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Pharmacokinetic-Pharmacodynamic Modeling of Activity of Ceftazidime during Continuous and Intermittent Infusion

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We developed and applied pharmacokinetic-pharmacodynamic (PK-PD) models to characterize in vitro bacterial rate of killing as a function of ceftazidime concentrations over time. For PK-PD modeling, data obtained during continuous and intermittent infusion of ceftazidime in *Pseudomonas aeruginosa* killing experiments with an in vitro pharmacokinetic model were used. The basic PK-PD model was a maximum-effect model which described the number of viable bacteria (N) as a function of the growth rate (λ) and killing rate (ε) according to the equation $dN/dt = \{\lambda - \varepsilon \cdot [C^{\gamma}/(EC_{50}^{\gamma} + C^{\gamma})]\} \cdot N$, where γ is the Hill factor, C is the concentration of antibiotic, and EC_{50} is the concentration of antibiotic at which 50% of the maximum effect is obtained. Next, four different models with increasing complexity were analyzed by using the EDSIM program (MediWare, Groningen, The Netherlands). These models incorporated either an adaptation rate factor and a maximum number of bacteria (N_{max}) factor or combinations of the two parameters. In addition, a two-population model was evaluated. Model discrimination was by Akaike's information criterion. The experimental data were best described by the model which included an N_{max} term and a rate term for adaptation for a period up to 36 h. The absolute values for maximal growth rate and killing rate in this model were different from those in the original experiment, but net growth rates were comparable. It is concluded that the derived models can describe bacterial growth and killing in the presence of antibiotic concentrations mimicking human pharmacokinetics. Application of these models will eventually provide us with parameters which can be used for further dosage optimization.

The most commonly used in vitro parameter to quantify the activity of antibiotics against a certain bacterium is the MIC. This parameter reflects the effect of exposure of a certain inoculum size to a constant concentration of the antibiotic for a period of 16 to 20 h (10). The disadvantage of the MIC, however, is that this parameter does not take the pattern of killing over time into account since an effect is measured at one end point only. Alternatively, in vitro killing curves are used to describe the time course of the antibacterial effect; in order to find the important parameters describing the killing behavior of the antibiotic over time, data can then be fit to pharmacodynamic models (6–8, 11). For instance, killing rate constants can be obtained by plotting the logarithm of the number of CFU obtained at different antibiotic concentrations over time. By comparing killing rate constants at these concentrations, the killing behavior of the antibiotic can be characterized. By using this approach, it has been shown that the killing of bacteria by β-lactam antibiotics is relatively concentration independent at values well above the MIC, with maximal activity at concentrations four to five times the MIC, and that it proceeds in time (12). Therefore, the pharmacodynamic parameter most commonly used to describe killing behavior of β-lactams is time above the MIC. Killing rate constants at concentrations much higher than the MIC are more or less similar.

Although widely employed to characterize the susceptibility of a bacterium, these methods do not reflect the situation in vivo, where the antibiotic concentration is subject to considerable fluctuation due to elimination and multiple dosing regimens. In order to simulate in vivo conditions more closely, several in vitro pharmacokinetic models that mimic human pharmacokinetics during bacterial killing studies have been developed (for examples, see references 1 and 9). To date, however, the mathematical characterization of the pharmacokinetic-pharmacodynamic (PK-PD) relationship has received relatively little attention. In some approaches linear models assuming exponential growth and killing rates were used. However, these models did not take the maximum number of bacteria (N_{max}) at the end of the growth phase into account (14, 15). An interesting model was presented by Eandi and Cecina, who in an exponential-growth-rate model incorporated a term for bacterial adaptation to account for emergence of resistance (3). Pharmacodynamic nonlinear models, such as the Hill or sigmoid maximum-effect (E_{max}) model, which are frequently used for other classes of drug, have not been as common for antibiotics (11). Mattie and coworkers applied the sigmoid E_{max} model to their data, but the antibiotic concentration-time profile did not mimic in vivo pharmacokinetics. As a result the integrated pharmacodynamic model used is fairly complicated and cannot be easily incorporated in computer programs for dosage regimen optimization (7, 8). Recently, an E_{max} model was incorporated in computer software for clinical computations of bacterial growth and killing dynamics (5). By using these models, it will be possible not only to gain insight on the distribution of an antibiotic in the different compartments but also to simulate the effect of the antibiotic on bacteria in these compartments under different conditions and thereby to predict the outcome. To effectively use these models, however, both the values of parameters and PK-PD models describing kill and regrowth kinetics of bacteria during various dosing regimens are needed.

