Pharmacokinetics in vivo and pharmacodynamics ex vivo/in vitro of meropenem and cefpirome in the Yucatan micropig model: continuous infusion versus intermittent injection

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Objective: To investigate the pharmacodynamic disposition of two recently developed β-lactam antibiotics, meropenem and cefpirome, in the Yucatan micropig model, and to compare the bactericidal activity of these drugs against bacteria in this in vitro/ex vivo micropig model after administration by both intermittent injection and continuous infusion.

Methods: Cefpirome (1 g) was given to the micropig over a 12-h period by direct intravenous injection and 6-h continuous infusion (500 mg). Meropenem (250 mg) was administered either by 30-min intravenous and 8-h continuous infusion. The two drugs were assayed by HPLC. The pharmacodynamics of these drugs were evaluated by means of (1) serum killing curve against *Klebsiella pneumoniae* producing extended-spectrum β-lactamase, stably derepressed *Enterobacter cloacae* and methicillin-susceptible penicillinase-producing *Staphylococcus aureus*, and (2) calculations of index of surviving bacteria (ISB).

Results: The bactericidal activity of meropenem against *K. pneumoniae* and *E. cloacae* in this in vitro/ex vivo model was excellent, with a 4 log decrease at peak concentrations. Meropenem produced a mixed concentration- and time-dependent, killing effect against *E. cloacae* and *K. pneumoniae*. The ISB value ranged from 25% to 30% for *E. cloacae*. With concentrations above MIC for *S. aureus* (1 mg/L), cefpirome has a time-dependent bactericidal activity, as shown by the ISB ranging from 20% to 80% after 4 h and between 20% and 40% after an 8-h drug exposure. For both antibiotics, the higher concentrations obtained just after intermittent injection had a rapid and strong killing effect against the strains tested, but the trough levels had no bactericidal activity. The continuous infusions produce consistent concentrations of antibiotic that can be maintained above the MIC, and the bactericidal activity of which ranges from 2 to 4 $\log_{10}$ decrease of inoculum.

Conclusions: In the present study the micropig has been shown to be an adequate model for the pharmacodynamic investigation of cefpirome and meropenem. In general, continuous infusion appears to optimize the pharmacodynamic profile of the two tested β-lactam antibiotics. However, against Gram-negative bacilli, the administration of a loading dose prior to continuous infusion of β-lactams would eliminate the only potential pharmacokinetic disadvantage of continuous infusion and ensure the rapid onset of antimicrobial activity.

Key words: Meropenem, cefpirome, micropig, pharmacokinetic, pharmacodynamic, intermittent injection, continuous infusion

INTRODUCTION

Many antimicrobial β-lactams have been recently developed for clinical use, including a new carbapenem (meropenem) and an extended-spectrum cephalosporin (cefpirome). Meropenem is highly resistant to the hydrolytic activity of plasmid-mediated extended-spectrum β-lactamases (ESBLs) and highly stable to class C β-lactamases (chromosomal cephalosporinases) [1,2]. It differs from the currently available member of this class, imipenem–cilastatin, by having a 1β-methyl substitution which improves stability to renal dehydropeptidase-I [3]. Cefpirome is a semisynthetic

cephalosporin with a broad spectrum of antimicrobial activity. In comparison with third-generation cephalosporins, cefpirome demonstrates increased in-vitro activity against *Staphylococcus*, *Enterococcus* and *Enterobacter* spp. [4]. Cefpirome has been reported to have good β-lactamase stability combined with rapid penetration of the outer membrane [5]. The optimal dosing regimen for an antimicrobial agent is dependent on both the pharmacokinetics and pharmacodynamics of the drug. Continuous infusion of β-lactams has been advocated for years as an alternative method of administration on the basis of their pharmacodynamics [6–8]. The time during which the drug concentrations exceed the MIC is thought to be the major determinant of efficacy with β-lactam antibiotics. Most β-lactam antibiotics exhibit these pharmacodynamic characteristics particularly with Gram-negative bacilli [6,9]. The aim of this study was (1) to validate the Yucatan micropig as a reliable model for pharmacokinetic investigation of meropenem and cefpirome, and (2) to compare the serum killing curves in an ex-vivo/in-vitro micropig model of two cefpirome and meropenem regimens administered by continuous infusion and by intermittent injection.

ANIMALS AND METHODS

Animals

Three adult female Yucatan micropigs were included in each group. They ranged from 26 to 39 kg. The pigs were anesthetized and a polyurethane catheter (60 cm×2 mm) was surgically placed in the external jugular vein for blood collection. The details of catheter maintenance are described in our previous reports [10].

