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Relationships between Antimicrobial Effect and Area under the Concentration-Time Curve as a Basis for Comparison of Modes of Antibiotic Administration: Meropenem Bolus Injections versus Continuous Infusions

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In comparative studies of different modes of administration (MAs) simulated in in vitro dynamic models, only one dose of antibiotic is usually mimicked. Such an experimental design can provide a prediction of the antimicrobial effect (AME) of a given combination of drug, clinical isolate, and infection site, but may be inappropriate for accurate comparison of MAs. An alternative design providing comparison of different MAs with various antibiotic doses in a wide range and with evaluation of the respective relationships between AME and the AUC was proposed and examined. Two series of meropenem pharmacokinetic profiles, i.e., monoexponentially decreasing concentrations (bolus doses) and constant concentrations (6-h continuous infusion), were in vitro simulated. The simulated initial concentrations (C_0 [from 0.062 to 48 μg/ml]) and steady-state concentrations (C_{ss} [from 0.016 to 8 μg/ml]) were chosen to provide similar AUC for 0 to 6 h (AUC_{0-6}) ranges for both MAs (from 0.070 to 50.0 μg · h/ml and from 0.09 to 48.0 μg · h/ml, respectively). The AME of meropenem on *Staphylococcus aureus* ATCC 25923 (MIC, 0.063 μg/ml) was determined at each time (t) point as a difference (E) between the logarithms of viable counts (N) in the control cultures without antibiotic (N_C) and in cultures exposed to antibiotics (N_A). Time courses of E observed at different C_0 or C_{ss} levels were compared in terms of the areas under the E-t curves ($ABBC_t$). The finite values of the $ABBC_t$ observed by the end of the 6-h observation period, which are equivalent to the area between bacterial count-time curves observed in the absence and presence of antibiotic (ABBC), were plotted versus the respective AUCs produced by each of the MAs. The ABBC versus AUC curves had a similar pattern: a plateau achieved at high AUCs followed by a steep rise in ABBC at relatively low AUCs was inherent in both of the MAs. The superiority of bolus dosing over the infusions could be documented only for meropenem concentrations below the MIC. At higher C_0 or C_{ss} (i.e., at an AUC of ≥0.4 μg · h/ml), the ABBC versus AUC curves plotted for each of the MAs could practically be superimposed. On the whole, both MAs appeared to be equiefficient in terms of the ABBC. These results suggest that AUC analysis of the AME may be a useful tool for comparing different MAs. Such comparative studies should be designed in a manner that provides the use of similar AUC ranges, since the AUC may be considered as a common pharmacokinetic denominator in comparing one MA or dosing regimen to another.

Comparative evaluation of different modes or regimens of antibiotic administration is one of the important aims to be reached by the use of in vitro dynamic models. Such models have already been applied to compare the efficacy of bolus administration and continuous infusion of ceftazidime (3), gentamicin (12, 21), sisomicin (7, 10), and vancomycin (5); as well as different dosing regimens of ampicillin (27); piperacillin alone and in combination with tazobactam (26); ceftazidime (3, 23); imipenem alone (17, 20, 22) and in combination with amikacin (20); and amikacin alone and in combination with imipenem (20), vancomycin (5), and ciprofloxacin (18). In most of these studies, pharmacokinetic profiles were simulated to mimic those observed in humans after drug administration at the same daily dose, typically the average therapeutic dose, or in a narrow dose range. Being completely reasonable in terms of predicting the therapeutic outcome for a given triad of drug, clinical isolate, and infection site, such an approach may be inappropriate to predict the effect at other dose levels. Moreover, this approach is not adequate for accurate comparison of dosing regimens, if the effects documented are close to either minimum or maximum values, because under those circumstances, equiefficient doses or concentrations cannot be established (8).