In order to determine the parameters to be included in a

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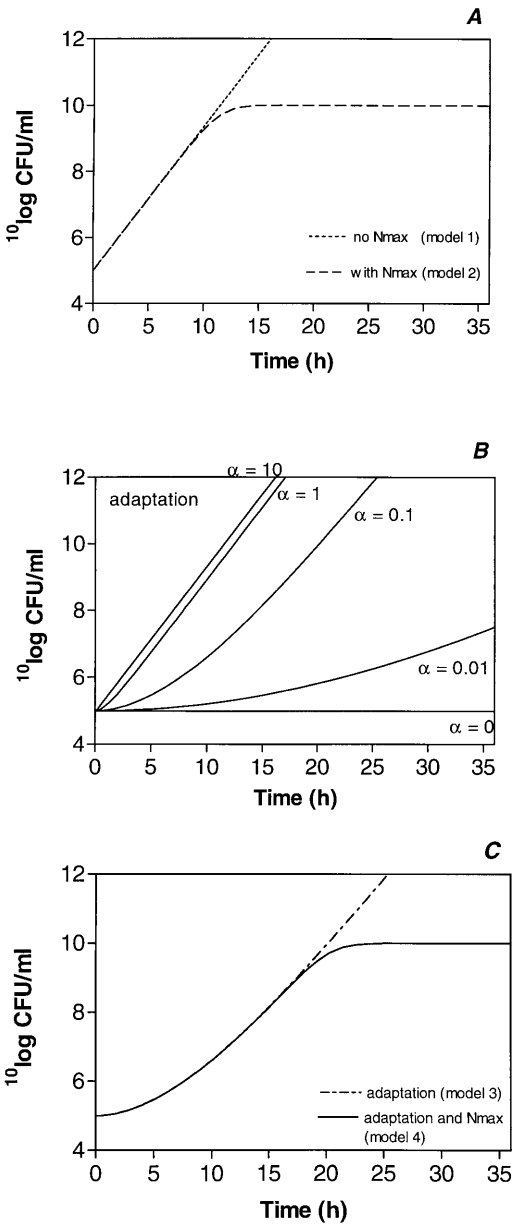

FIG. 1. Computer simulation of the bacterial growth-time curves. (A) Simulation without a term for the N_{max} in the culture (model 1) and simulation with an N_{max} of 10 (model 2). The fixed values are a growth rate of 1 h^{-1} and no bacterial killing (maximum killing rate of 0). (B) Simulation representing the influence of the adaptation rate (α) on bacterial growth-time curves by using model 3. The values in the model for the adaptation rate varied from 0 to 100 h^{-1}. The fixed values are a growth rate of 1.0 h^{-1} and no bacterial killing (maximum killing rate of 0). (C) Simulation with a term for the adaptation rate but without a term for the N_{max} in the culture (model 3) and simulation with an adaptation rate and an N_{max} of 10 (model 4). Fixed values are a growth rate of 1.0 h^{-1}, no bacterial killing (maximum killing rate of 0), and an adaptation rate of 0.1 h^{-1}.

PK-PD model to adequately describe the antibacterial behavior of ceftazidime, we describe here the use of five different models of increasing complexity. The data were obtained from experiments using an in vitro pharmacokinetic model simulating human ceftazidime pharmacokinetics during continuous and intermittent infusion for three different *Pseudomonas aeruginosa* strains (9).

