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Development of a Population Pharmacokinetic Model and Optimal Sampling Strategies for Intravenous Ciprofloxacin

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Data obtained from 74 acutely ill patients treated in two clinical efficacy trials were used to develop a population model of the pharmacokinetics of intravenous (i.v.) ciprofloxacin. Dosage regimens ranged between 200 mg every 12 h and 400 mg every 8 h. Plasma samples (2 to 19 per patient; mean ± standard deviation = 7 ± 5) were obtained and assayed (by high-performance liquid chromatography) for ciprofloxacin. These data and patient covariates were modelled by iterative two-stage analysis, an approach which generates pharmacokinetic parameter values for both the population and each individual patient. The final model was used to implement a maximum a posteriori-Bayesian pharmacokinetic parameter value estimator. Optimal sampling theory was used to determine the best (maximally informative) two-, three-, four-, five-, and six-sample study designs (e.g., optimal sampling strategy 2 [OSS2] was the two-sample strategy) for identifying a patient's pharmacokinetic parameter values. These OSSs and the population model were evaluated by selecting the relatively rich data sets, those with 7 to 10 samples obtained in a single dose interval ($n = 29$), and comparing the parameter estimates (obtained by the maximum a posteriori-Bayesian estimator) based on each of the OSSs with those obtained by fitting all of the available data from each patient. Distributional clearance and apparent volumes were significantly related to body size (e.g., weight in kilograms or body surface area in meters squared); plasma clearance (CL_T in liters per hour) was related to body size and renal function (creatinine clearance [CL_{CR}] in milliliters per minute per 1.73 m^2) by the equation $CL_T = (0.00145 \cdot CL_{CR} + 0.167) \cdot$ weight. However, only 30% of the variance in CL_T was explained by this relationship, and no other patient covariates were significant. Compared with previously published data, this target population had smaller distribution volumes (by 30%; $P < 0.01$) and CL_T (by 44%; $P < 0.001$) than weight- and CL_{CR}-matched stable volunteers. The OSSs provided parameter estimates that showed good to excellent concordance with those obtained from all available data. Even with only two well-timed plasma samples, estimates of CL_T (or area under the concentration-time curve [AUC]) were unbiased and precise (e.g., r^2 for AUC for all data versus AUC for OSS2 was >0.99) and concentration-time profiles were accurately reconstructed. These results will be used to model the pharmacodynamic relationships between ciprofloxacin exposure and response and to aid in developing algorithms for individual optimization of ciprofloxacin dosage regimens.

Intravenous (i.v.) ciprofloxacin has been used for the treatment of a variety of infections, and its pharmacokinetics have been comprehensively evaluated in single- and repeated-dose studies with healthy volunteers. The drug exhibits linear pharmacokinetics at doses of 25 to 400 mg. In contrast to those from healthy volunteers (6, 9, 12, 15, 22, 32) or stable patients with renal insufficiency (9, 32), very few usable data (10, 16, 20, 23, 33) have been published for any target populations. Also, there are no pharmacokinetic data derived from patients receiving doses of 400 mg every 8 h, a regimen currently being studied for severe infections. This report is a description of the pharmacokinetics of i.v. ciprofloxacin in severely ill patients who received doses of between 200 mg every 12 h and 400 mg every 8 h.

Pharmacokinetic and pharmacodynamic analyses of antibiotics have greatly assisted in the evolution of methods for individualizing antimicrobial therapy and, hence, optimizing clinical outcome (2, 8, 27, 34). It is logistically difficult (but critically important) to determine pharmacokinetic parameters for target populations and, for some drug-disease combinations, for individual patients. The traditional method for determining the pharmacokinetics of a drug in an individual is to measure multiple (6 to 10) plasma drug concentrations following the first or a steady-state dose. This approach has several drawbacks. First, the time and expense associated with obtaining and assaying so many samples limit the number of subjects who can be studied. Many important target populations (e.g., critically ill, elderly, or pediatric patients) may be harmed by overly aggressive phlebotomies or have limited venous access. As a consequence, studies are often performed with healthy subjects with the intention of extrapolating the results to target populations. Since response cannot be measured with these volunteers, few useful pharmacodynamic data can be obtained in these studies. This has led to the exploration of measures of antibiotic activity which might be predictive of efficacy, the most useful of which is the measurement or calculation of bacteristatic or bactericidal activity indices (2, 8, 27).