Drugs assay

Meropenem and cefpirome concentrations in serum were determined by an HPLC technique as previously described [11,12]. Briefly, serum (500 μL) was deproteinized with 500 μL of acetonitrile in a 5-mL screw-capped glass tube on a vortex mixer. The tube was gently shaken by rotation (20 rev/min) and then centrifuged for 10 min at 1000g. The supernatant was transferred to another screw-capped glass tube and 3.2 mL of methylene chloride was added. After rotation (20 rev/min) for 10 min and centrifugation at 1000g for 10 min, 5- and 20-μL aliquots, respectively, of the upper aqueous layer were injected into the apparatus for meropenem and cefpirome assay.

Study design

The injection of the antibiotics into micropigs was performed through a winged infusion set introduced

into an ear vein. On the basis of the mean weight of the animals (35 kg, i.e. roughly half the weight of a human), the administered doses were half of those commonly used in clinical practice. Cefpirome was given by direct intravenous injection (1 g) and 6-h continuous infusion (500 mg). Blood samples were drawn via the jugular catheter before administration and at 1 min, 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h after bolus injection. For continuous infusion, blood samples were obtained before infusion and at 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h and 6 h after the beginning of administration. Meropenem (250 mg) was given by 30-min short and 8-h continuous infusion. For 30-min short infusion, the blood samples were drawn before administration and at 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h and 8 h. With administration by continuous infusion, the scheme for blood sampling was slightly different: before administration and at 15 min, 30 min, 1 h, 1.5 h, 2 h and each hour afterwards until 8 h. For continuous infusion, cefpirome (500 mg) and meropenem (250 mg) were diluted in sodium chloride (0.9%); packaged in a 50-mL syringe, and infused constantly with an infusion pump over 6 h for cefpirome and over 8 h for meropenem.

Pharmacokinetic analysis

Standard kinetic parameters were determined [13]. The peak serum levels (C_{max}), residual serum concentrations (C_{min}) and steady-state concentrations (C_{ss}) were obtained by direct observation of the individual kinetic profiles. The area under the serum concentrations–time curves (AUC) was calculated using the trapezoidal rule and included all experimental data points. The terminal half-life was estimated by linear regression analysis using computerized Software (Siphar, Simed, France). Total body clearance was calculated as being the given dose divided by the AUC and was normalized to body weight. In the case of continuous infusion, the clearance was calculated as being the drug infusion rate (mg/min) divided by the steady-state concentration and was normalized to body weight. Results are given as mean (±standard deviation).

Test bacteria

The pharmacodynamics of both drugs, whichever the mode of administration, as well as the kinetics of bactericidal activity of animal serum were investigated using fresh clinical isolates of methicillin-susceptible penicillinase-producing *Staphylococcus aureus*, ESBL-producing *Klebsiella pneumoniae* and stably derepressed *Enterobacter cloacae* producing a high-level cephalosporinase.

MIC and MBC determination

Minimum inhibitory concentrations (MICs) were determined by serial macrodilution in Mueller-Hinton (MH) broth, with dilutions ranging from 256 mg/L to 0.125 mg/L. The inoculum was prepared from an overnight culture suitably diluted to obtain 10^6-10^7 CFU/mL. Inoculated plates (MH agar) for minimum bactericidal concentration (MBCs) determination were read after overnight incubation. An MBC was defined as the lowest concentration leaving only 0.01% surviving bacteria.

Pharmacodynamic analysis

Each serum sample was diluted from 1/2 to 1/256 in MH broth plus 5% bovine serum albumin and was inoculated with a suspension of the test strains. The starting inoculum consisted of an overnight culture appropriately diluted to give 10^6-10^7 CFU/mL. The bacteria were used in the stationary phase. At fixed intervals h_0, h_2, h_4 and h_6 (except for S. aureus, for which counts were performed over 8 h) a sample of the culture was taken and serially diluted (10-fold) in saline. The 'carryover' phenomenon was thus avoided by using this dilution technique. Each dilution was then seeded on an MH medium using a spiral system. After overnight incubation at 37°C, the colonies, corresponding to the surviving organisms, were automatically counted using a 'Scan 500' camera system (Intersciences, France).