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MATERIALS AND METHODS

Theory. When a pharmacological effect is observed immediately and is directly related to the drug concentration, a linear model, an E_{max} model, or a sigmoid E_{max} pharmacodynamic model can be applied to describe the relationship between concentration and effect. The most simple model is the linear nonsaturable model, in which the change in number of bacteria over time is defined as the number of viable bacteria (N) as a function of the growth rate and killing rate in relation to the concentration (14). For antibiotics, the basic premise of the models used is that the response in the model as described by the measurement of CFU over time is directly related to the various parameters in the model. One important parameter incorporated in the models is an E_{max} parameter. Therefore, our most simple model was the E_{max} model as recently described by Maire et al. (5). The bacterial killing is assumed to be a result of growth and killing rates and can be described with an exponential-growth model. The rate of change of the response over time can be described by

$$\frac{dN}{dt} = \left\{\lambda - \varepsilon \cdot \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\right\} \cdot N \qquad \text{(model 1)}$$

where λ represents the growth rate, ε represents the maximum killing rate, C represents the concentration of antibiotic, EC_{50} represents the concentration of the antibiotic at which 50% of the E_{max} is obtained, and γ represents the Hill coefficient. The Hill coefficient represents the steepness of the concentration-effect curve. For β-lactam antibiotics, values for this factor are in the higher range, indicating that the E_{max} is quickly reached. The larger the Hill coefficient, the steeper the linear phase of the log concentration-effect curve. This is the pharmacological explanation for the more time-dependent than concentration-dependent killing behavior of β-lactams.

In the above-mentioned model, the growth rate is uncontrolled. However, because of limitations of space, nutrients, and other factors, there should be an N_{max} to which the in vitro culture can grow during or after a certain amount of time. During short experiments, such as those with killing curves of 6 h, the N_{max} is usually not an important factor, but in experiments of longer duration it is. The N_{max} parameter was incorporated in a second model as follows:

$$\frac{dN}{dt} = \left\{\lambda \cdot \left(1 - \frac{N}{N_{max}}\right) \cdot N - \varepsilon \cdot \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\right\} \cdot N \qquad \text{(model 2)}$$

Another factor which has to be taken into account is emergence of resistance. There are basically two mechanisms. The first is a gradual increase in resistance over time. This can be accounted for by incorporating an adaptation rate (α) term in the model as follows:

$$\frac{dN}{dt} = \left\{\lambda \cdot (1 - e^{-\alpha t}) - \varepsilon \cdot \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\right\} \cdot N \qquad \text{(model 3)}$$

If the N_{max} parameter is included as well, a fourth model can be constructed:

$$\frac{dN}{dt} = \left\{\lambda \cdot (1 - e^{-\alpha t}) \cdot \left(1 - \frac{N}{N_{max}}\right) \cdot N - \varepsilon \cdot \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\right\} \cdot N \qquad \text{(model 4)}$$

A second mechanism by which the emergence of resistant microorganisms can be explained is by assuming the presence of small numbers of bacterial subpopulations with different degrees of susceptibility in the primary inoculum. One approach to describe emergence of resistance is to use a two-population model. The two-population model does not contain the adaptation rate parameter, but an N_{max} parameter can be included. Since the MICs for emerging resistant microorganisms can be measured during the experiments, these microorganisms can be incorporated in a two-population model as a separate population. Model 5, therefore, is similar to model 2 but has two kinetic equations to account for the rate of change in N for each of the two different bacterial populations over time (subscripts are used to distinguish the parameters for the two populations).

$$\frac{dN}{dt} = \left\{\lambda_1 \cdot \left(1 - \frac{N_1}{N_{max}}\right) \cdot N_1 - \varepsilon_1 \cdot \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\right\} \cdot N_1 + \left\{\lambda_2 \cdot \left(1 - \frac{N_2}{N_{max}}\right) \cdot N_2 - \varepsilon_2 \cdot \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\right\} \cdot N_2 \qquad \text{(model 5)}$$

It is useful to define the pharmacodynamic MIC (ZMIC) as the concentration at which the bacterial population is stable, i.e., the special case of the bactericidal curve where the killing rate equals the growth rate, i.e., $dN/dt = 0$, and N is constant over time. This enables one to compute the relation between the ZMIC and the EC_{50} (2).