These shortcomings, inherent in any experimental design mimicking only one dose or two or three doses that varied within a narrow range, may be overcome if different modes of administration or dosing regimens are examined within a wide range of doses or concentrations. It makes it possible to establish the concentration-effect relationship for each mode or regimen and to compare them in terms of these relationships. In fact, the antimicrobial effect may be related not so much to the concentration as it is, but more to the area under the concentration-time curve (AUC), since the final effect depends both on drug concentration and exposure time (6). AUC analysis of the antimicrobial effect has been used to compare the efficacy of short- and long-term infusions of sisomicin in a dynamic model in vitro simulating exponentially decreasing concentrations followed by a rise in the initial concentration (7,

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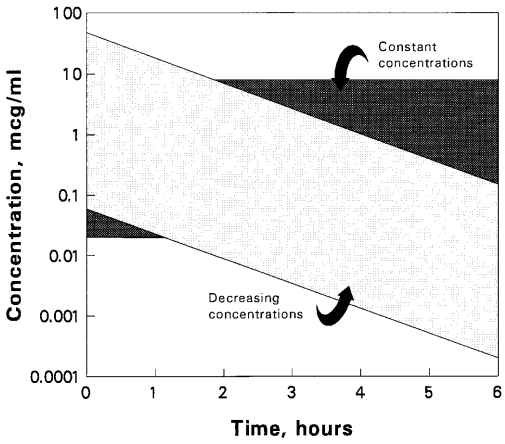

FIG. 1. In vitro-simulated pharmacokinetic profiles of meropenem.

10). A distinct dependence of aminoglycoside effect against *Escherichia coli* on the AUC was seen, without reaching a maximum, even at a very high AUC, and a multiphase shape of the effect-log AUC curves has been reported.

In the present study, the same approach was applied to compare two modes of meropenem administration, i.e., a bolus administration and a continuous infusion, in terms of the relationship between the antimicrobial effect on *Staphylococcus aureus* and the AUC. Meropenem was chosen as an antibiotic having a saturable effect on some bacteria, including *Staphylococcus aureus* (2).

MATERIALS AND METHODS

Antibiotic and bacterial strain. Meropenem, kindly supplied by Zeneca Pharmaceuticals (ICI), was used in the study. Stock solutions of meropenem were prepared freshly in phosphate-buffered saline (pH 7.5). One strain of *Staphylococcus aureus*, ATCC 25923, was used. The MIC determined in brain heart infusion (BHI) broth (Oxoid, Basingstoke, United Kingdom) at an inoculum size of 5×10^5 CFU/ml was 0.063 μg/ml. Samples withdrawn from 18-h cultures were stored at −70°C.

Simulated pharmacokinetic profiles. Two series of meropenem pharmacokinetic profiles, i.e., monoexponentially decreasing concentrations (bolus doses) and constant concentrations (6-h continuous infusion), were in vitro simulated. The respective initial concentrations (C_0 [from 0.062 to 48 μg/ml]) and steady-state concentrations (C_{ss} [from 0.016 to 8 μg/ml]) were varied in wide ranges (Fig. 1), in order to provide similar AUC from 0 to 6 h (AUC_{0-6}) ranges for both series (from 0.070 to 50.0 μg · h/ml for decreasing concentrations and from 0.09 to 48.0 μg · h/ml for constant concentrations). Pharmacokinetic parameters of meropenem in humans to be used for the in vitro simulations were taken from the literature (1, 4, 13, 15, 24).

In vitro dynamic model and operating procedure. An in vitro dynamic model described previously (22) was used in the study. Briefly, the model was represented by two connected flasks, one of them with fresh BHI broth and another one, the central unit, with the broth containing only a bacterial culture (control growth experiments) or bacterial culture plus antibiotic (killing and regrowth experiments). The central unit was incubated at 37°C in a shaking waterbath. Peristaltic pumps (Peristaltic 2000; Verder, Vleuten, The Netherlands) circulated fresh nutrient medium to the bacteria or bacterium-antibiotic-containing medium from the central 50-ml unit at a flow rate of 48 ml/h. Hence, the clearance provided by the chosen flow rate together with the volume of the central unit ensured exponential elimination of bacteria and the antibiotic from the system at an elimination rate constant of 0.955 h^{-1}. Accurate simulations of the desired pharmacokinetic profiles were provided by maintaining a constant volume of the central unit and a constant flow rate. The volume and the flow rates were proved to be constant during each of the experiments.

