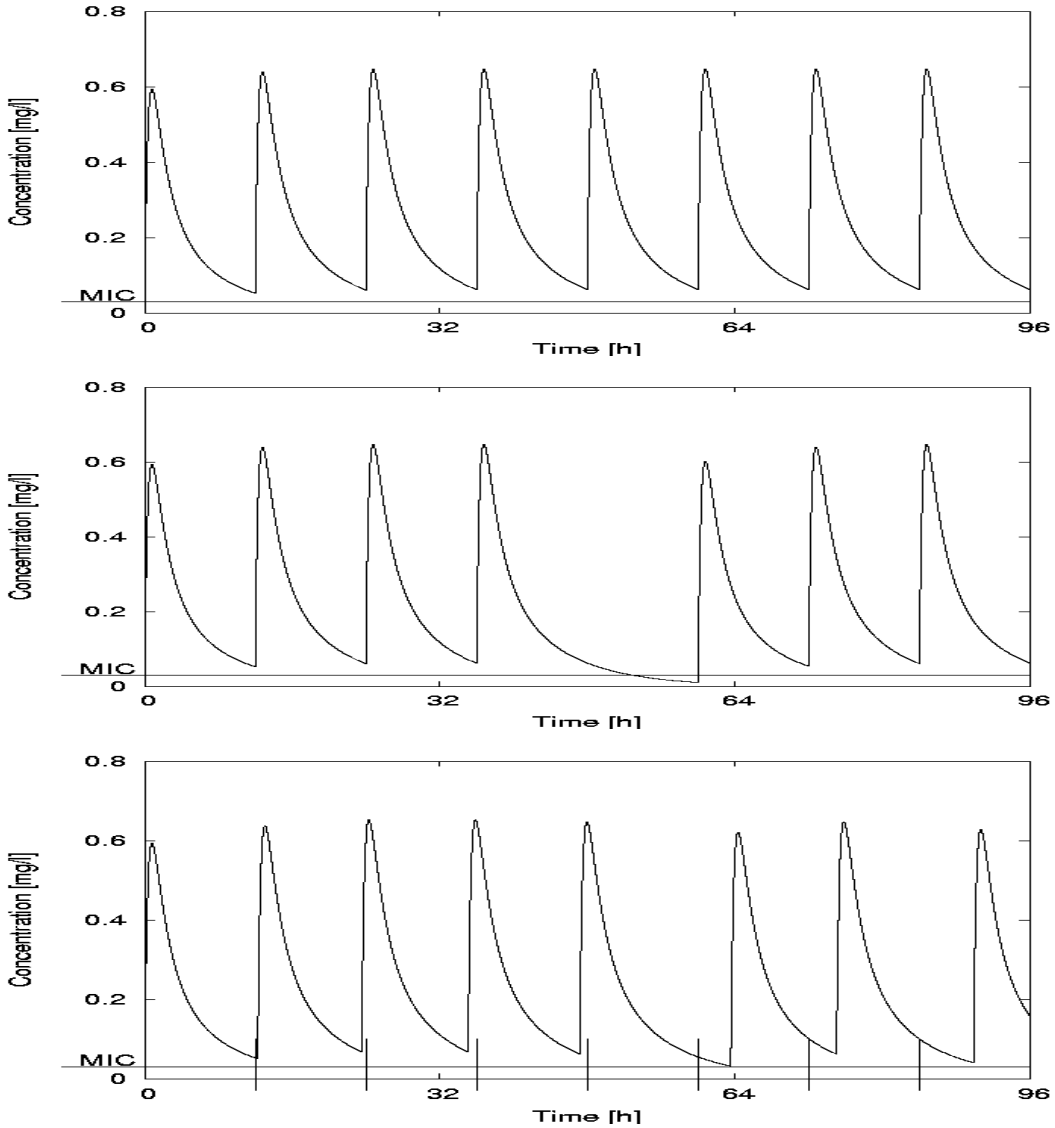

Figure 2. Examples of simulated plasma concentration-time curves in 96 hours window following dosing 250mg/12h for different patterns of non-adherence: regular dosing, omission (p=0.1) and irregular dosing (vertical bars denote instants of regular doses and were randomized by using Gamma distribution with mean equal to 12 hours and standard deviation (SD) equal to 2 hours). MIC level is indicated. In example with omission $C(t)$ gets below MIC, it does not happen if the dose is only delayed.

