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Comparative Cerebrospinal Fluid Diffusion of Imipenem and Meropenem in Rats

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Abstract

The main objective of this study was to compare the cerebrospinal fluid (CSF) diffusion of imipenem and meropenem at steady state, following intravenous infusions at various rates in rats. A preliminary experiment was conducted to estimate the elimination half-lives of these two carbapenem antibiotics, and then to evaluate the infusion duration necessary to reach steady state.

CSF diffusion of imipenem was essentially linear over the wide range of infusion rates (66–1320 $\mu g\,min^{-1}$) and corresponding steady-state plasma concentrations (11·7–443·0 $\mu g\,mL^{-1}$). Conversely the CSF diffusion of meropenem was saturable, with a predicted maximum CSF concentration equal to 1·3 $\mu g\,mL^{-1}$.

Extrapolation of these data to the clinical situation may not be possible since the rats had normal blood–brain and blood–CSF barriers whereas patients with diseases such as meningitis may not. However, it is suggested that the observed differences in the diffusion characteristics of imipenem and meropenem may be partly responsible for their differences in toxicity and efficacy at the central level.

Imipenem is the leading compound of the carbapenem antibiotics. It possesses a broad spectrum of antibacterial activity against most Gram-positive and Gram-negative aerobic and anaerobic bacteria including *Pseudomonas aeruginosa*, *Bacteroides fragilis* and *Listeria monocytogene* (Buckley et al 1992). It is also highly active against most pathogens commonly isolated from cases of bacterial meningitis (Clissold et al 1987) and has therefore been proposed as an alternative in the treatment of meningitis (Klugman & Dagan 1995). However, severe CNS side-effects, including seizures, considerably limit the use of imipenem in meningitis. These undesirable effects are more likely to occur in children or in patients with renal impairment or pre-existing CNS disorders (Calandra et al 1985) and the first clinical trial of imipenem for the treatment of meningitis in children, was actually terminated because of an excess of seizures (Wong et al 1991).

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Meropenem is a new carbapenem already launched in several countries. As opposed to imipenem, which is extensively hydrolysed by the renal enzyme dehydropeptidase I (DHP-I) in man, and therefore co-administered with an enzyme inhibitor, cilastatin (Drusano 1986), meropenem is stable against this enzyme and is given as a single agent (Fukasawa et al 1992). It has a similar, but potentially wider, spectrum of activity than imipenem (Edwards et al 1989; Jorgensen et al 1991b). Nausea and vomiting and inflammation at the injection site seem to occur less frequently in patients receiving meropenem than in those receiving imipenem/cilastatin (Calandra et al 1985; Norrby et al 1995).

Interestingly, animal studies have suggested that meropenem may have less potential to cause seizure than imipenem/cilastatin (Patel & Giles 1989; De Sarro et al 1995; Sunagawa et al 1995). Accordingly we have recently been able to induce generalised tonic-clonic seizures in genetically epilepsy-prone Dilute Brown Agouti DBA/2J (DBA/2) mice, by infusing imipenem/cilastatin intravenously, but not meropenem (Dupuis et al 2000). To assess whether these differences in

epileptogenic activity could be due to differences in CSF diffusion, we have made investigations in rats, with special attention to the search for saturable processes.

Materials and Methods

Animal care and surgery

This work was done in accordance with the Principles of Laboratory Animal Care (NIH Publication no. 85-23, revised 1985), and the study was approved by the local ethic committee. Male Sprague-Dawley rats (225–280 g; 257 ± 21 g, mean $\pm$ s.d.) from Depres Breeding Laboratories (St Doulchard, France) were housed in the animal breeding facilities of the Laboratory (authorisation no. 0028). The rats were placed in wire cages in a 12-h light–dark cycle for one week to adjust to the new environment and to overcome possible stress incurred during transit. They had free access to food (Extra-labo M20, Pietrement Laboratories, France) and water. Twelve rats were used for pharmacokinetic studies after single dose administration, and others were used for the CSF diffusion study. One day before the experiment, a polyurethane catheter was implanted in the right jugular vein for drug administration, as previously described (Delon et al 1997, 1999). In the pharmacokinetic study, rats had a second catheter implanted in the right carotid artery for blood sampling. Rats were housed individually in plastic cages. Food was withdrawn 12 h before the experiment, but rats had free access to water until drug administration.

Solutions for administration

Tienam (imipenem monohydrate-sodium cilastatin salt; Merck, Sharp & Dohme Laboratories, France) and meropenem trihydrate (Zeneca-Pharma, France) were dissolved in 0·9% NaCl, to obtain final concentrations in the range of 0·8–16·0 mg mL^{-1} for imipenem and 2·2–22·0 mg mL^{-1} for meropenem.