The system was filled with sterile BHI broth and placed in an incubator with a thermostat set at 37°C. The central unit was inoculated with an 18-h culture of *Staphylococcus aureus* before the antibiotic was added, and the resulting exponentially growing cultures approximated 5×10^5 CFU/ml. When constant concentrations were simulated, meropenem was added both to the flask with the fresh medium and to the central unit. When the exponentially decreasing concentrations were simulated, the antibiotic was added to the central unit only.

Bioassay of meropenem. To validate the in vitro model, meropenem concentrations in the central unit were determined in triplicate by an agar-plate diffusion technique (19), with Difco nutrient agar seeded with *Escherichia coli* NIHJ as the test organism. The lower limit of sensitivity was 0.013 μg/ml. Standard concentrations were prepared daily in 0.05 M phosphate buffer (pH 7.0). Best fit standard curves were obtained by linear regression analysis. The linearity between zone diameters and logarithms of meropenem concentration was observed within the range 0.125 and 32 μg/ml. The coefficients of variation ranged from 5 to 10%.

The measured concentrations of meropenem were close to the designed values, with no systematic deviation from expected values (data not shown).

Quantitation of bacterial growth and killing. In each experiment, 0.1-ml samples were withdrawn from the central unit 15 times during a 6-h observation period. These samples were diluted with phosphate-buffered saline and plated on DST agar (Oxoid Ltd., London, United Kingdom). Antibiotic carryover at low counts was avoided by washing the bacteria. After overnight incubation at 37°C, bacterial colonies were counted, and the numbers of CFU per milliliter were calculated (16). The experiments with each simulated pharmacokinetic profile were performed in duplicate or triplicate. The limit of detection was 2×10^2 CFU/ml.

Quantitative evaluation of the antimicrobial effect. The antimicrobial effect was defined as a difference (E) between the logarithms of viable counts (N) in the control cultures without antibiotic (N_C) and those of cultures exposed to antibiotics (N_A) or as a logarithm of the N_C/N_A ratio (9):

$$E = \log N_C/N_A = \log N_C - \log N_A$$

Time (t) courses of E observed at different C_0 or C_{ss} levels were compared in terms of the areas under the E-t curves, which are equivalent to the areas between bacterial count-time curves observed in the absence and presence of antibiotic within the ranges from point zero up to different sampling times ($ABBC_t$). The highest (finite) values of the $ABBC_t$ observed by the end of the observation period (t = 6 h) are equivalent to the ABBC, the parameter described recently (11). The values of $ABBC_t$ and ABBC were calculated by trapezoidal rule. The respective values of the AUC (AUC_{0-6}) of meropenem were calculated analytically with the pharmacokinetic parameters.

RESULTS

Time-kill curves of *Staphylococcus aureus* exposed to exponentially decreasing or constant concentrations of meropenem are shown in Fig. 2 (to avoid overloading the figure with crossed and/or juxtaposed curves, only selected data are presented), and the respective time courses of the antimicrobial effect expressed as $E = \log N_C - \log N_A$ are presented in Fig. 3 (to avoid overloading the figure with crossed and/or juxtaposed curves, only selected data are presented). As seen in Fig. 3, regardless of the simulated profiles or mimicked modes of meropenem administration, the E-t curves had a similar pattern: typically there were very weak, if any, changes followed by a pronounced increase of the effect during the first 1 to 2 h. Moreover, for both types of the pharmacokinetic profiles, a concentration (C_0 or C_{ss})-dependent increase in the effect could be established for only a small portion of the C_0 and C_{ss} ranges (from 0.06 to 1.00 μg/ml and from 0.02 to 0.25 μg/ml, respectively). No further increase in E occurred at higher C_0 and C_{ss}. Similar conclusions can be made by comparing the more smooth time courses of the integrative estimates of the effect, i.e., areas under the E-t curves (Fig. 4 [to avoid overloading the figure with crossed and/or juxtaposed curves, only selected data are presented]). Again, systematically increased effects expressed as $ABBC_t$ were observed within relatively small ranges of C_0 or C_{ss}, whereas a further increase in C_0 or C_{ss} was not accompanied by the respective enhancement of the effect.