Another fruitful avenue of investigation has been the development of new mathematic tools which improve the precision and efficiency of pharmacokinetic-pharmacodynamic studies with the target populations. These tools in-

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clude population analysis (13, 24, 25, 29, 31), maximum a posteriori (MAP)-Bayesian parameter estimation (5, 25), and application of optimal sampling theory (OST) (3, 5, 7) to pharmacokinetic-pharmacodynamic study designs. Population analysis can accommodate sparse, data-rich, and/or mixed sampling strategies to determine parameter means, covariance matrix, and patient covariates (factors predictive of parameter values) for the total population. Most approaches to population analysis do not provide parameter estimates for the individuals who were studied. MAP-Bayesian analysis (25) is an approach which uses both the likelihood distributions from a population analysis and subject-specific observations to estimate individual parameter values. This approach is especially useful when data are sparse and/or noisy (contain substantive random error). OST is a tool for aiding study design which is used primarily to determine data acquisition schedules (but can be used to determine input strategies) which are optimally informative about the parameters of interest. This tool may be especially useful when only a sparse number of observations per subject is feasible. This report illustrates ways in which these techniques may be integrated to determine relationships which were difficult to impossible to obtain by traditional methods.

The current analysis applies iterative two-stage analysis (IT2S), an approach to population analysis which provides both individual parameter estimates and the population model (13, 24, 31), to data from previously reported phase III efficacy trials (23, 28). The results of this analysis were then used to implement a MAP-Bayesian estimator and to determine optimally informative and efficient sampling strategies which may be used in future trials and/or in an adaptive feedback control algorithm (25). The individual parameter estimates will then be used, as described in the companion article (14), to characterize the pharmacodynamic relationships between ciprofloxacin exposure and the probability of microbiologic and clinical cures and time to bacterial eradication.

MATERIALS AND METHODS

Clinical and pharmacokinetic data acquisition. All data were derived from two clinical trials of i.v. ciprofloxacin conducted at the Millard Fillmore Hospital. Patients were evaluated for efficacy, safety, and pharmacokinetics (23, 28). All subjects from whom plasma drug concentration data were obtained were included in the current analyses (n = 74). Plasma samples (2 to 19 per patient; mean ± standard deviation (SD) = 7 ± 5) were obtained and assayed for ciprofloxacin. In the first study (23), patients were given 200 or 300 mg of i.v. ciprofloxacin every 12 h. Traditional data sets (7 to 10 samples during one dose interval) were obtained for 29 of 48 patients after the first dose (n = 14) or at steady state (n = 15). Plasma samples from these patients were scheduled to be drawn predose and at 0, 0.5, 1, 2, 3, 4, 6, 8, and 11 h after a 1-h infusion. The remaining patients in the first study and all of those in the second (28) had fewer samples obtained in any one dose interval. Every set of samples obtained around a dose included at least a near-peak (0.5 h after the end of the i.v. infusion) and a trough concentration; many patient data sets had samples obtained in several dose intervals. From 28 patients, two or more trough-peak pairs were obtained; 17 had only a single pair of samples. In the second study, patients (26 included in the current analysis) received ciprofloxacin at 400 mg i.v. every 8 h. All samples were assayed by high-performance liquid chromatography (21). The within- and between-day coefficients of variation, for this assay, averaged 2 to 7%.

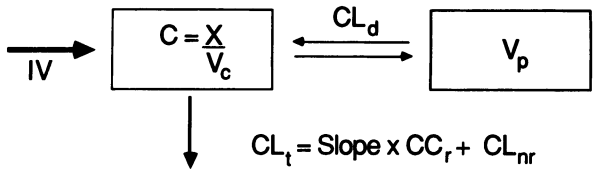

FIG. 1. Two-compartment open model used to fit i.v. ciprofloxacin data. IV, 0-order infusion rate; C, concentration; X, amount of drug in the central compartment; V_c, V_1; CC_r, estimated CL_{CR}; CL_{nr}, nonrenal clearance.

Population pharmacokinetic analysis. The structural model used to describe ciprofloxacin pharmacokinetics was open and linear, and it had two compartments (Fig. 1). This model was chosen on the basis of Akaike's Information Criterion (1) applied to the 29 traditional data sets. The parameters estimated were the apparent volumes of distribution in the central (V_1) and peripheral (V_p) compartments and the distributional ($CL_D = V_1 \cdot k_{pc} = V_p \cdot k_{pc}$; k_{cp} and k_{pc} are the intercompartmental rate constants) and total (CL_T) clearances. The terminal half-life ($t_{1/2\beta}$), V_β, (also called Varea or V_z) and volume of distribution at steady state (V_{SS}) were computed as a function of the following fitted parameters:

$$k_{el} = CL_T/V_1,\ k_{cp} = CL_D/V_1,\ k_{pc} = CL_D/V_p$$

$$\beta = (k_{el} + k_{cp} + k_{pc})/2 - \sqrt{(k_{el} + k_{cp} + k_{pc})^2/4 - k_{el} \cdot k_{pc}}$$

$$t_{1/2\beta} = \ln(2)/\beta,\ V_\beta = CL_T/\beta$$

$$V_{SS} = V_1 + V_p$$

where k_{el} is the elimination rate constant. A three-compartment model was also fit to the data sets with relatively extensive sampling. Model discrimination was by Akaike's Information Criterion (1).