Dosage omission. Dosage omission, in contrast to irregular dosing, generally leads to a decrease of $C(t)$ below MIC (Figure 2). In other words, it is omitting a dose, rather than even

badly mis-timing an unmissed dose to the extent of 8 - 16 h interval that actually challenges the MIC. Note that for omission of one dose, the measure t MIC takes value 7.24 h. Measuring the area between MIC and the concentration curve, AUC MIC, we obtain for such a single omission the value 0.85 $\mathrm{h} * \mathrm{mg/liter}$. Unfortunately, what is the effect on the treatment efficacy remains another question.

If the probability of a single omission is p and the omissions are independent events, then probability that during the cure the concentration does not drop below MIC is $(1-p)^n$, where n is the total number of doses. For small probability of omission (p 0.02), this can be linearly approximated by *1 - pn*, as demonstrated in Figure 3.

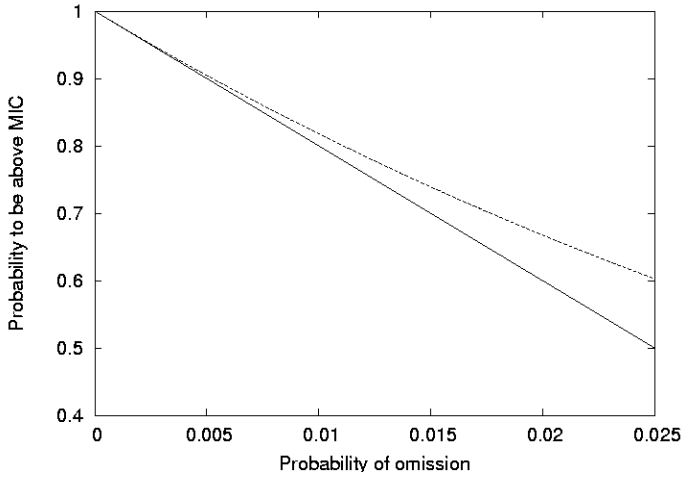

Figure 3. Probability that dosing over 10 days does not lead $C(t)$ values below MIC in dependency on the probability of omission of a single dose. The lower line is the linear approximation of this probability.

As shown in Figure 3. even a very small probability of omission ($p \approx 0.005$) implies that $C(t)$ drops at least once in ten cases (treatments) below MIC.

Irregular dosing intervals. Figure 4. shows the histograms of the measures t MIC and AUC MIC for 10 days treatment and dosing error (deviation from regular dosing) that was characterized by a standard deviation 2 h (cf. Eq. 6, a=36, b=1/3). In more than 75% of cases the concentration does not drop below MIC for such a small variation of the timing. It can be seen that while the histogram of t MIC decreases gradually, for AUC MIC most of the cases are concentrated in the first bin.

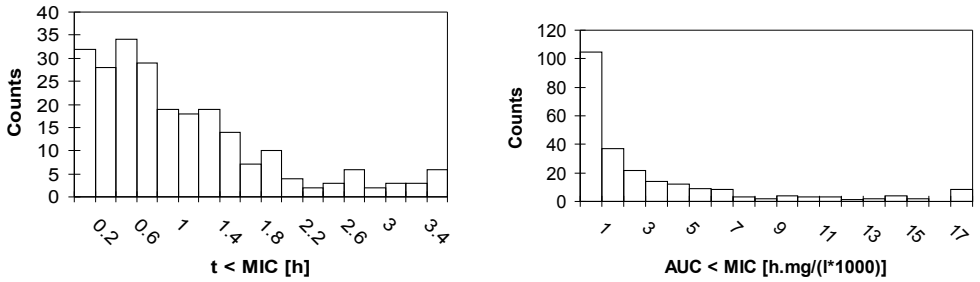

Figure 4. Histograms of measures (a) t □MIC and (b) AUC MIC obtained for Gamma distribution with E(T)=12, Var(T)=4. From the simulation of 1000 runs, 761 of them never got below MIC and were excluded from the histograms.