Since the antimicrobial effect at any time depends not only on the antibiotic concentration but also on the exposure time, for comparison of the efficacy of the two modes of meropenem administration, the finite, time-independent values of $ABBC_t$ (i.e., those observed at t = 6 h) were used. These values, which are equivalent to the total area between bacterial count-time curves observed in the absence and presence of antibiotic (ABBC [11]), were related not to meropenem concentrations but to the AUC within the same time range.

As seen in Fig. 5, the increase in ABBC was associated with

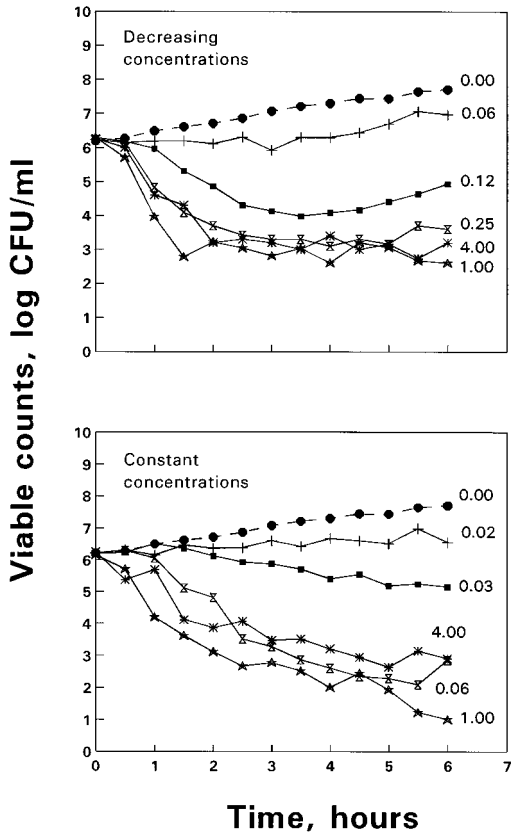

FIG. 2. Meropenem-induced killing curves of *S. aureus* exposed to exponentially decreasing and constant concentrations of the antibiotic. The simulated values of C_0 and C_{ss} (in micrograms per milliliter) are specified in each case.

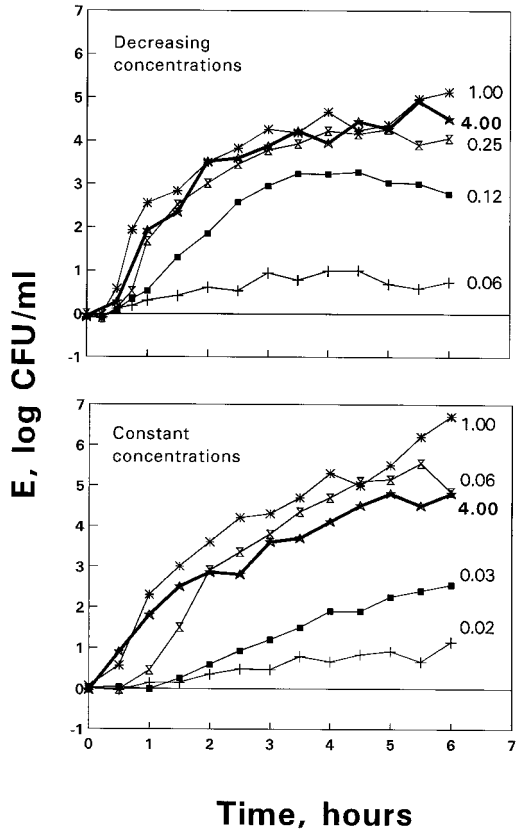

FIG. 3. Time courses of the antimicrobial effect of meropenem, expressed as a difference (E) between logarithms of viable counts in the absence and in the presence of the antibiotic. The bold line represents a less-pronounced effect than that of the preceding lower concentration. For other explanations, see the legend to Fig. 2.