Study design and sample collection

Drug administrations were conducted between 14 00 and 18 00 h.

Pharmacokinetic study. The day after surgery, rats received a single dose of imipenem/cilastatin (100/100 mg kg^{-1}) or meropenem (100 mg kg^{-1}) as an intravenous bolus dose in the jugular vein. Blood samples (200 μL) were collected from the carotid artery at various times after drug administration: 0, 2·5, 5, 10, 15, 20, 25 and 30 min for meropenem and 0, 2·5, 5, 10, 15, 20, 30, 45 and 60 min for imipenem. Then, blood was transferred into heparinized tubes and immediately centrifuged to collect plasma.

CSF diffusion study. The jugular vein cannula was connected to a motor-driven syringe pump (Program 2, Vial Inc., France) containing drug solution, with a flow rate set at 5 mL h^{-1}. Various input rates (R_0) ranging between 66 and 1820 μg min^{-1} of carbapenem were randomly assigned. Rats were kept under a heating lamp to maintain body temperature. Immediately after the end of infusion (60 and 25 min for imipenem and meropenem, respectively), CSF and plasma samples were collected as previously described (Delon et al 1997, 1999). Samples containing imipenem were immediately diluted (1:1, v/v) with a stabiliser (0·5 M HEPES pH 6·8–ethyleneglycol–HPLC grade water, 1: 0·5:0·5, v/v/v). All samples were kept frozen at -80°C, until analysis.

Analytical methods

A previously described HPLC assay (Carlucci et al 1990) was used with minor modifications for imipenem determinations. CSF samples were assayed by direct injection onto the column. Plasma samples were prepared by mixing with methanol (1:1, v/v) to precipitate protein. After centrifugation, a 20 μL sample of the supernatant was injected onto the column. A recently developed HPLC method was used for meropenem measurements (Dupuis et al 1998). Meropenem was assayed in CSF by direct injection as for imipenem. Plasma samples were diluted (1 : 9, v/v) by addition of 0·01 M pH 4·8 acetate buffer containing 4 mg L^{-1} ceftazidime as internal standard. Meropenem was isolated by solid-phase extraction onto a preconditioned SPE column (Isolute C_{18} EC). After elution, following washing, 20 μL of eluate were injected onto the column. The chromatographic system consisted of a model L 6000 Merck-Hitachi pump and a Waters 717 plus refrigerated autosampler connected to a Waters 484 UV absorbance detector ($\lambda = 296$ and 313 nm, for meropenem and imipenem, respectively). Chromatographic data were recorded and processed using a Waters 746 integrator. The limits of quantitation of imipenem and meropenem were, respectively, 0·125 and 0·0625 μg mL^{-1} in CSF and 0·5 and 0·125 μg mL^{-1} in plasma. Intra-day coefficients of variation calculated for each compound at two concentrations were $\leq$10%. Corresponding inter-day coefficients were $\leq$13% for both

compounds. The recovery was within 92·8 and 95·4% for meropenem.

Data analysis

Pharmacokinetic study. Pharmacokinetic parameters were determined in each individual rat by a non-compartmental approach. Total body clearance (CL_T) was calculated as $CL_T = dose/AUC$, where AUC is the total area under the plasma concentration vs time curve. The AUC was calculated using the trapezoidal rule; the area remaining under the curve after the last measured concentration, C(last), was determined from C(last)/k. The rate constant, k, and its corresponding half-life ($t_{\frac{1}{2}}$) were estimated by linear least-squares fit of data points (time, log concentration), in the terminal phase of the decline. The apparent volume of distribution (Vd) was obtained from CL_T/k.

CSF diffusion study. For each carbapenem, clearance at steady state was estimated by two procedures. A mean clearance estimate was obtained from the reciprocal value of the slope of the straight line calculated by linear-regression analysis of the individual plasma concentration at steady state (C_{SS}) vs R_0 data; a second estimate was obtained by averaging individual clearance values obtained from the ratios between R_0 and corresponding C_{SS}.