As expected t MIC increases with variability of dose-timing. In Figure 5. are shown results of 1000 simulation runs for each fixed standard deviation of the dosing error σ. The situation at σ=2 corresponds to that illustrated in Figure 4., but there only the cases in which $C(t)$ drops under MIC are taken into account. This explains why in Figure 5. the mean time spent under MIC is almost zero.

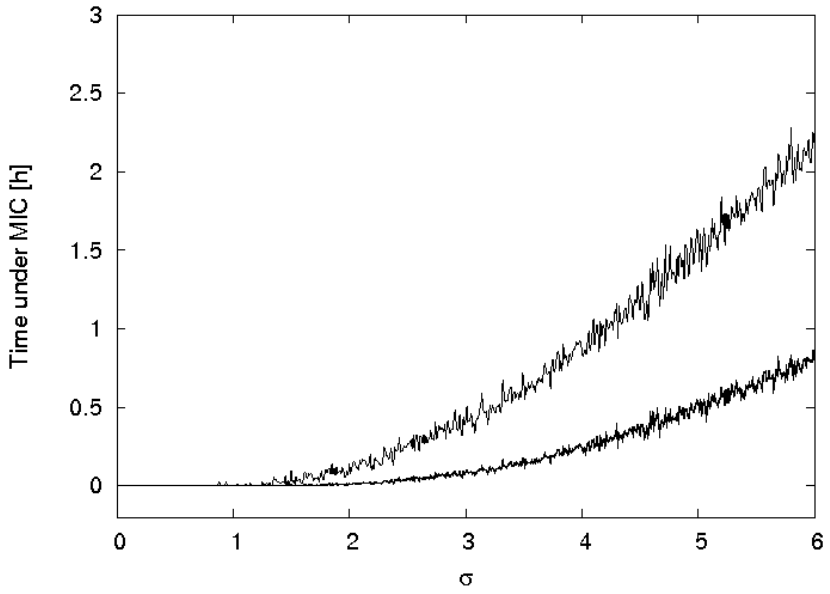

Figure 5. Dependency of measure t MIC on the standard deviation of dose-timing (dosing error) for irregular dosing: the mean (lower curve), mean standard deviation (upper curve). For each value of σ, with step 0.01, 1000 simulation runs were performed and the mean and its standard deviations were calculated.

It is obvious from Figure 5. that for errors in timing of doses with SD 1.5 h, the concentration practically never drops below MIC. Increasing this variability, the measure starts to grow but rather slowly, however, the standard deviation grows more steeply. Of

course, the mean curve decreased by the standard deviation gets below zero. It only proves that the distribution of measure t MIC is not symmetrical around zero (see Figure 4.).

Delayed dosing. If the delay is shorter than 4.76 h, the concentration does not drop under MIC. This is a direct consequence of the fact that the time under the MIC for omission of one dose is 7.24 h. Thus the probability that the concentration decreases below MIC is equal to probability to get a realization of the exponential random variable larger then 4.76, which is equal to $\exp(-4.76/\mu)$, where μ is the mean delay time. This is illustrated in Figure 6., where the probability that $C(t)$ drops below MIC is plotted as a function of the mean delay time. It is apparent from the figure that if the mean delay is below one hour this probability is negligibly small. From this point it starts to grow almost linearly reaching the value 0.2 at the mean delay 3 [h].