Pharmacokinetic modelling was accomplished by IT2S (13, 24, 31), an approach which derives both a description of the population (parameter means, variance and correlation, and the residual variance) and individual estimates (pharmacokinetic parameter point estimates and asymptotic covariance matrices) for each subject. The residual (error) variance model assumed that the SD of the observations were linearly related (with a positive slope) to the true value. The IT2S computer program (13) was developed with modules from the ADAPT II package of programs (4, 5). Computations were performed on a DOS-compatible, 33-MHz 80486 computer. In brief, the IT2S analysis proceeded as follows (see the Appendix for further details). (i) The 29 subjects with traditional data sets (7 to 10 samples during a dose interval) were modelled individually by using maximum likelihood (ADAPT II). (ii) The results (parameter value estimates and residual variance) were used to derive an initial population model of ciprofloxacin pharmacokinetics and to implement (in ADAPT II) a MAP-Bayesian parameter value estimator (MAP-B). (iii) All of the data sets (data rich and data sparse) were then fit with MAP-B. (iv) The results (individual point estimates and covariance matrices) were used to refine (24, 31) the population model and to recreate the MAP-B. (v) All data sets were again fit by using the new estimator, and the population model was further refined. (vi) This population model was compared with that from the previous iteration. When different, MAP-B was refined and the last two steps

TABLE 1. Summary of patient characteristics

Characteristic	Mean	Interpatient CV%	Range
Age (yr)	68	16	24–91
CL_{CR} (ml/min/1.73 m^2)[a]	63	48	17–151
Wt (kg)	70	24	33–151

[a] Estimated by the method of Jelliffe (18).

were repeated. When the population model was stable, the analysis was complete. The final population pharmacokinetic model was also incorporated into a MAP-B for subsequent applications.

OSSs. The 29 relatively data-rich (the traditionally sampled) patient files were used to develop (per OST [3]) and evaluate efficient, data-sparse optimal sampling strategies (OSSs) (7). The SAMPLE module in ADAPT (5) was used to determine the D-optimal (3) study designs (those which minimize the total parameter value uncertainty) for all 29 patients. The individual best data acquisition schedules, during the first dose interval and once at steady state in a multiple-dose regimen, were derived. SAMPLE was constrained to consider times between 15 min after the end of i.v. administration and the end of the dose interval. A Bayesian variant (11) in which the OST program was provided information about the population parameter means and variances was used so that strategies with fewer than four times could be considered. (This may be accomplished within the ADAPT sample module by specifying the population mean parameter values as outputs which are observed, as are plasma drug concentrations.) The individual best two- (OSS2), three- (OSS3), four- (OSS4), five- (OSS5), and six- (OSS6) sample designs were determined. These were used to develop candidate-fixed (all subjects studied at the same times) sampling strategies, which were the most informative overall, for the 29 patients being considered. Discrimination between candidate-fixed strategies was based on the individual information indices provided by the SAMPLE module. The final OSSs were those that provided the best average information index across the 29 parameter sets.

The biases and precision of the OSSs were characterized (30) for the same 29 data sets. The parameter estimates determined as described above (first step under "Population pharmacokinetic analysis") on the basis of all available data for each subject were used as the "gold standard," the best values available. Parameter values were also estimated on the basis of OSS2 to OSS6 by fitting (by using the MAP-Bayesian estimator) only the observations in the strategy under consideration. The percent mean error (%ME) was computed as one measure of bias, and the percent mean absolute error (%MAE) was a measure of precision:

$$\%\mathrm{ME} = \frac{100}{n} \Sigma \frac{\mathrm{OSS}_{ij} - \mathrm{GS}_i}{\mathrm{GS}_i} \quad \text{and}$$

$$\%\mathrm{MAE} = \frac{100}{n} \Sigma \frac{|\mathrm{OSS}_{ij} - \mathrm{GS}_i|}{\mathrm{GS}_i}$$

in which n is the number of subjects (29), OSS_{ij} is a parameter estimate in the ith subject (i varied between 1 and 29) for the jth OSS (j varied between 2 and 6), and GS_i is the gold standard, the parameter value, for that subject on the basis of all available data.

TABLE 2. Population pharmacokinetic parameter values by IT2S analysis

Parameter	Mean	Interpatient CV%	Range
V_1 (liters/kg)	0.69	26	0.2–1.2
V_p (liters/kg)	0.51	33	0.2–2.0
V_β (liters/kg)	2.0	31	0.96–5.0
CL_D (liters/h/1.73 m^2)	38	24	16–64
CL_T (liters/h/1.73 m^2)	17	44	4.4–37
$t_{1/2\beta}$ (h)[a]	6.5	50	1.6–22

[a] $t_{1/2\beta}$, terminal half-life.