the respective changes in AUC for a relatively small range of low values of AUC: there was no further increase of ABBC at high AUCs. Moreover, the ABBC versus AUC curves plotted for each of the modes of meropenem administration could be practically superimposed at an AUC of $\geq$0.4 $\mu g \cdot h/ml$, when minimum changes in ABBC occurred (AUC-independent portions of the curves). For example, at an AUC of 15 $\mu g \cdot h/ml$, which corresponds to the minimum dose of meropenem used clinically (250 mg) (4), the values of ABBC for bolus administration and continuous infusion were almost equal: 21.5 and 22.0 log CFU/ml) · h, respectively. As for still lower AUCs, the effect of bolus administration was definitely superior to that of the infusions. For example, at an AUC of 0.2 $\mu g \cdot h/ml$, a more than 1.5-fold difference was found between the respective ABBC values for two modes of meropenem administration. On the other hand, the antimicrobial effect expressed as half of the maximum ABBC was achieved at $\approx$2-fold lower AUC after bolus administration than that after continuous infusion of meropenem (Fig. 5). A very weak and hardly remarkable trend toward a decrease in the ABBC at two highest AUCs was established with mimicking of meropenem infusions but not with bolus dosing.

DISCUSSION

The antimicrobial effect of antibiotics administered by different modes may be better related to the AUC than to the drug concentration at any time (7). AUC analysis of the antimicrobial effect has been successfully applied to compare the efficacies of such treatments as short- and long-term infusions of sisomicin in an in vitro dynamic model (7, 10), different dosing regimens of ampicillin (27), and use of cefuroxime against different bacteria (25) in addition to others. In the present study, the AUC analysis was used to compare bolus administration with continuous infusions of meropenem.

Series of monoexponential pharmacokinetic profiles with the same half-life but with different C_0 and various C_{ss} of meropenem were in vitro simulated in a dynamic model. As described earlier (9), the antimicrobial effect (E) at every t after the antibiotic had been added to exponentially growing cultures of *Staphylococcus aureus* was defined as the difference between the Logarithms of N_C and N_A. The finite values of the area under the E-t curves, $ABBC_t$, observed at the end of the observation period (i.e. ABBC [11]) were compared to the respective values of AUC. As a result, a specific relationship between ABBC and AUC was established for each of the modes of meropenem administration. The ABBC versus AUC curves were of similar shape: a plateau achieved at high AUCs, followed by the steep rise in ABBC at relatively low AUCs, was inherent in both the modes.

Being practically superimposed within the AUC-independent range (at an AUC of $\geq$0.4 $\mu g \cdot h/ml$), these curves were shifted at lower AUCs: higher ABBCs were associated with bolus dosing of meropenem. These differences are quite predictable, since continuous infusions yielding AUCs lower than 0.4 $\mu g \cdot h/ml$ correspond to meropenem concentrations lower than the MIC (C_{ss} of $<$0.063 $\mu g/ml$), whereas the bolus doses

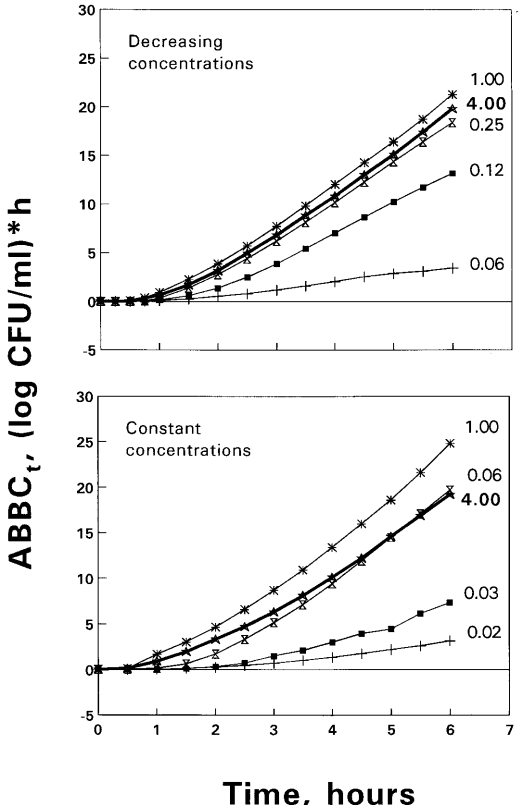

FIG. 4. Integral presentation of the data shown in Fig. 3. Time courses of the areas under the *E-t* curves (ABBC$_t$) are shown. For other explanations, see the legends to Fig. 2 and 3.