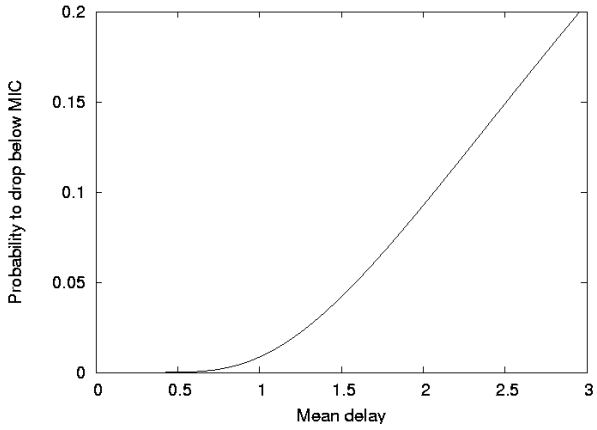

Figure 6. Dependency of probability that $C(t)$ drops below MIC on the mean delay time.

Analogously to Figure 4., the histograms of the measures t MIC and AUC MIC for 10 days dosing assuming an exponentially distributed delay in dosing (Eq. 7) with mean delay time 3 h are depicted in Figure 7.

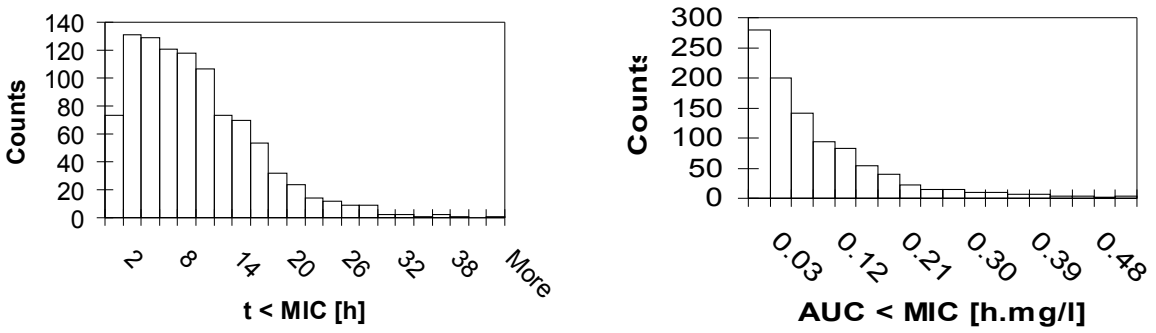

Figure 7. Histograms of (a) t MIC and (b) AUC MIC obtained for exponentially distributed delay in dosing (mean delay time 3 hours). From the simulated 1000 runs 16 of them never got below MIC and were excluded from the histograms.

The mean delay is quantity about which we can only speculate and it is of primary interest to see how it influences the plasma concentration of the drug. Figure 8. shows the dependency of the mean of t < MIC and its standard deviation on the mean for exponentially distributed delay times.

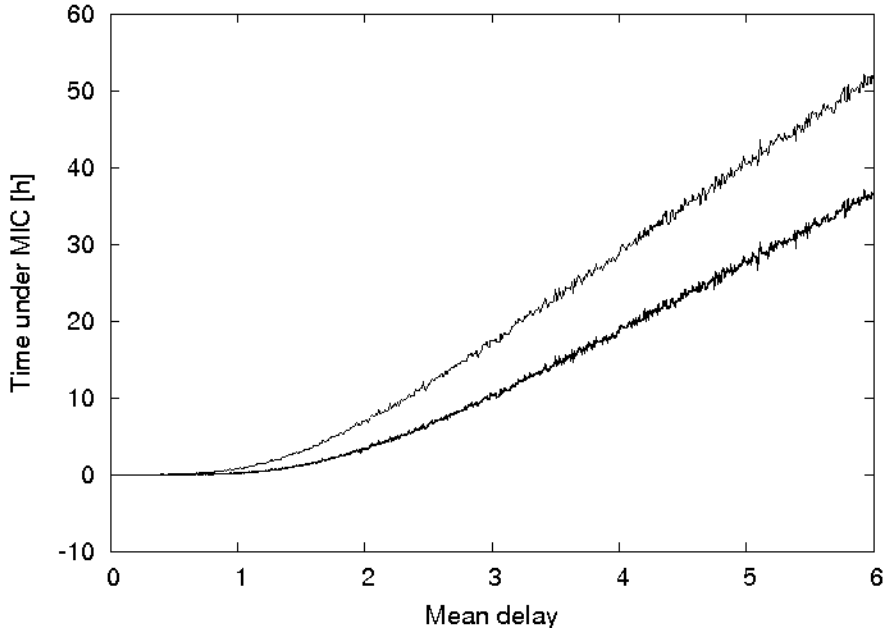

Figure 8. Dependency of measure t MIC on the mean delay time for exponentially delayed dosing: the mean (lower curve), mean standard deviation (upper curve). For each value of mean delay, with step 0.01, 1000 simulation runs were performed and the mean and its standard deviations were calculated.