TABLE 1. R^2 and Akaike values for models of activity of ceftazidime against *P. aeruginosa* during infusion[a]

Model	Mode of infusion	R^2 for strain[b]			Akaike value[c]
		P1	P4	P16	
1	Continuous	<0.1	<0.1	0.23 (0.05–0.52)	124 (56–176)
	Intermittent	<0.1	<0.1	<0.1	152 (122–183)
2	Continuous	0.36 (0.20–0.51)	0.62 (0.56–0.68)	<0.1	17 (−2–36)
	Intermittent	0.23 (0.15–0.30)	0.20 (0.12–0.24)	0.37 (0.33–0.40)	21 (4–40)
3	Continuous	0.77 (0.74–0.80)	0.62 (0.34–0.89)	0.89 (0.89–0.90)	66 (18–110)
	Intermittent	0.41 (0.27–0.63)	0.42 (0.18–0.86)	0.76 (0.70–0.82)	113 (78–152)
4	Continuous	0.75 (0.55–0.88)	0.70 (0.57–0.83)	0.93 (0.92–0.94)	−8 (−29–16)
	Intermittent	0.74 (0.70–0.79)	0.78 (0.72–0.87)	0.89 (0.89–0.90)	−15 (−28–−1)

[a] Values are means (ranges).
[b] The numbers of experiments available for analysis were as follows: for P1, three; for P4, three (continuous infusion) and two (intermittent infusion); and for P16, two. Values of <0.1 indicate that data could not be fitted to the model.
[c] The numbers of experiments available for analysis were eight for continuous infusion and seven for intermittent infusion.

$$\mathrm{ZMIC} = \left(\frac{\lambda \cdot \mathrm{EC}_{50}^{\gamma}}{\varepsilon - \lambda}\right)^{\frac{1}{\gamma}} \quad (1)$$

Strains, pharmacokinetics, and killing curves. The modeling was performed with data obtained from *P. aeruginosa* killing experiments during continuous and intermittent infusion of ceftazidime by using an in vitro pharmacokinetic model as described previously (9). Briefly, a two-compartment in vitro model consisting of one central compartment and several peripheral compartments consisting of disposable dialyzer units (ST23; Baxter, Utrecht, The Netherlands) was used to expose the bacteria in the peripheral compartments to changing antibiotic concentrations mimicking human pharmacokinetics. Three *P. aeruginosa* strains, P1, P4, and P16, for which the MICs were 1, 4, and 16 mg/liter, respectively, were exposed to concentrations of ceftazidime during continuous (300 mg/liter/day) and intermittent (100 mg/liter every 8 h) infusion over 36 h in the in vitro pharmacokinetic model. During continuous infusion, the steady-state concentration was around 20 mg/liter. Peak concentrations during intermittent infusion were around 100 mg/liter, and trough concentrations were around 1 mg/liter (9).

PK-PD modeling. The differential equations for models 1 to 5 were used in the EDSIM program (version 2.0; MediWare, Groningen, The Netherlands), which is based on object-oriented modeling. With the program the user is able to create any type of model by using three basic objects: inputs, compartments, and connections. The differential equations are solved by numerical integration. The method used here was the fourth-order Runga-Kutta method with adaptive step size control. Before each modeling session, the pharmacokinetic parameter values for that specific experiment were estimated. These parameter estimates were kept constant during the actual PK-PD modeling. Next, the data were fitted to pharmacodynamic models 1 to 5 as described above with a log-weighted adjustment. The N and EC_{50} were fixed at the actual values, whereas the growth rate, maximum killing rate, adaptation rate, Hill coefficient, and N_{max} were not fixed. The Hill coefficient obtained in the initial computations was always higher than 5 to 10 and was therefore fixed in subsequent calculations, which further stabilized the model. To determine which model performed best, coefficients of determination (R^2) were calculated. In addition, model discrimination was based on Akaike's information criterion (13) and the F test. As a further validation of the model, data obtained during continuous infusion were fitted to an intermittent-infusion model and vice versa.