Expression of results

For each dilution of each micropig serum sample, the surviving bacteria, expressed on a log_{10} scale, were plotted against duration of incubation (from 0 to 6 or 8 h). Thus, for each dilution, a curve of number of CFU per mL versus time was obtained, the area under which could be calculated using a simple trapezoidal rule. The calculated ratio of this experimental AUC to the starting inoculum AUC (equivalent to starting inoculum multiplied by the duration of incubation, 6

or 8 h) was considered as the index of surviving bacteria (ISB), expressed as a percentage of starting inoculum. Thus, the lower the ISB, the higher the bactericidal activity of the corresponding dilution. A 10^2 CFU/mL value was considered as the limit of detection of the counting method.

For each dilution of each serum, an ISB was calculated. As an antibiotic concentration corresponded to each dilution (i.e. the concentration measured in the sampled serum divided by the factor of dilution), we could plot the ISB value against the antibiotic concentrations to demonstrate the mode of killing of both antibiotics.

RESULTS

Susceptibility results as determined by an end-point method

The MICs of meropenem were 0.25 and 0.5 mg/L for ESBL-producing K. pneumoniae and stably derepressed E. cloacae, respectively. The MICs and MBCs were similar for those strains. Both MICs and MBCs of cefpirome for methicillin-susceptible, penicillinase-producing S. aureus were 1 mg/L, and they were 64 and 128 mg/L, respectively, for E. cloacae.

Pharmacokinetic and pharmacodynamic parameters

The pertinent pharmacokinetic parameters of meropenem and cefpirome for both dosing regimens are given in Tables 1 and 2, together with a comparison with human values.
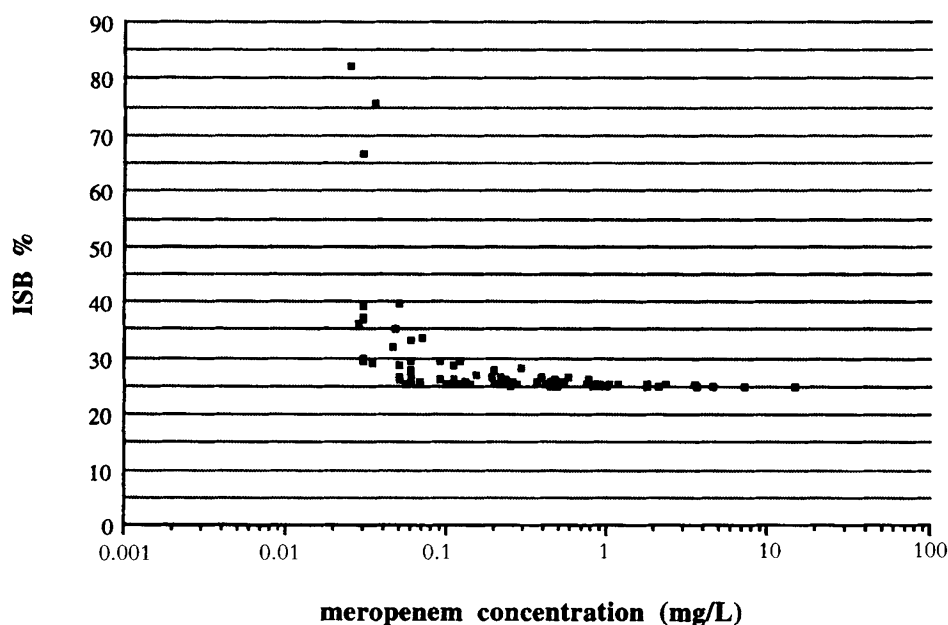
Meropenem

At meropenem concentrations above 0.1 mg/L (Figure 1), the ISB values for E. cloacae were stable at about 25–30% after a 4-h contact period between bacteria and antibiotic. Between 0.01 and 0.1 mg/L, there is clearly concentration-dependent killing activity. The bactericidal activity of meropenem related to the concentration achieved at the end of short antibiotic

Table 1 Pharmacokinetic characteristics of meropenem and comparison with human values

Characteristic (units)	Value (mean±SD)		
	Micropig		Human
	Short infusion	Continuous infusion	Short infusion
$T_{1/2}$ (h)	0.78±0.34	0.46±0.01	0.80±0.02
C_{max} (µg/mL)	29.8±1.27	–	24.8±1.40
C_{min} (µg/mL)	<0.1	–	<0.2
C_{ss} (µg/mL)	–	2.38±0.50	–
$AUC_{0-8 h}$ (µg h/mL)	27.4±2.4	17.5±4.10	27.2±2.20
C_{lp} (mL/min per kg)	4.6±1.00	7.3±0.77	3.68