Three distinct models were fitted to the C_{CSF} versus C_{SS} values: a linear model, a non-linear model and a composite model, according to equations 1–3 (Gengo et al 1989).

$$\text{Linear model: } C_{CSF} = K_d \times C_{SS} \quad (1)$$

where K_d is the distribution coefficient between CSF and plasma.

$$\text{Non-linear model: } C_{CSF} = (C_{CSF,max} \times C_{SS})/(C_{SS,50} + C_{SS}) \quad (2)$$

where $C_{CSF,max}$ is the maximum concentration achievable in the CSF, and $C_{SS,50}$ the plasma concentration at which C_{CSF} equals 50% of $C_{CSF,max}$.

$$\text{Composite model: } C_{CSF} = (K_d \times C_{SS}) + (C_{CSF,max} \times C_{SS})/(C_{SS,50} + C_{SS}) \quad (3)$$

C_{CSF} vs C_{SS} values were fitted by iterative non-linear least-squares regression analysis using WinNonlin version 1·1 (SCI Software, N. C. Carry, USA). Due to the limited range of C_{CSF} variations, a uniform weighting was applied. The goodness-of-fit of each model was assessed by residuals analysis and the precision and the bias of parameter estimates (Gabrielsson & Weiner 1997). Sum of squared residuals (SSR), correlation coefficient (r) between observed and predicted values and Akaike information criterion (AIC) were used for model discrimination (Yamaoka et al 1978).

Results are presented as mean ± s.d.

Results

Pharmacokinetic study

Plasma concentrations vs time profiles after intravenous bolus administration to rats showed a mono-exponential decay both for imipenem and meropenem as illustrated in Figure 1. Estimates of the apparent volumes of distribution of both compounds were virtually identical ($Vd = 79·0 \pm 11·8$ mL and $74·9 \pm 15·8$ mL for imipenem and meropenem, respectively), but total clearance of meropenem ($CL = 12·3 \pm 2·6\ mL\ min^{-1}$) was threefold that of imipenem ($CL = 4·6 \pm 1·0\ mL\ min^{-1}$). Accordingly, the elimination half-life of imipenem ($t_{\frac{1}{2}} = 11·9 \pm 1·2$ min) was 3 times that of meropenem ($t_{\frac{1}{2}} = 4·1 \pm 0·7$ min).

CSF diffusion study

Steady-state plasma concentrations determined at the end of the intravenous infusions in rats were $11·7–443·0\ \mu g\ mL^{-1}$ for imipenem and $20·2–258·0\ \mu g\ mL^{-1}$ for meropenem. A linear relationship was noted between C_{SS} values and R_0 for both carbapenems, indicating that clearance was constant throughout these wide concentration ranges (Figure 2). Steady-state clearance estimates of imipenem obtained from the reciprocal of the slope of the C_{SS} vs R_0 curves and those estimated by averaging the individual R_0/C_{SS} ratios, were 3·4 and $4·2\ mL\ min^{-1}$, respectively. Corresponding estimates for meropenem were 8·5 and $8·8\ mL\ min^{-1}$, respectively.

Drug concentrations determined in CSF ($0·3–6·1\ \mu g\ mL^{-1}$ and $0·1\text{-}2·9\ \mu g\ mL^{-1}$ for imipenem and meropenem, respectively) were much lower than corresponding plasma concentrations. Among the three models tested to characterise the CSF diffusion of imipenem and meropenem with dose, only the linear and the non-linear models gave valuable results (Figure 3). Very high coefficients of variation were most often associated with the various parameter estimates obtained with the composite model (Table 1), which was hence rejected. For imipenem data, diagnostic parameters were virtually identical and did not allow clear distinction between the linear and the non-linear

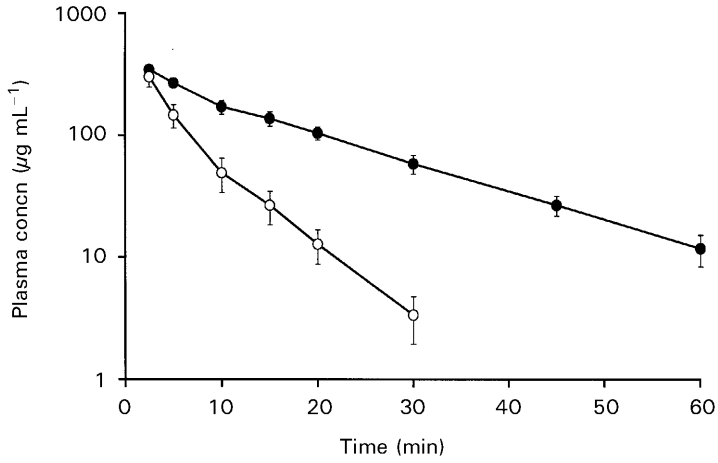
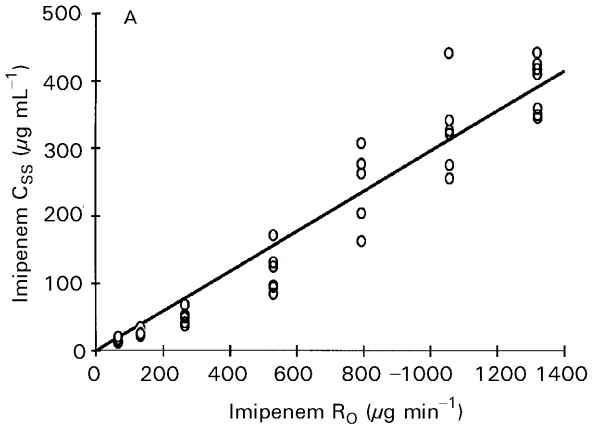