RESULTS

Model simulations. In Fig. 1A a computer simulation of the effect of the N_{max} as a parameter in the model is shown. The effects of different adaptation rates in the models are shown in Fig. 1B. The influence of the adaptation rate and N_{max} as determined by computer simulation is summarized in Fig. 1C.

Model fitting. The results of the fitting are summarized in Table 1. The mean R^2 and the mean Akaike values of the fits for the three *P. aeruginosa* strains obtained during the two modes of ceftazidime administration with PK-PD models 1 to 4 are shown. With increasing complexity, i.e., with the incorporation of an N_{max} term and a term for the adaptation rate, the performance of the models improved. All more complex models were significantly better at explaining the data than simpler models ($P < 0.001$ for all comparisons; F test). The most complex model (model 4) that included an N_{max} term and an adaptation rate term described the data best in terms of R^2 and Akaike's criterion. Table 2 summarizes the growth, maximum killing, and adaptation rates obtained by fitting the data to model 4. Figure 2 shows typical simulations with model 4 for each strain during ceftazidime administration by both modes. From the figure several patterns can be observed: (i) for the P1 strain, the general pattern of the fitted curve is the same during continuous infusion as during intermittent infusion; (ii) the patterns of the P1 and P4 strains are comparable during continuous infusion but not during intermittent infusion; and (iii) during intermittent infusion the P4 and P16 strains show typical regrowth phases, coinciding with ceftazidime concentrations below the MIC. The data were not fitted better by using a two-population model (model 5), except for those experiments where resistant microorganisms did emerge during the experiment; then the data were fitted better only for the P16 strain. However, the model was applicable only if the MICs were set at an unrealistic, lower value than the actually measured MICs. In other words, with measured MICs for the resistant strains, the model could not describe the data well. If, however, the MIC for the resistant population was set two twofold dilutions lower than the actually measured MIC, the model could be used in some cases (results not shown).

DISCUSSION

In this study, we have developed PK-PD models to describe data previously reported for *P. aeruginosa* strains exposed to continuous and intermittent infusion of ceftazidime. Computer simulation was applied to determine which parameters need to

TABLE 2. Estimates of growth rate, maximum killing rate, and adaptation rate during continuous and intermittent infusion

Mode of infusion	Strain	Hourly rate[a]		
		Growth	Maximum killing	Adaptation
Continuous	P1	4.15 (0.60)	2.13 (0.70)	0.11 (0.06)
	P4	3.96 (0.01)	1.80 (0.15)	0.11 (0.01)
	P16	7.38 (2.57)	5.34 (1.17)	0.15 (0.04)
Intermittent	P1	5.59 (0.60)	3.79 (1.23)	0.22 (0.12)
	P4	4.83 (0.26)	3.32 (0.54)	0.14 (0.03)
	P16	2.42 (0.37)	1.96 (0.17)	0.07 (0.01)

[a] Parameter estimates are means (standard deviations). Values were obtained by fitting to model 4 in vitro ceftazidime data for continuous and intermittent infusion.