Table 2 Pharmacokinetic characteristics of cefpirome in micropig, and comparison with human values

| | Value (mean±SD) | | |
| | Micropig | | Human |
Characteristic (units)	Intermittent injection	Continuous infusion	Intermittent injection
$T_{1/2}$ (h)	1.44±0.25	1.35±0.42	1.8±0.20
C_{max} (µg/mL)	544.6±157.3	–	200
C_{min} (µg/mL)	1.16±1.0	–	1
C_{ss} (µg/mL)	–	20.9±4.10	–
AUC (µg h/mL)	308.9±45.1	108.7±16.7	312.6
Cl_p (mL/min per kg)	1.59±0.10	1.88±0.37	1.80±0.20

Figure 1 Relationship between ISB (see text) and meropenem concentrations for *E. cloacae* after 4 h of contact.

infusion (C_{max}) was rapid and strong, with about a 4 $\log_{10}$ decrease of starting inoculum occurring after a 6-h period of drug exposure (Table 3). When considering the bactericidal activity of the 1/2-diluted serum as a function of times of sampling (Figure 2), 4 h after short infusion of meropenem the micropig serum concentrations fell below 0.1 mg/L and bacterial regrowth occurred. Continuous infusion appeared to provide adequate concentrations in serum during the interval of administration, as bactericidal activity against *E. cloacae* was maintained throughout this interval (Figure 2). The killing activity of meropenem against *K. pneumoniae* was excellent. It appeared that it was similar to that shown for *E. cloacae*. The evaluation of the serum bactericidal activity expressed by the starting inoculum decrease showed that with high

concentrations of meropenem (end of short infusion), the strain was rapidly and thoroughly killed (more than 4 $\log_{10}$ decrease after a 6-h exposure) (Table 3). As previously seen with *E. cloacae*, bacteria began to regrow 6 h after intermittent meropenem injection. Conversely, meropenem conserved its antimicrobial activity throughout the continuous infusion (Figure 3).

Cefpirome

The evaluation of the bactericidal activity of serum against *S. aureus* showed that the pharmacodynamic behavior of cefpirome is clearly concentration independent. Above the MIC for *S. aureus* (1 mg/L), the ISBs ranged from 20% to 80% after 4 h (Figure 4A) and slowly decreased to 20–40% after 8 h of exposure to serum (Figure 4B). The C_{ss} achieved after

Table 3 Serum (diluted to 1/2) bactericidal activity of meropenem and cefpirome. Results expressed in increase (+) or decrease (−) of $\log_{10}$ CFU/mL compared to starting inoculum after 6 h (*K. pneumoniae* and *E. cloacae*) and 8 h (*S. aureus*) drug exposure

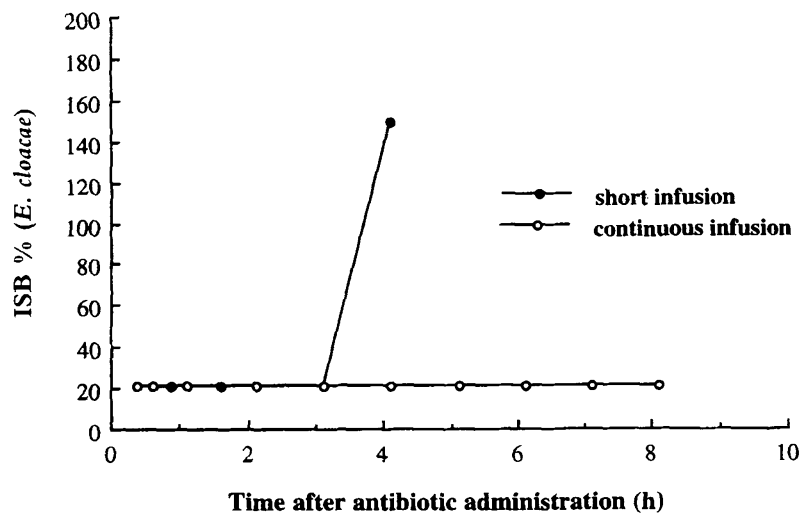| Antibiotic	Strain	C_{max} (s.i.) Concentration (µg/mL)	Δ log	C_{min} (s.i.) Concentration (µg/mL)	Δ log	C_{ss} (c.i.) Concentration (µg/mL)	Δ log
Meropenem	*K. pneumoniae*	29.8	−4.2	<0.1	+1.4	2.04	−3.9
	E. cloacae	29.8	−4.2	<0.1	+0.5	2.04	−3.6
Cefpirome	*S. aureus*	544.6	−2.6	1.16	+0.5	18.4	−1.7
	E. cloacae	544.6	−3.4	1.16	+1.2	18.4	−2.0

s.i., short infusion; c.i., continuous infusion.