Figure 1. Mean (± s.d.) plasma concentrations vs time profiles in six healthy rats following an intravenous bolus administration of 100 mg kg^{-1} of imipenem (●) or meropenem (○). Lines connect the points for identification purposes.



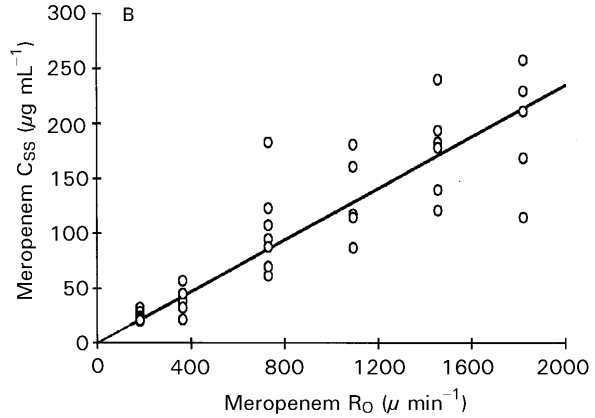
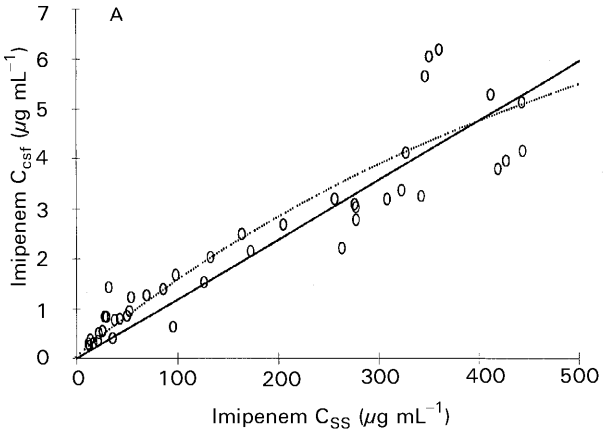


Figure 2. Imipenem (A) and meropenem (B) plasma concentration at steady state (C_{SS}) vs infusion rate (R_0). The solid line represents the best linear least-square fit to the data points.



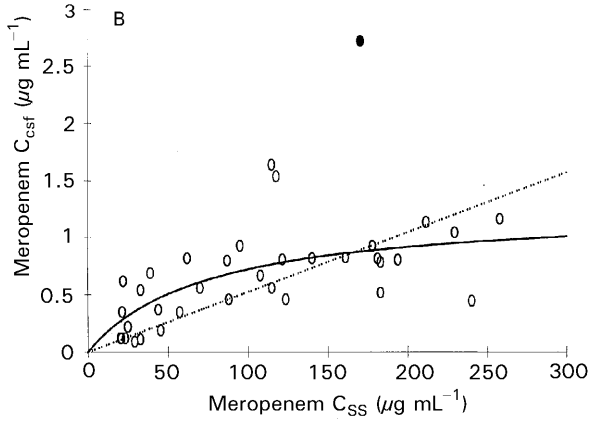


Figure 3. Imipenem (A) and meropenem (B) cerebrospinal fluid concentration (C_{CSF}) vs plasma concentration at steady state (C_{SS}). Solid lines represent the best linear least-square fit to the data points, linear model for imipenem and saturable model for meropenem, and dashed lines correspond to the rejected model. One point (●) was treated as an outlier.

models (Table 2). Best estimates of the parameters characteristic of the non-linear model ($C_{CSF,max}$ and $C_{SS,50}$) were by far outside the range of values encountered during this experiment, since $C_{CSF,max}$ predicted by the model was 13·9 μg mL^{-1}, when the highest value observed experimentally was 6·1 μg mL^{-1}, and the $C_{SS,50}$ best estimate was 826 μg mL^{-1}, when the highest plasma concentra-

tion measured was only 443 $\mu g\,mL^{-1}$. By contrast, the non-linear model provided a better fitting of the meropenem data than the linear model, as indicated by the analysis of residuals and lower AIC values (Table 2), with best estimates of $C_{CSF,max}$ and $C_{SS,50}$, respectively, equal to 1·3 $\mu g\,mL^{-1}$ and 75·1 $\mu g\,mL^{-1}$, within the range of experimental values.