RESULTS

Study population. Patient characteristics are summarized in Table 1. Of the 74 patients, 35 were female and 39 were male; 41 received 200 mg i.v. every 12 h, 8 received 300 mg every 12 h, 1 received 400 mg every 12 h, and 24 received 400 mg every 8 h; and 58 were being treated for a lower respiratory tract infection, 9 had wound-soft tissue infections, 4 had bacteremias, and 3 had complicated urinary tract infections. The patients were mostly elderly; only 20 of 74 patients were less than 65 years of age, and only 7 were less than 55 years of age.

Population pharmacokinetics. The results of the population pharmacokinetic analysis are shown in Table 2. A two-compartment model was statistically superior with these data (probably because of the 1-h infusion and the fact that no samples were drawn during the infusion and only a subset of patients had a sample earlier than 15 min after the end of the i.v. administration). Apparent distribution volumes and clearances were significantly related to body size (either body surface area in meters squared or weight in kilograms). Neither β nor terminal half-life was significantly related to CL_{CR} (data not shown). Interpatient variability in nonnormalized CL_T (Fig. 2) was substantial. Multiple linear regression was performed to determine whether any patient covariates accounted for a significant portion of this variance. Only body size and renal function (estimated [18] normalized CL_{CR}) were significant ($P < 0.001$); neither age (most patients were elderly), gender, site of infection (most patients had lower respiratory tract infections), nor dose size

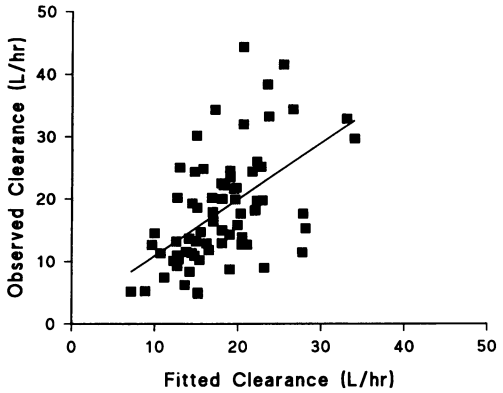

FIG. 2. Observed ciprofloxacin plasma clearance (based on all available data) versus the CL_T predicted from weight and CL_{CR} for 73 acutely ill patients. The diagonal is the line of best fit which did not differ from the line of identity.

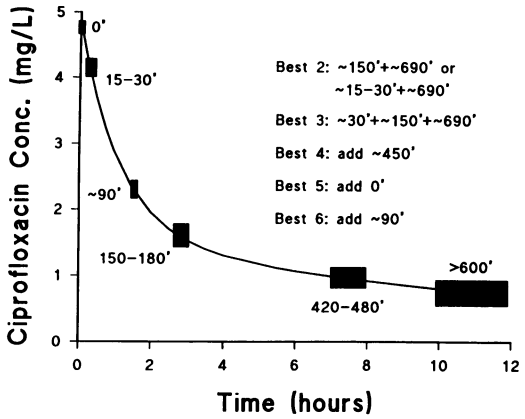

FIG. 3. Plot of ciprofloxacin plasma concentration versus time post-i.v. infusion, showing the information-rich times (■) to sample for parameter estimation. In the inset, the best OSS2, OSS3, OSS4, OSS5, and OSS6 are defined.

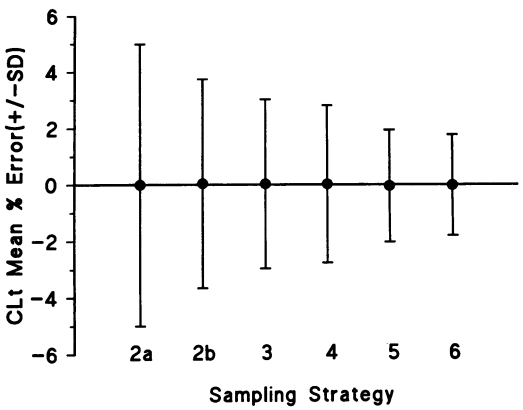

FIG. 4. %ME (●) ± SD (error bars) in estimation of CL_T as a function of sampling strategy. See the text and Fig. 3 for definitions of sampling strategies.

had any predictive value ($P > 0.2$). An equation to enable a priori predictions of CL_T was derived, $CL_T = (0.00145 \cdot CL_{CR} + 0.167) \cdot$ weight ($n = 73$, $r = 0.54$, $P < 0.001$), in which CL_{CR} is in milliliters per minute per 1.73 m^2 and weight is in kilograms. Normalization by body surface area was somewhat (not significantly) better than by weight, but the above formula is easier to use in a bedside dosing algorithm. Figure 2 depicts for 73 patients (one data set did not have sufficient information to estimate CL_{CR}) the observed CL_T versus that predicted by the above formula (fitted clearance in Fig. 2). Clearly, the variance in CL_T is substantial, as is the residual, unexplained variance: $r = 0.54$, ME ± SD was −0.15 ± 7.5 liters/h (unbiased), MAE ± SD was 5.7 ± 4.8 liters/h.