Bacterial population. Up to now we have investigated the effect of non-adherence on the simple pharmacodynamic measures introduced above. Now, we turn our attention directly to the effect on the bacterial population. Before that, let us illustrate (Figure 9.) the behavior of the model in dependency on different values of proportion between resistant and sensitive population. The decrease in bacterial density during the time course of therapy as simulated using the pharmacodynamic model of [Wiuff 2005] (Eqs.1-3) with innate killing rate is also presented. The model is constructed in such a way that without the innate killing the size of the resistant bacterial population cannot decrease. However, for comparison with the original paper, the innate killing rate is neglected in further analyses, but can be easily included.

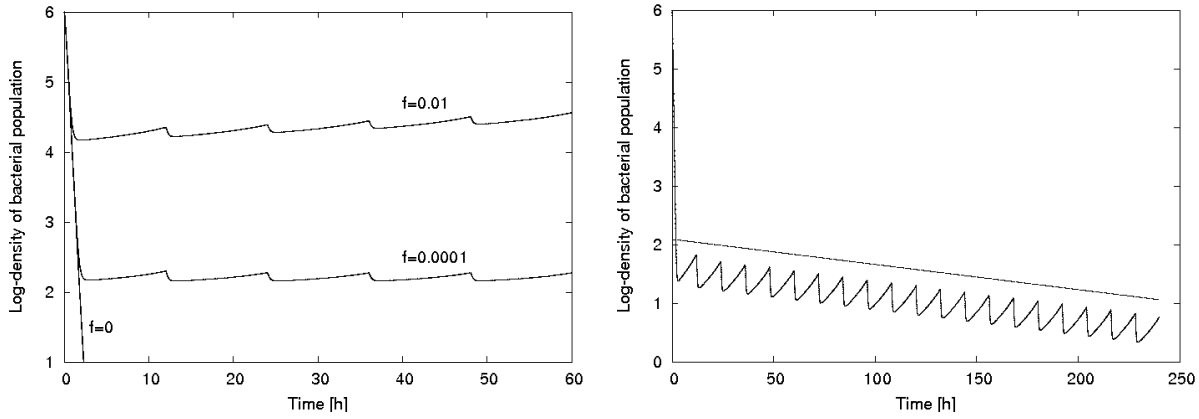

Figure 9. Decrease (left panel) in bacterial density during ciprofloxacin therapy 250mg/12h for regular dosing. Corresponding values of f are given in the picture. In the right panel is illustrated the effect innate capability to contribute to bacterial kill (f=0.0001, innate killing rate m_1=0.01 [1/hour]). The monotonic curve gives the density of resistant population and the saw-like curve depicts the density of sensitive bacterial population.

The model of bacterial population is characterized by high robustness against small non-adherence to the dosing schedule. This has been verified by several simulation runs in which the irregular dosing was applied and which are not illustrated. Thus using the model, we study only the effect of dose omission. The bacterial density of the population is given in Figure 10. for relatively high probability of the dose omission, p=0.25. Thus there appeared three omissions of a single dose, but also one omission of two consecutive doses. It shows a surprising effect that a single dose omission is very rapidly "forgiven" and the system returns to the steady-state corresponding to the regular dosing. On the other hand, if two consecutive doses are missed, the bacterial density never reaches the original level. This, of course, may have a substantial effect on the whole therapy. Of course, we have to remind that the result strongly depends on the choice of the parameters.