Figure 2 Bactericidal activity against *E. cloacae* (6-h exposure) of micropig serum diluted to 1/2 versus time profiles following administration of meropenem by intravenous short infusion and continuous infusion.
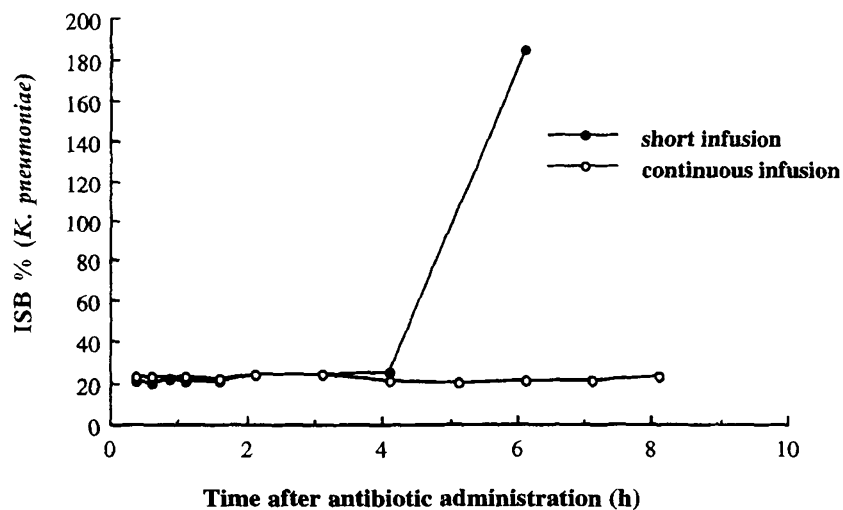