The pharmacokinetics of ciprofloxacin seen with this target population were also contrasted to data previously reported (9) by Drusano et al. describing subjects who were not infected. When our patients were compared with these 32 stable volunteers, with CL_{CR} ranging between 0 and normal, our patients had smaller (by 30%) apparent volumes of distribution (mean ± percent coefficient of variation [CV%] for V_β was 2.7 liters/kg ± 32% in the stable volunteers; group means differed; $P < 0.01$). Drusano et al. also derived (9) a formula which related body size and renal function to observed ciprofloxacin CL_T. This formula was applied to the present population to examine, for subjects matched by body size and CL_{CR}, the concordance in CL_T between the two studies. The present patient population had systematically lower total CL_T by a mean ± standard error of 44 ± 8% ($P < 0.001$). Half-lives at a given CL_{CR} were similar in studies (data not shown). The present population also had somewhat greater residual variance in CL_T; Drusano et al. reported (9) an r of 0.71 for observed versus fitted CL_T, compared with 0.54 with the current patients.

OSSs. Application of OST to the problem of determining data-sparse, fixed study designs for the estimation of ciprofloxacin pharmacokinetics in the present population yielded the results represented in Fig. 3. Though there were small differences in OSSs determined for a first versus a steady-state dose interval, we were able to find a single strategy which was close to optimal (per information index) for both intervals; thus, no differentiation is necessary for the number of doses given. Figure 3 is a plot of ciprofloxacin plasma concentrations versus the time after the end of an i.v. infusion, with black bars indicating the information-rich times to acquire samples. When the SAMPLE program was constrained to only two times, it chose a trough and either a 2.5-h sample (OSS2b) or one at nearly its peak (15 to 30 min, OSS2a). OSS2b was somewhat superior with the 29 subjects overall. The best OSS3 was a near-peak (15 to 30 min after the end of infusion), a 2.5-h sample, and a trough. For OSS4, a 7- to 8-h sample was added; for OSS5, a true peak was added; and for OSS6, a 1.5-h sample was added.

Figure 4 displays the accuracy and precision of estimates of CL_T as a function of sampling strategy. The labels along the horizontal axis are for the six strategies considered (OSS2a to OSS6). Data along the vertical axis are percents error (OSS estimate of CL_T versus the gold standard). The closed circles are the %ME for each strategy (none of the OSSs were biased, and none of the %MEs were different from 0). The error bars show the %ME ± SD and are another measure of precision. For precision of estimates of CL_T, arguably the most important of the pharmacokinetic parameters for ciprofloxacin, OSS2a < OSS2b < OSS3 and OSS4 < OSS5 and OSS6. By several measures, OSS3 was the most efficient study design [efficiency ∝ (information content/number of samples)]. The performance of OSS3 is described below in some detail.

Figure 5 shows for CL_T, CL_D, V_1, and V_{SS}, respectively, the gold standard parameter estimates (based on all data) versus the OSS3 estimates. Diagonals are the lines of best fit; none of the parameter estimates was significantly biased. In precision of estimates, characterized by either correlation coefficients or %MAE, $CL_T > V_1 > V_{SS} > CL_D$.

Table 3 summarizes the tests of bias (%ME versus 0) and quantification of precision (%MAE) for these same data. It is clear from the sample statistics that on average, OSS3 agreed well with the gold standard. This was corroborated by the lack of bias in any of the four parameters. Except for with CL_D (which is a poorly identifiable parameter in general), the precision was quite good, as can be seen by the %MAE values.

Despite the poor agreement between gold standard and OSS3 estimates of CL_D, OSS3 (and the other OSSs) did an excellent job of tracking the actual time course of plasma drug concentrations. This is clearly evident in Fig. 6 and 7. Figure 6 shows, for all of the samples not used in OSS3 (n = 168 samples from 29 patients), the observed versus the predicted (based on OSS3 only) plasma drug concentrations.