provide concentrations threater than or equal to the MIC. In fact, the superiority of bolus dosing over the infusions may be valuable only for meropenem concentrations below the MIC. On the whole, both modes of meropenem administration appeared to be equiefficient in terms of the ABBC. In other words, regardless of the mode of administration, similar effects would be produced by a given AUC (or dose of meropenem

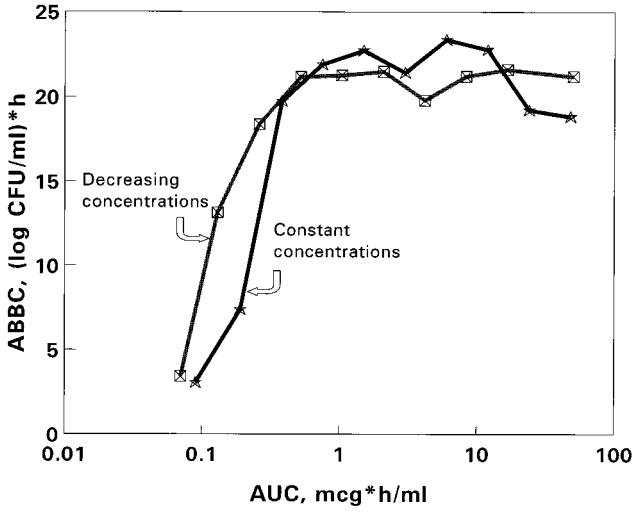

FIG. 5. AUC-dependent changes in the ABBC observed with exponentially decreasing and constant concentrations of meropenem.

because AUC is directly proportional to the dose) but, of course, not by actual concentrations, since a given concentration at a given time after drug bolus administration cannot be directly compared to a constant concentration maintained by continuous infusion. From this point of view, comparative studies should be designed in a manner that provides the use of similar AUC ranges, and not concentration ranges, for each mode or regimen of drug administration. In this respect, the AUC may be considered as a common pharmacokinetic denominator in comparing one mode or regimen of administration to another. Recently, this principle of experimental design was used to compare different modes of administration of meropenem (14) and gentamicin (21) and different dosing regimens of vancomycin (5) in in vitro dynamic models.

The conclusion about identical efficacies of meropenem at decreasing and constant concentrations may be applied for the treatment of systemic infections induced by meropenem-sensitive strains of *Staphylococcus aureus*. However, if a clinical isolate is not so sensitive and/or the site of infection is not in systemic circulation, as simulated in our in vitro study, but in peripheral tissues, which differ from plasma pharmacokinetically, the two modes of meropenem administration may or may not be equally efficient. For example, because of relatively slow tissue penetration, peak concentrations of many drugs in tissue are often lower than those in plasma. The tissue drug concentrations observed after drug infusion may be critically small and insufficient to provide a stable effect, whereas those achieved after the same bolus dose may not be. In that case, unlike in our study, the mode-induced differences inherent in the ABBC versus AUC curves at low AUCs may become decisive. Similar considerations occur when the AUC-independent effect of meropenem at high AUCs is interpreted. Again, depending on the MIC and tissue availability, the usual clinical dose of meropenem given as a bolus or continuous infusion may or may not provide the AUC in peripheral tissue within the range in which the antimicrobial effect is AUC independent.

The reservations presented above might be interpreted as restrictions inherent in in vitro dynamic models as an approach to an optimal design of antibiotic dosing. In fact, these reservations have been made to avoid inappropriate interpretation of the findings obtained: these restrictions can be overcome if the experiments are performed with in vitro simulation of the respective pharmacokinetic profiles. Moreover, any profiles can be simulated and any bacteria may be tested in dynamic models. Hence, to predict meropenem efficacy in infections of peripheral tissues or against less-sensitive microorganisms, further studies are necessary. The rationales for designing such studies and interpreting the results are given by our results.

Overall, these results suggest that AUC analysis of the antimicrobial effect is a useful tool to compare different modes and regimens of antibiotic administration.

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