Figure 3 Bactericidal activity against *K. pneumoniae* (6 h exposure) of micropig serum diluted to 1/2 versus time profiles following administration of meropenem by intravenous short infusion and continuous infusion.
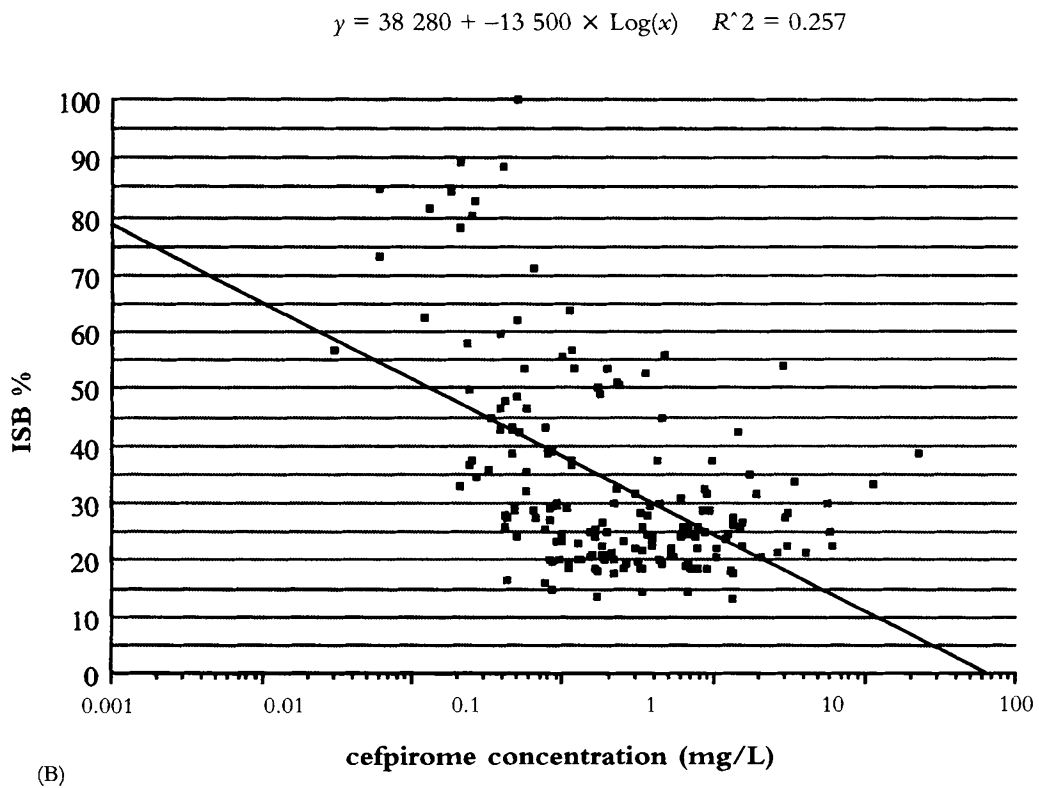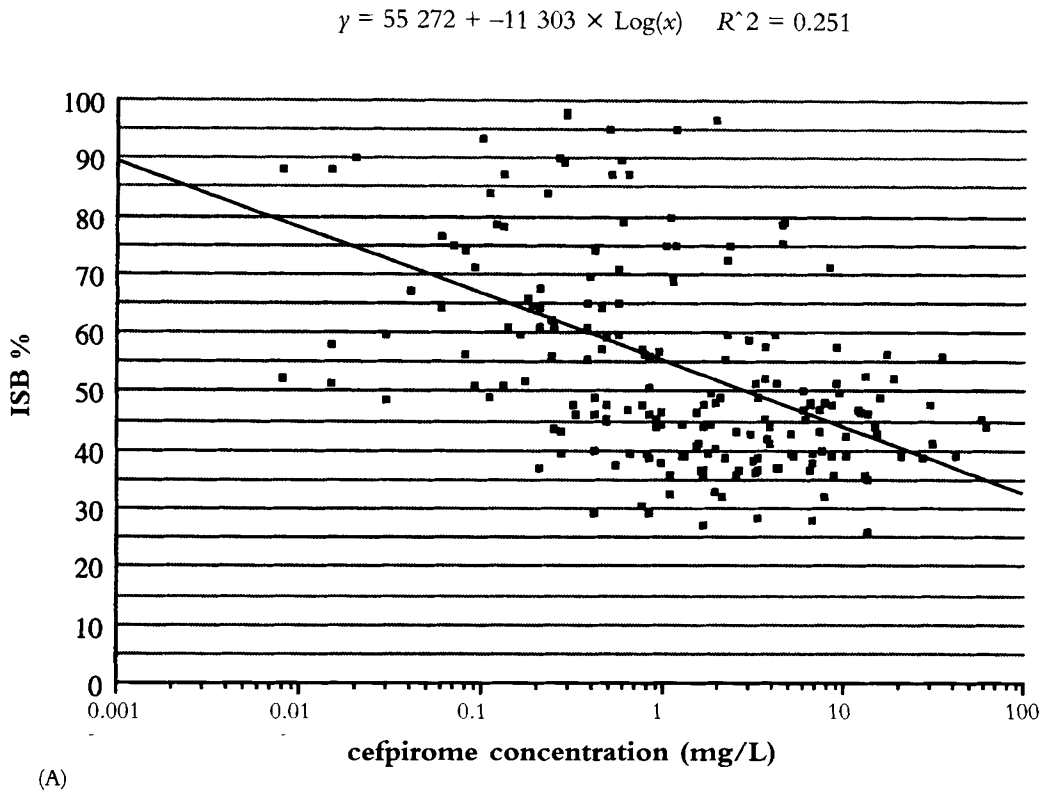
$$y = 55\ 272 + -11\ 303 \times \text{Log}(x) \quad R\char94 2 = 0.251$$

(A)

$$y = 38\ 280 + -13\ 500 \times \text{Log}(x) \quad R\char94 2 = 0.257$$

(B)

Figure 4 Relationship between ISB and cefpirome concentrations for *S. aureus* after 4 h (A) and 8 h (B) of contact.
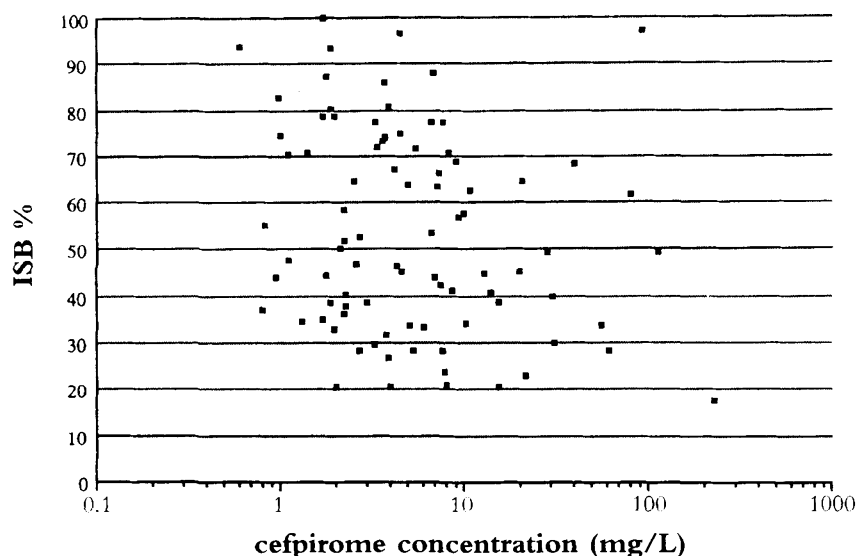
Figure 5 Relationship between ISB and cefpirome concentrations for *E. cloacae* after 6 h of contact.