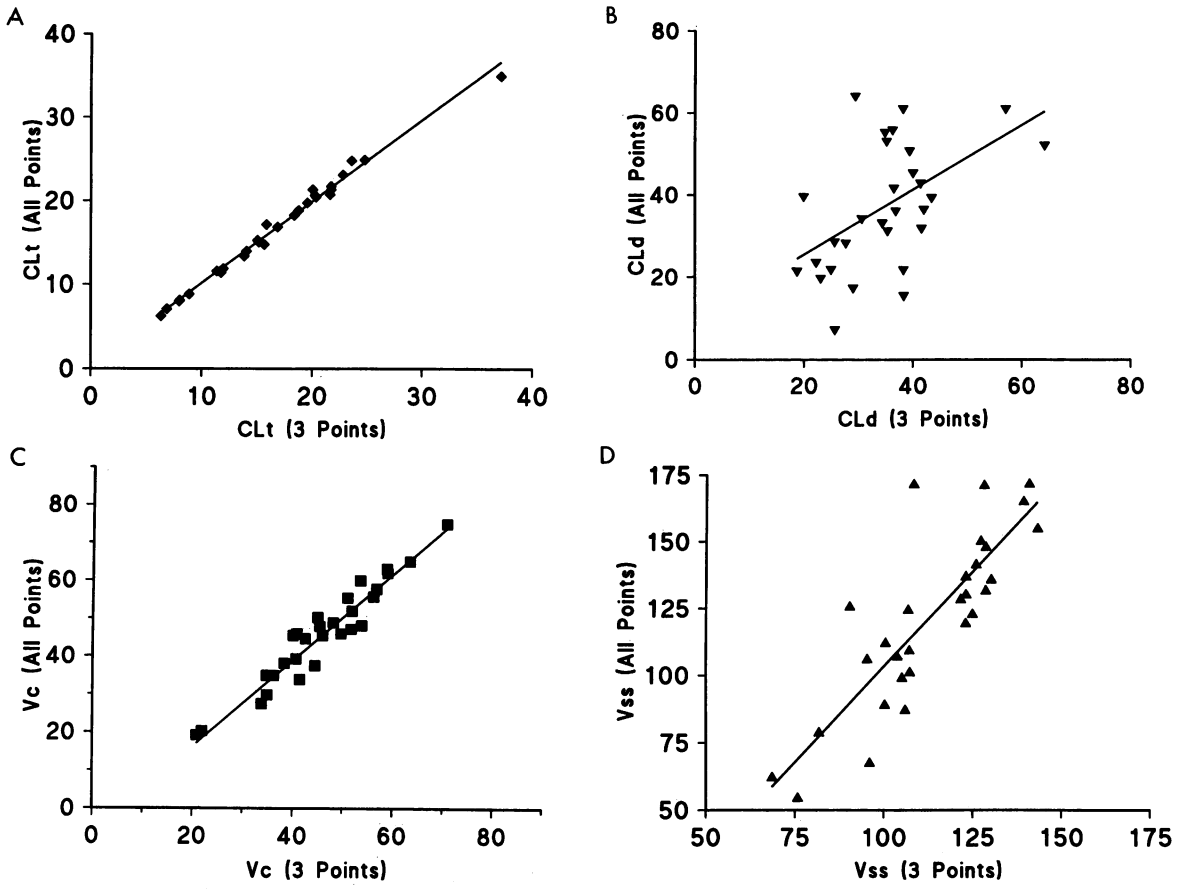

FIG. 5. Pharmacokinetic parameter values based on all available data versus those estimated with three optimally timed samples (OSS3) for the 29 extensively sampled data sets. The diagonals are the lines of best fit which did not differ from the line of identity for any parameter. For panels A, B, C, and D, respectively, r is 0.99, 0.52, 0.96, and 0.84.

The diagonal is the line of best fit which was not different from the line of identity. The ME ± SD was −0.01 ± 0.3 μg/ml (unbiased), the MAE ± SD was 0.2 ± 0.2 μg/ml, and r was 0.96.

Another important measure of concordance between perceived (fitted) and actual plasma concentration profiles is shown in Fig. 7. For OSS2a, -3, -4, -5, and -6, the gold standard AUCs (determined from all available data for each patient) were regressed versus those estimated by using the sparse-data study designs. The OSS estimates of AUC were unbiased (data not shown), and Fig. 7 shows the effect of the number of observations (horizontal axis) versus two other measures of precision, the coefficient of determination (Fig. 7, r^2) and the sum of squared residuals (Fig. 7, SSR). As the number of points used went from 2 to 6, the sum of squared residuals went from 5.5 to 1.8 and the coefficient of determination went from 0.993 to 0.999.

TABLE 3. Ciprofloxacin parameter value estimates based on all available data and three optimal observations[a]

Parameter	Gold standard[b]	OSS3[c]	%ME	%MAE
CL_T (liters/h)	17 ± 6.6	17 ± 6.7	0.03 ± 3.0	2.0 ± 1.8
CL_D (liters/h)	37 ± 15	35 ± 10	11 ± 62	35 ± 52
V_1 (liters)	46 ± 13	46 ± 11	1.6 ± 9.9	7.7 ± 6.3
V_{SS} (liters)	121 ± 33	113 ± 20	−2.9 ± 17	13 ± 11

[a] Tabulated values are the means ± SDs.
[b] All available data.
[c] Three optimal observations.