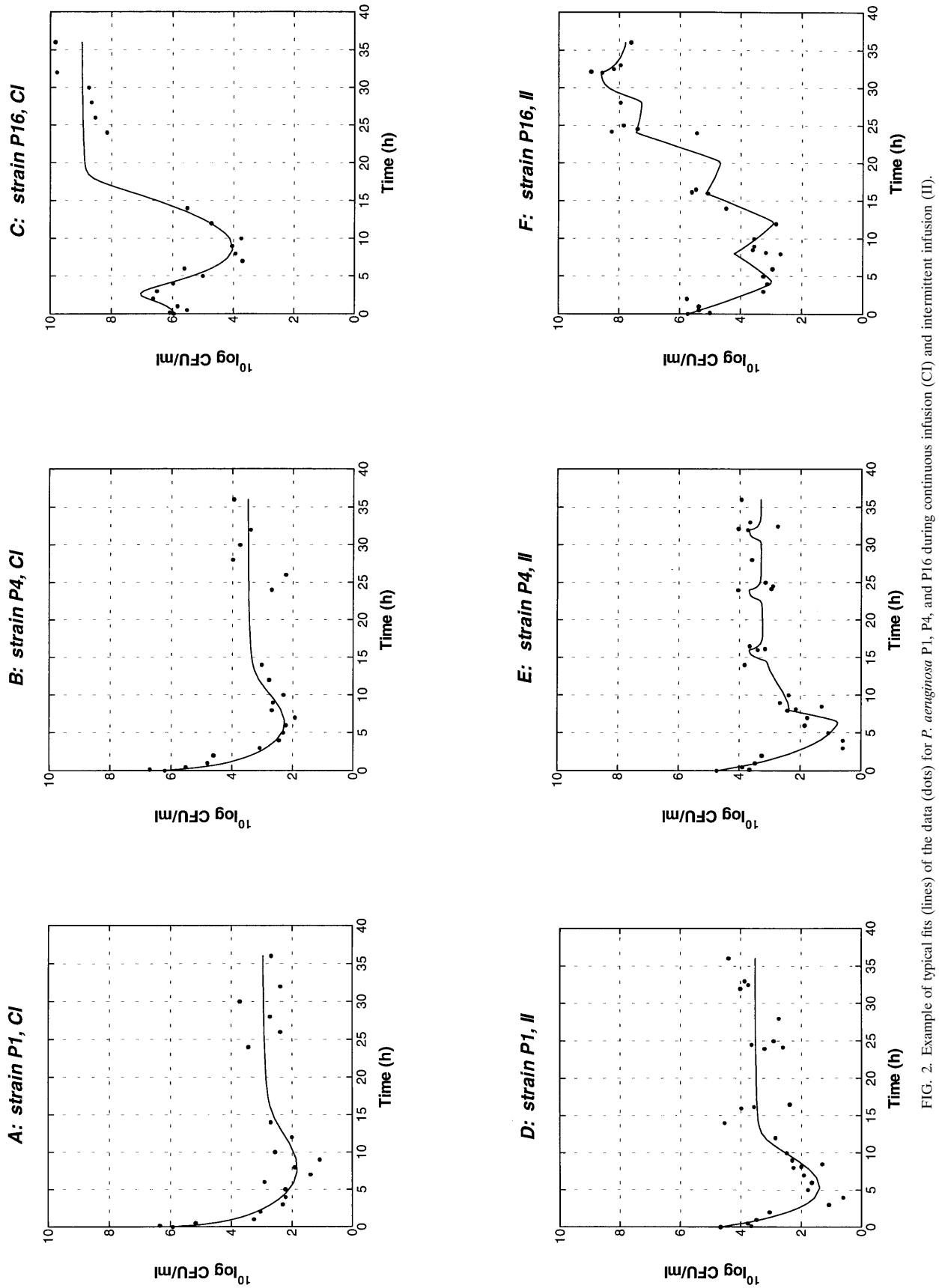

FIG. 2. Example of typical fits (lines) of the data (dots) for *P. aeruginosa* P1, P4, and P16 during continuous infusion (CI) and intermittent infusion (II).

be incorporated in such a model. The results indicate that the data were best fitted to a PK-PD model that included a term for the N_{max} in the culture and a term for the adaptation rate. The latter term is necessary to account for emergence of resistance. A model without a term for the adaptation rate did not describe the data adequately. The maximal growth and killing rates obtained by fitting the experimental data were higher than the rates normally observed. For instance, the growth rate of strain P1 during continuous infusion was 4.15 h^{-1}. This would imply a doubling time of around 10 min. Similarly, during intermittent infusion this value is around 8 min. It is, however, important to realize that values for the rate terms in the models used are apparent values and maximum rates and as such cannot be used for comparison with parameter values reported by other methods. Usually, these rate constants are defined differently, e.g., as net rate constants representing the difference between net growth with antibiotic and growth without antibiotic (7, 8). In our models the net killing is the resultant of the growth and killing rates and is obtained by fitting the data without any constraint. The rates do show some correlation in the final correlation matrix, which indicates interdependence. When expressed as the difference between the fitted growth and maximal killing rates, more realistic values are obtained, which are in keeping with the net rates as determined in the original experiment (9). Furthermore, it has to be emphasized that the killing rates as obtained are maximum killing rates and that killing itself is not the same at the different time points.