continuous infusion produced a nearly 2 $\log_{10}$ decrease of starting inoculum after 8 h of drug exposure. Following bolus injection, bacteria began to regrow when serum reached trough concentration (i.e. C_{min}) (Table 3). In contrast, increasing cefpirome concentration (C_{max}, bolus injection) did not enhance the killing rate observed at C_{ss} of continuous infusion (Table 3).

Against *E. cloacae*, by the mean of time-killing curves, bactericidal activity of cefpirome was observed in the early phase with low concentrations, despite the high MIC (64 mg/L). No correlation was observed between cefpirome concentrations and ISB values (Figure 5). The bolus dosing schedule produced a high peak antibiotic serum concentration for cefpirome which permitted rapid and pronounced bactericidal activity against *E. cloacae* (i.e. C_{max}) (Table 3). Therefore, more than a 3 $\log_{10}$ decrease occurred (6-h exposure). As previously seen, in the early phase of bactericidal killing, cefpirome maintained antimicrobial activity throughout the continuous infusion. Conversely, regrowth occurred when the concentration fell to trough level after bolus injection (i.e. C_{min}) (Table 3).

DISCUSSION

The increasing number of immunocompromised patients and the rising incidence of bacterial infections have added impetus to the development of dosage

regimens that will achieve the most benefit with the least amount of drug [14]. With regard to β-lactam antibiotics, there still is controversy about dosage. In clinical practice the β-lactams are administered intermittently. However, the length of time for which MICs can be exceeded is generally considered to correlate well with therapeutic efficacy and this favors frequent administration or continuous infusion [6,7].

The several methods used to evaluate the new antibiotics, particularly in permitting a comparison of their relative efficacy against a given microorganism, reflect a very limited perspective on the in-vivo situation. The MIC is not a reliable reflection of antibiotic activity, as it shows a fixed 24-h endpoint and as many antibiotics are not stable for a whole 24-h period of contact in certain conditions. For example, we have recently demonstrated that cefepime and meropenem are unstable in serum at room temperature [11,15]. Conversely, the MIC does not provide information on the total effect of a certain dose of the antibiotic in a larger range of concentrations, as is characteristically encountered in the patient.

Micropigs have been recognized as being an appropriate non-rodent model for pharmacologic studies owing to physiologic similarities to humans [16]. Despite these potential advantages, micropigs are seldom used in pharmacokinetic investigations and hence few kinetic data are available. The pharmacokinetics of meropenem and cefpirome given by short infusion and bolus injection, respectively, in the

micropig were close to those in humans receiving the same dosage. So, on this basis, the micropig seems to constitute the most reliable model in which to study the pharmacodynamics of these two β-lactams [12].

The ex vivo/in vitro time–kill curves demonstrate that meropenem produces rapid bactericidal activity against *E. cloacae* and *K. pneumoniae* at the relatively high concentrations (about 30 mg/L) that may be reached after short infusion of half the usual doses (given that serum was diluted 1/2). However, meropenem is similar to other β-lactams, in that, above a threshold level, higher concentrations of drug will not kill the organisms faster or more extensively. We conclude that meropenem has so-called 'mixed' pharmacodynamic behavior. The bactericidal activity of any β-lactam antibiotic is usually said to be dependent upon time of contact with the bacteria rather than on the occurrence of high peaks of antibiotic concentration. In fact, we have already observed that the pharmacodynamic behavior of β-lactams depends on both the bacteria and the antibiotic. Furthermore, in the same bacteria–antibiotic pair, this relationship is complex and evolves with the resistance level of bacteria. We have already shown in an in vitro/ex vivo human model that against *S. pneumoniae*, amoxicillin shows mixed pharmacodynamic behavior which is considered as being time and concentration dependent [17]. In fact, it depends on the level of susceptibility of the strain and must be interpreted by taking into account the concentrations achieved at the infected site. While the results obtained in our study favor continuous infusion of meropenem, the rapid killing obtained by somewhat higher levels favors a loading dose that could optimize the bactericidal effect. In an in vitro infection model, Cappelletty showed that ceftazidime monotherapy administered as a continuous infusion at 20 and 10 μg/mL with a loading dose is as effective as administration of intermittent bolus [18]. Avoidance of unnecessarily high values during all the intervals would result in lower daily doses, thus reducing costs while retaining efficacy by avoiding the therapeutic gap. The absence of a postantibiotic effect (PAE) both in vitro and in vivo with meropenem has already been demonstrated. In the neutropenic mouse thigh infected with *Escherichia coli*, *S. aureus* or *Pseudomonas aeruginosa*, the PAE of meropenem was negligible (under 0.3 h). In an in vitro model, this effect was estimated at 0.23 h after 1-h period of contact between meropenem and one strain of *K. pneumoniae* [19]. Hessen et al studied the PAE in the rat model of pseudomonas endocarditis, and showed an absence of this effect in vivo. The bacterial counts increased as soon as levels of imipenem in the vegetations fell below the MIC [20]. Furthermore, the absence of this effect