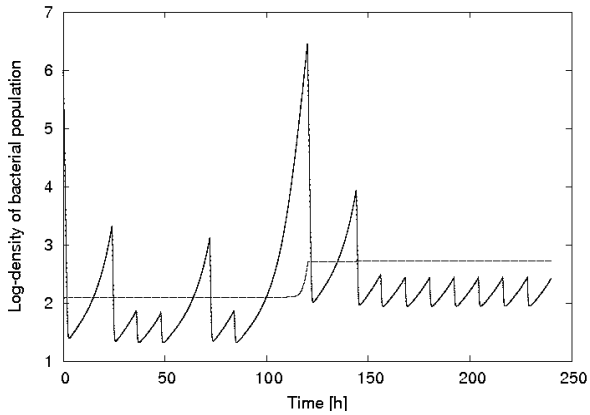

Figure 10. Bacterial density during ciprofloxacin therapy for omission of a dose. Dosage omissions probability p=0.25, f=0.0001, dosage 250mg/12h. The monotonic curve gives the density of resistant population and the saw-like curve depicts the density of sensitive bacterial population.

Different dosing schedule. All the above results are for 250 mg/12 h dosing. Now let us compare these predictions with those obtained for 500 mg/24 h dosing schedule. Although in the latter case, the plasma concentration drops slightly below MIC for approximately 3 hours even for regular dosing (Figure 11.), it is open to question whether this significantly affects antibiotic efficacy.

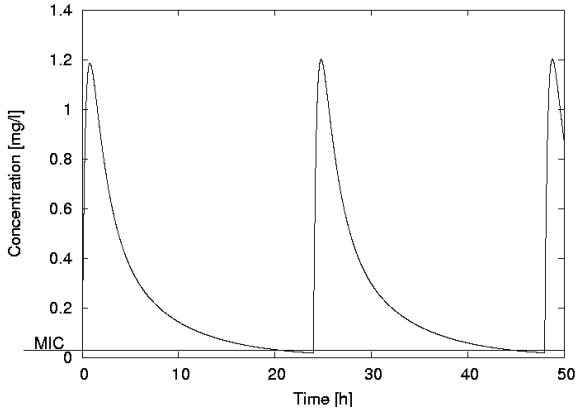

Figure 11. Plasma concentration-time curve in 50 hours window following dosing 500mg/24h in regular intervals, MIC level is indicated. Decrease of $C(t)$ below MIC is apparent.

More importantly, the bacterial density seems to behave quite similarly in 500mg/24h as in 250mg/12h schedule, see Figure 12. It is partly in contrast with previous measures, for example t MIC. We can see that the minimal density of bacterial population in 500mg/24h is only slightly below the minima for 250mg/h schedule. Taking into account the fact that, when applied only once a day, the probability of non-adherence is lower, we could conclude that under once a day administration the cure is less influenced by the irregularities, especially omissions, in dosing. This is in a complete agreement with [Sanchez-Navaro et al. 2002b].

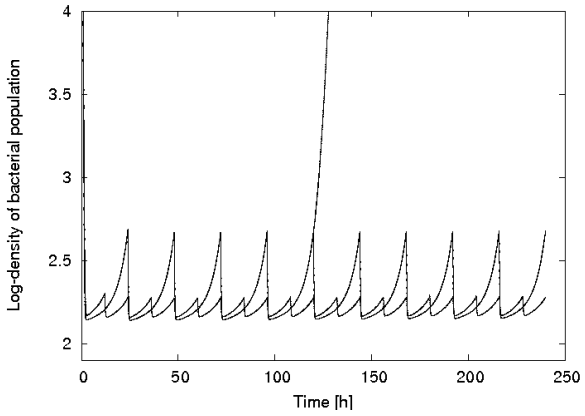

Figure 12. Bacterial density during ciprofloxacin therapy for 500 mg/24 h regular dosing (higher maxima), regular dosing 250mg/12h (lower maxima), discontinuation of the treatment at time 100 is illustrated. Parameters are the same as in Fig. 9.