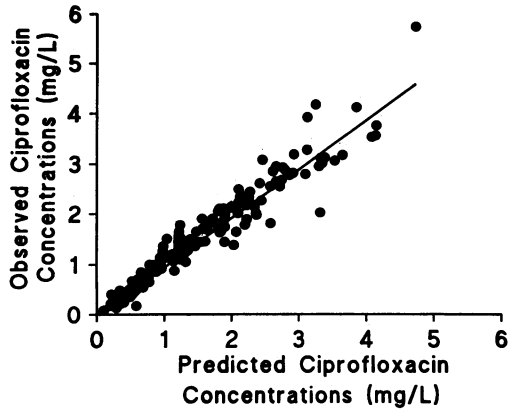

FIG. 6. Plasma drug concentrations (measured) versus values predicted by analysis of OSS3. The data represent the 168 samples from 29 patients which were not part of OSS3. The diagonal is the line of best fit which did not differ from the line of identity (r = 0.96).

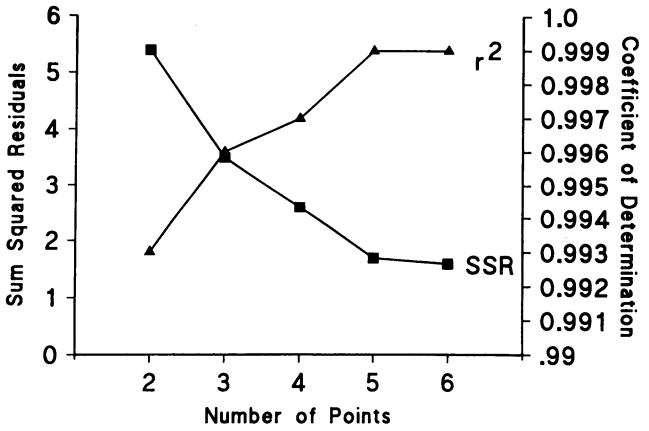

FIG. 7. The precision in estimation of AUC as a function of the number of optimally timed samples included in the analysis. Two measures of precision, the sum of squared residuals (SSR) and the coefficient of determination (r^2), are shown from plots of gold standard AUC versus OSS AUC. By both of these measures, it appears that little benefit is accrued beyond five samples.

DISCUSSION

Overall, the model and techniques used fit the ciprofloxacin plasma concentrations very well and parameter estimates were accurate and precise, even when only sparse data were available. Our subjects' mean V_β was 30% smaller and their CL_T was 44% smaller than those of stable volunteers matched by size and CL_{CR} and reported (9) by Drusano et al. (half-lives were similar). Also, the present population had a somewhat more variable and less predictable CL_T. Of these findings, the systematically smaller CL_T was the most important. Possible explanations, which should be pursued in subsequent trials, include an age effect beyond age-related loss of renal function, a consequence of infection, other concomitant drugs and/or diseases, and differences between ambulatory and bedridden patients, etc. Though age was not a significant predictor of pharmacokinetics in this analysis, too few young patients were available to adequately test this covariate. Other investigators have previously suggested this to be an important factor (16, 17, 19), but the study designs, analysis, and reporting of the data have been poor to date, and the question begs further study (26).

Interpatient variance in ciprofloxacin clearance was substantive (e.g., there was a 10-fold range in observed values). A relationship between CL_T and weight and CL_{CR} was developed, but only 30% of this variance was predictable by the resulting equation. This equation may be used, for similar patients, in an a priori dosing algorithm, and it should be an improvement over present guidelines (which were developed with stable volunteers and were shown to be biased with these patients). Application of current package insert dosing guidelines with these patients would have resulted in average steady-state concentrations ranging between 0.65 and 7.0 μg/ml ($\bar{x} \pm$ CV% = 1.9 μg/ml ± 53%). The use of a dosing algorithm developed from the derived equation should be more accurate (unbiased), but it would be predicted to only reduce the range of achieved concentrations from 11-fold to approximately 7-fold. This substantive and poorly predictable variance in CL_T suggests to us that adaptive feedback control (individual optimization based on measured plasma drug concentrations) may be warranted for patients with severe infections caused by bacteria for which the MICs were moderate to high (e.g., MIC ≥ 0.5 μg/ml). Further support for this contention may be found in the companion article on the population pharmacodynamics of ciprofloxacin (14).