In in vitro experiments, after an initial decrease in CFU a regrowth occurs. The reasons for the observed regrowth are not fully understood (6–8). A pharmacological explanation would be that adaptation is the result of a gradual increase in the MIC for the bacteria. However, a model in which the EC_{50}, which can be regarded as an apparent MIC, was defined as a function of the adaptation rate could not describe the data. From equation 1, it can be seen that the relationship between ZMIC and EC_{50} is rather complex. In order to deal with this phenomenon we therefore modified the PK-PD model by introducing a term for the adaptation rate related to the growth rate as described by Eandi and Cecina (3). With this model we were able to adequately describe our data by means of three parameters (growth rate, maximum killing rate, and adaptation rate).

Adaptation, on the other hand, may represent a small fraction of the original bacterial population that is phenotypically resistant. The model with terms for two populations gave inferior results when the MICs for the resistant microorganisms isolated during the experiment were applied in the model, or no fit could be found. However, the fact that the use of lower MICs in the PK-PD model yielded good results indicates that this model may still be useful in some cases and that the way the MICs were measured is not representative of the "true" MIC present during the experiments. On the other hand, the MICs for the emerging resistant strains did increase over time, indicating that an adaptation rate more accurately describes this phenomenon than does a two-population model.

The simulations with the fitted parameters show CFU-time curves which are in agreement with the pharmacodynamic behavior of β-lactams. If, for β-lactam antibiotics, bacterial killing is related to the length of time the antibiotic remains above a threshold value, e.g., the MIC as defined in the model, it follows that the dosage regimen that maintains concentrations well above this value will be better able to prevent regrowth of the pathogen (12). During continuous infusion, the attained concentration of ceftazidime was approximately 20 mg/liter and the killing curves for the *P. aeruginosa* strains for which the respective MICs were 1 and 4 mg/liter indeed appeared to be quite similar (Fig. 2A and B). Also, the estimates of the parameter values for these experiments are within the same range (Table 2). Similarly, the concentrations of ceftazidime during intermittent infusion remained above the MIC for the P1 strain, and this curve (Fig. 2D) shows the same pattern, as the trough concentrations in these experiments were 1 to 2 mg/liter. For the *P. aeruginosa* strain for which the MIC was 4 mg/liter, the pattern of killing during intermittent infusion appears to be different. At concentrations of ceftazidime below the MIC, slight regrowth occurs (Fig. 2E). This is even more accentuated for the P16 strain (Fig. 2F). When this strain is subjected to continuous infusion of ceftazidime, initial growth occurs until the MIC is reached (Fig. 2C). This clearly demonstrates the clinical importance of a loading dose when applying continuous infusion.

The second important phenomenon which can be observed with this curve is that adaptation appears to play an important role. While during intermittent infusion at least some killing is observed when concentrations are far above the MIC after dosing, resistant strains appear earlier during continuous infusion, while the adaptation rate is higher than it is during intermittent infusion (Table 2). This may have consequences for therapy, since this means that during continuous infusion, concentrations should indeed be several times the MIC, at least for *P. aeruginosa.*

We have chosen to model the data with the sigmoid E_{max} model, as it gave a valid description of the relationship between antibiotic concentration and killing. However, we used an empirical equation to account for changes in susceptibility and for emergence of resistant bacterial subpopulations. It would be of great interest to explore further this type of modeling with emphasis on the underlying mechanisms, i.e., a more mechanism-based description of changes in susceptibility, by relating EC_{50}s to traditional MICs (4, 9). Such PK-PD models available in computer software will provide a further tool to analyze antibiotic regimens and may present the future optimal clinical index of therapeutic effectiveness (2).

We conclude that the derived models can describe bacterial growth and killing in the presence of antibiotic concentrations mimicking human pharmacokinetics. Application of these models will eventually provide us with a rationale for the proper selection of the optimal dose, mode of administration, and duration of antibiotic therapy.

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