Discontinuation of the antibiotic therapy is a common error and often it has substantially negative effect. In Figure 12 is shown trajectory of bacterial density for the last dose taken in the middle of the treatment. At least under this model assumption, it leads to exponential growth of the bacterial population. The population starts to grow with the rates $\Psi_{\max}{}^{S}$ and $\Psi_{\max}{}^{T}$ which are quite high.

DISCUSSION AND CONCLUSIONS

In this study, computer simulations were applied to determine the effects of various patterns of non-adherence on the exposure-response relationship for ciprofloxacin. We are well aware that the approximate models used to describe partial adherence are oversimplifications of a complex phenomenon, however, this is the basic property of models. Nevertheless, we believe that the simulations may add to our understanding of the consequences of different types of non-adherence on the efficacy of antibiotic therapy, with ciprofloxacin taken as an example.

The validity of the underlying pharmacodynamic measures t > MIC and AUC > MIC has been discussed previously [Corvaisier et al. 1998, MacGowan et al. 2000]: while these measures correlate with the antibacterial effect (whereby AUC > MIC was the best predictor), they provide only indirect information on the consequences of poor adherence and reflect only partly the effect of changes in time course of plasma concentration. A more direct answer is provided by the bacterial kill curves simulated for different types of non-adherence using response the model developed in [Wiuff et al. 2005]. Here, it has to be stressed again that it is an approximation because the killing rate given by equation (1) would not be static but in reality it would depend on the length of exposure of the bacterial population to the antibiotic. At least the probability f of the transition from sensitive to resistant subpopulation of the bacterial population would change with time.

Forgetting a dose (omission) and unprecise timing of the dose application are probably the most common types of non-adherence in outpatients undergoing an antibiotic therapy with dosing intervals of 12 or 24 hours, respectively. The simulations reveal that in contrast to dosage omission, errors in timing of doses may have only a negligible effect on the antibacterial effect of ciprofloxacin. Of course, the discontinuation of the therapy, classified

also as non/adherence, is of different nature. This type of non/adherence is hardly random and non-intentional.

On one hand, the simulations suggest that for regular dosing the 250 mg/12 h regimen is superior to 500mg/24 h as it does not permit the concentration curve to decrease below MIC. This is in agreement with theoretical results of [Sanchez-Navaro et al. 2002a], which are further discussed in [Sanchez-Navaro et al. 2002b]. One should keep in mind that our simulations were based on the specific pharmacokinetic and pharmacodynamic parameters of ciprofloxacin published in [Meagher et al. 2004] and [Regoes et al. 2004], respectively. Note that the pharmacodynamic parameters of the E_{max} model (including the MIC of 0.03 μg/ml) were estimated for an Escherichia coli strain [Regoes et al. 2004]. On the other hand, it would be also interesting to know, whether in the present example the adherence to the once-daily administration might be higher than to the twice-daily regimen. [Sanchez-Navarro et al. 2002a] clearly mentioned that once-daily regimen increases drug compliance. They were aware of the argument against the administration once a day related to the minimum concentration in plasma, but disclaimed it especially for older patients. Furthermore, they claimed that "according to pharmacokinetic/pharmacodynamic criteria, C_{min} values are not essential for the efficacy of fluoroquinolones".

Not all drugs have the same relationship between dose and concentration, and concentration and effect, respectively. This leads to the concept of forgiveness, which is a capacity to keep drug efficacy despite poor compliance. [Boissel and Nony 2002] simulated poor adherence to the prescribed dosing schedule and they concluded that while the drugs differ in terms of capacity for forgiveness, the physician should be able to select the proper drug taking this fact into account. To do so, an access to appropriate indicators of forgiveness has to be available.

Although more sophisticated, stochastic models of non-adherence have been developed and fitted to known dosing histories [Wong et al. 2003], no relevant data are available for antibiotic therapy. Furthermore, omission of a single dose may account for most adherence errors during a therapy over only 10 days, where ‘drug holidays’ (more than one consecutive dose is missed), may play a minor role than for long-term therapies. Our aim was to simulate the lack of adherence to antibiotic therapy for ciprofloxacin as an example. As for any results obtained by simulation, the results are dependent on the underlying models and parameters.

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