Optimal data-sparse sampling strategies, employing two to six samples drawn during a single dose interval, have been developed for i.v. ciprofloxacin and are presented herein. Nearly optimal fixed strategies were developed with the same times for a study after the first dose or one at steady state. Even two well-timed samples (e.g., at 2.5 h post-i.v. and at trough or at 15 to 30 min post-i.v. and at trough) could probably be used effectively for adaptive feedback control. This degree of precision was accomplished despite substantive interpatient variability (e.g., CL_T varied 10-fold and V_{SS} varied 3.5-fold). Only estimates of CL_D showed poor agreement (unbiased but imprecise) between OSS3 and the gold standard (Fig. 5B). However, distributional characteristics are poorly identifiable, even by traditional sampling strategies, and the excellent accuracy and precision of CL_T estimates (Fig. 4 and 5A), AUC (Fig. 7), and plasma drug concentrations (Fig. 6) show this poor agreement to be of no practical importance. Additional samples improved the precision of parameter estimation and the prediction of plasma drug concentrations, but there appeared to be little benefit beyond five or six samples (Fig. 4 and 7). The most efficient (in information content per observation) of the strategies was OSS3 (a near-peak at 15 to 30 min, a sample at 2.5 h, and a trough). It performed quite well for individual parameter estimation, and it is the strategy we would recommend as part of an adaptive feedback control algorithm. For pharmacokinetic studies, especially with patients who might not be from a similar population, we would recommend OSS5 or OSS6.

Most of the available data on the pharmacokinetics of ciprofloxacin have been gathered with stable volunteers. Very little with sufficient detail to be useful has been published describing disposition in any target population, and the few exceptions (10, 33) have small numbers of subjects. Studies of larger size with these more pertinent populations are logistically difficult to accomplish. The usual approach to antibiotic development worldwide is to carefully characterize pharmacokinetics and to develop dosing guidelines with logistically simpler subjects (e.g., healthy volunteers and stable subjects with renal dysfunction) and to assume that patients' pharmacokinetics will be similar. It is very important that this assumption be verified, starting in phase III of drug development and continuing into the postapproval period.

This analysis provides a description of ciprofloxacin pharmacokinetics in acutely ill patients. Even after differences in renal function and body size were considered, ciprofloxacin disposition in this target population deviated significantly from that in volunteers. As traditional study designs are difficult to accomplish in large target population trials with critically ill patients, this article illustrates how some of the newer mathematical tools can facilitate pharmacokinetic-pharmacodynamic studies of complex target populations. These tools include IT2S population analysis, MAP-Bayesian parameter estimation, and OST. These results can now be used to develop pharmacodynamic relationships between drug exposure and the likelihood and rate of cure. The next step is to integrate these pharmacokinetic data with the pharmacodynamics of bacterial killing in vivo. This effort is the primary focus of the companion article (14).

APPENDIX

IT2S. The program that we have developed (13) for population analysis uses the IT2S algorithm, as first proposed by Prévost (24) and later described by Stiemer et al. (31). In brief, the program proceeds as follows. The user must derive an initial estimate of the population pharmacokinetic-pharmacodynamic model (the vector of parameter means, the population covariance matrix, and the model for residual variance in outputs). This could be obtained from the literature, by a standard two-stage approach (31) with the relatively complete data sets in the analysis to be performed or a pooled-data approach (31) with the current data set, or by other methods.

The initial population model is used to develop a MAP-B. We used the module developed by D'Argenio and Schumitzky, which they incorporated into the ADAPT (5) package of pharmacokinetic-pharmacodynamic software. The MAP-B is then used to fit each of the individual data sets and to provide for each set p_i (a vector of that subject's parameter estimates) and cov_i (a p-by-p lower-triangular, asymptotic covariance matrix for the ith data set, in which p is the number of fitted model parameters). This vector and matrix quantify the likelihood distribution of parameter estimates for the individual data set being modelled. For example, the diagonal elements of this covariance matrix are the squared standard errors of the parameter estimates.

The core of the IT2S algorithm is the combination of these individual results into a refined estimate of the population model. The vector of population parameter means (P) is updated by computing the arithmetic average of the individual parameter vectors, $\text{P} = n^{-1} \Sigma p_i$, where n is the number of data sets. The population covariance matrix (COV) is computed as a function of both the dispersion of the point estimates and the average of the individual covariance matrices. To accomplish this, two lower-triangular, p-by-p matrices are computed and then added. One of these matrices (COV_A) is the average of all of the individual covariance matrices obtained by MAP-B: $\text{COV}_\text{A} = n^{-1} \Sigma \text{cov}_i$. The other ($\text{COV}_\text{B}$) is a covariance matrix of the parameter point estimates. Across the study sample, the covariance of parameters 1 and 2 ($\text{cov}_{1,2}$) may be computed as $\text{cov}_{1,2} = r_{1,2} \cdot s_1 \cdot s_2$, in which $r_{1,2}$ is the correlation between parameters 1 and 2 and s_1 and s_2 are the SDs of the parameters. The updated estimate of the population covariance matrix is computed as $\text{COV} = \text{COV}_\text{A} + \text{COV}_\text{B}$.

These elements of the updated population model (P and COV) are incorporated into MAP-B, and all of the data sets are fit again. This process is continued until the population model stops changing. The program computes a maximum likelihood objective function for each iteration and when the relative absolute change in this function (between iterations) is less than 10^{-4}, convergence is achieved.

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