I read with interest the report by Lodise and colleagues on the penetration of meropenem into the epithelial lining fluid (ELF) of 17 patients with ventilator-associated pneumonia (VAP) (6). Briefly, they report a median penetration rate of meropenem into ELF of 25.4%, but Monte Carlo simulations predict an enormous variability (25th to 75th percentiles, 9.0 to 70.14%; 10th to 90th percentiles, 3.7 to 178%), which would leave many patients with insufficient drug exposure at the site of infection and thus possibly a poor clinical outcome.

Like the authors themselves, I am somewhat surprised by the huge magnitude of variability of ELF penetration reported in this study, which exceeds by far the variability in the cited studies on the ELF penetration of piperacillin (median, 42%; interquartile range [IQR], 32 to 63.5%), ertapenem (median, 32%; IQR, 28 to 46%), ceftazidime (mean ± standard deviation [SD], 20.6 ± 8.9%), and cefepime (mean concentration ± SD, 13.5 ± 3.3 mg/liter in plasma and 14.1 ± 2.8 mg/liter in ELF), all reported by Boselli et al. in patients with VAP or severe nosocomial pneumonia (1–4). Whereas it is of course possible that ELF penetration of meropenem is actually more variable, I suggest an explanation based on the macropharmakokinetic properties and the employed sampling strategy.

In the cases of piperacillin, ceftazidime, and cefepime, steady-state concentrations (CSS) were determined during continuous infusion. With this method, it is impossible to describe the time course of ELF penetration but very simple to determine the area under the concentration-time curve (AUC = steady-state concentration × time) and thus the total drug exposure. As for ertapenem, the half-life of about 8 h may still permit the assumption that simultaneous concentrations in serum and ELF are close to equilibrium and representative of total penetration.

In the present study, meropenem was given as an intermittent infusion (0.5 or 3 h) every 8 h. Given its short half-life (1 to 2 h), equilibrium between ELF and plasma is unlikely at any given time point, and only comparison of AUCs, as described by the authors, is valid. However, due to the practical limitations of ELF sampling, only one specimen was obtained per patient, and the full concentration-time course and AUC in ELF was estimated from this single concentration.

Despite the usefulness of contemporary modeling software, I feel that this overestimates the information content of the actual raw data, which basically are 17 paired plasma and ELF samples from a multicenter study, apparently designed for different primary endpoints. This approach is likely to introduce much methodological uncertainty, adding to the already important error due to the analytical problems involved in the determination of ELF concentration (5).

Therefore, I consider it likely that the variability derived from the Monte Carlo simulation overestimates the true inter-individual variability, but this is no purely academic question. The answer could decide whether or not meropenem monotherapy for VAP is a rationale choice, and this calls for a more robust data basis from custom-tailed clinical trials. Emphasis should be put on an optimized dosing and sampling strategy, which may include continuous infusion, or analytical techniques allowing for serial measurements, e.g., intrapulmonary microdialysis.
typically low. Thus, it is difficult to fully quantify the interpatient variability in exposure profiles one would expect to observe in clinical practice from the typical pharmacokinetic study. In truth, the real concentration-time profile distributions observed in clinical practice have long tails. These drugs are used thousands of times per year, not 20 or 100 times per year. Monte Carlo simulation is used to evaluate the impact of the greater number of subjects on the concentration-time profile likely to be observed in clinical practice. In short, Monte Carlo simulation characterizes the full dispersion or spread of concentration-time exposure values (e.g., peak concentration, area under the curve) that would be seen in a large population after administration of a specific drug dose or regimen. This includes characterizing both the central tendencies in a concentration-time profile and outliers (patients with time-time exposure profiles $\neq$ standard deviations from the mean). It allows one to see the outliers in the far tails of the distribution and precisely assess if they have any impact on the likelihood of target attainment when using a fixed dose and schedule (3).

To illustrate the influence of sample size on the distribution of concentration-time profiles observed, we decided to examine data from one of the Boselli papers cited by Kees (2). We chose to examine the piperacillin-tazobactam paper, because the primary data were available. For the 20 patients with no or mild renal impairment, we averaged the three piperacillin plasma data and took the ratio of ELF to average piperacillin plasma concentration as the index of ELF penetration. The mean ± standard deviation of piperacillin ELF penetration was 0.468 ± 0.195. We employed these values to construct a number of Monte Carlo simulations. In the first set, we employed the same seed number and varied the number of iterates from a population size of 20 through a population size of 9,999. The intent of this was to demonstrate the impact of going from a small population ($n = 20$ subjects) to a large one ($n = 9,999$ subjects) on the observed distribution of concentration-time profiles. In the second set, we froze the number of iterates at 20 and employed a different seed number for each simulation, which we performed 10 times. The intent of this was to show the effect of a finite study size sampling on the observed results. In particular, we were interested in assessing the reliability of the means and standard deviations as well as minimal and maximal values from relatively small pharmacokinetic trials in reflecting the true outcome. In this case, we considered the observed piperacillin ELF penetration results (mean ± standard deviation = 0.468 ± 0.195) from the 20-subject pharmacokinetic study from Boselli et al. as the truth.

Results of the Monte Carlo simulations employing a log-normal distribution with sample sizes ranging from 20 to 9,999 subjects are shown in Table 1. As the number of iterates increases, the likelihood of sampling from the tails of the true distribution increases. This was reflected in the larger standard deviations and the spread of minimum and maximum values for the higher-number simulations. Please note that the minimum value observed goes from a penetration ratio of 0.714 to 1.970 as the number goes from 20 to 9,999 subjects. There, however, is much less impact on the minimum value observed. Over the range of 20 to 1,000 simulated subjects, the minimum value declines only by 25%. Only at 9,999 simulated subjects do we see a major decrease. This is because a log-normal distribution was employed, which is bounded from below at zero but is not bounded from above. This is why the simulated sample size has a greater impact on the maximum value observed than on the minimum value.

Results of the 20-subject Monte Carlo simulations with a different seed number for each simulation are shown in Table 2. Here, we see that the means range from 0.419 to 0.517, the standard deviations range from 0.128 to 0.217, and the minimal and maximal values range from 0.156 to 0.294 and 0.714 to 1.133, respectively. Clearly, there is a very large uncertainty about these values when the sample size is 20 patients. Please note that we did only 10 replicates. Had we performed more simulations, the range would be even greater.

Why do we perform Monte Carlo simulation? We can answer only for ourselves. Even the best clinical trial efforts seldom produce robust numbers for pharmacokinetics and pharmacodynamics. When we look at the adequacy of a proposed dose and schedule, it is important, as we stated above, to recognize that in clinical practice, thousands of patients will be treated, and some will come from parts of the distribution $\neq$ standard deviations above and below the mean. These patients exist. All one needs to do to recognize the importance of examining the tails of the distributions is examine the impact of the hyperdynamic state on drug clearance in ventilator-associated pneumonia (VAP) patients and the consequent much lower drug exposures which result in a markedly increased likelihood of failure (1). This type of analysis is necessary and important for looking at getting the dose and schedule correct for seriously ill patients, like those with VAP. We hope this response clarifies the need for Monte Carlo simulations in putting pharmacokinetic and pharmacodynamic data generated from finite pharmacokinetic studies into proper perspective.
REFERENCES