has been reported again with imipenem tested against Enterobacteriaceae in an in vitro model [21]. Finally, intermittent administration seems to be responsible for resistance to meropenem, particularly by d2-porin deficiency [22]. In conventional treatment regimens, meropenem is given intermittently [23,24]. Because of its rapid systemic body clearance, this may lead to concentrations in plasma below the effective threshold during part of the dosing interval and thus may impair efficacy. During continuous infusion, a level above this threshold may easily be maintained against tested bacteria and should prevent emergence of resistance. A loading dose of meropenem followed by a continuous infusion would be more effective than intermittent injection against Gram-negative bacilli.

The difference in cefpirome C_{max} (Table 2) between micropig and human (544.6 versus 200) is likely to be due to a slight difference in time sampling together with a very short distribution half-life. Only a few minutes delay may divide concentrations by two in this period. According to our data (Figure 4A,B), cefpirome shows time-dependent bactericidal activity against *S. aureus*. According to the coefficients of correlation (Figures 4A,B) which are rather low, it could be thought that cefpirome exhibits a time-dependent bactericidal activity against *S. aureus*. There is no clear relationship between concentrations and ISB (Figure 4A), but the overall values of ISB are lower after 8 h of exposure than after 4 h (Figure 4B), indicating at least a partial time-dependent mode of killing. Nevertheless, it should be noted on Figure 4B that below 1 mg/L, ISB values of more than 50% are frequently reached, which is never the case with concentrations above 1 mg/L. Thus, the mode of killing of cefpirome may also be dependent on the concentrations. Intermittent administration results in high peak concentrations in serum which do not kill *S. aureus* faster or more extensively than the lower concentrations obtained at steady state and which are about 20 times higher than the MIC. Trough concentrations may fall below the MIC for *S. aureus* at the end of the dosing interval (for one micropig this value was 0.5 mg/L) and regrowth could occur. Against *S. aureus*, continuous infusion thus appears to be the optimal administration technique to avoid the absence of bactericidal activity observed at the C_{min} that follows intermittent injection. As shown for *S. aureus*, the pronounced bactericidal activity of cefpirome against *E. cloacae* ($+3.4 \log_{10}$ decrease at C_{max}) seems to be concentration independent (Figure 5), and somewhat variable, probably in relation to the cephalosporinase production level. Once again, no bactericidal activity is observed at C_{min}. The 2 $\log_{10}$ decrease of inoculum resulting from the C_{ss} (18.4 mg/L) looks rather good

compared with the MIC (64 mg/L), but would probably be insufficient for treating infections due to strains with such high MICs.

Up to now, little information has been available concerning in-vitro models, animal models and clinical studies comparing the efficacy of continuous infusion of β-lactam antibiotics with that following intermittent injection [6–9]. In the present study, we used the Yucatan micropig model, which has been validated in pharmacokinetic terms for cefpirome and meropenem and is thus a pertinent model for the in vitro/ex vivo pharmacodynamic investigations of these β-lactams with several multiresistant strains. We conclude that continuous infusion seems to be more in accord with the pharmacodynamics of cefpirome and meropenem. Against Gram-negative bacilli, the administration of a loading dose prior to continuous infusion would eliminate the only potential pharmacokinetic disadvantage of continuous infusion and ensure the rapid onset of antimicrobial activity. Experimental infection will be the next step and work is currently in progress.

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