Discussion

Basic pharmacokinetic parameters of imipenem and meropenem estimated in the first part of this study were in agreement with previously published data (Hashizume et al 1987; Harrison et al 1989). Volumes of distribution of the two compounds were virtually similar and equal to about 5–6-fold rat plasma volume (Davies & Morris 1993). In contrast, clearance values of imipenem and meropenem differed by a factor of three. In this study cilastatin was co-administered with imipenem, but not with meropenem. Only imipenem is hydrolysed by the renal enzyme DHP-I in humans, but both compounds are hydrolysed by this enzyme in rats (Fukasawa et al 1992). The absence of cilastatin can therefore probably explain most of the three-fold higher total clearance of meropenem. Although it would have been interesting, for comparison purposes, to administer a mixture of meropenem and cilastatin, this was not possible due to the lack of availability of cilastatin. Assuming that imipenem was almost exclusively eliminated by renal excretion (Nilsson-Elhe et al 1991), its total clearance would be virtually equal to its renal clearance, which in turn is about 3-fold greater than its glomerular filtration rate in rats ($1{\cdot}3\,mL\,min^{-1}\,(0{\cdot}25\,kg)^{-1}$; Davies & Morris 1993), suggesting that renal tubular secretion occurs, in agreement with previously published data in human (Norrby et al 1984). The two estimates of clearance at steady state had a tendency to be slightly lower than corresponding clearances estimated after single-dose administration. Since there was evidence of a linear relationship between C_{SS} and R_0 for the two tested carbapenems (Figure 2), a dose dependency phenomenon cannot explain the differences between the estimates of clearance after single-dose administration and at steady state. A time effect also seems unlikely for a drug excreted unchanged in urine. Another possible explanation is that clearance was slightly overestimated after single-dose administration, as the AUC could have been underestimated due to a lack of experimental data points at early times, when a quick distribution phase may have been omitted.

The three-fold higher clearance of meropenem compared with that of imipenem, together with almost equal values for volume of distribution, was responsible for an elimination half-life value of meropenem close to half that of imipenem, in agreement with values previously reported by others in comparable conditions (Hashizume et al 1987; Harrison et al 1989). Determination of this parameter was especially interesting in this study since it was used to estimate the duration of infusion required to reach steady state. Since the half-lives of the two compounds differed, they were infused for different lengths of time, 60 min for imipenem and 25 min for meropenem, corresponding to 5 elimination half-lives for each compound. CSF diffusion of the two carbapenems was rather limited as indicated by the much lower concentrations in CSF than in plasma. CSF may belong to a deep compartment with slow exchanges and long equilibration times between CSF and plasma. In agreement with this, the apparent elimination half-life of imipenem was found, by several

Table 1. Best estimates of parameters characteristic of the three distinct models fitted to the CSF concentration vs plasma concentration following intravenous administration of imipenem and meropenem to rats.

Model	Imipenem	Meropenem
Linear		
K_d (CV)	0·012 (3·9%)	0·005 (9·2%)
Non-linear		
$C_{CSF,max}$ ($\mu g\,mL^{-1}$) (CV)	13·9 (42·2%)	1·3 (20·8%)
$C_{SS,50}$ ($\mu g\,mL^{-1}$) (CV)	827·0 (58·7%)	75·1 (52·6%)
Composite		
K_d (CV)	0·01 (15·0%)	0·003 (66·1%)
$C_{CSF,max}$ ($\mu g\,mL^{-1}$) (CV)	0·6 (99·7%)	0·4 (80·7%)
$C_{SS,50}$ ($\mu g\,mL^{-1}$) (CV)	15·3 (305·0%)	10·0 (297·0%)

K_d = distribution coefficient between CSF and plasma; $C_{CSF\ max}$ = maximum concentration achievable in the CSF; $C_{SS,50}$ = plasma concentration at which C_{CSF} equals 50% of $C_{CSF\ max}$; CV = coefficient of variation.

Table 2. Diagnostic parameters obtained for the best fit to CSF concentration vs plasma concentration according to the three distinct models.

Model	SSR	r	AIC
Imipenem			
Linear	20·2	0·93	128·2
Non-linear	18·3	0·92	126·2
Composite	17·8	0·93	126·8
Meropenem			
Linear	4·3	0·60	53·3
Non-linear	2·8	0·67	39·8
Composite	3·1	0·63	45·5

SSR = sum of squared residuals; r = correlation coefficient; AIC = Akaike information criterion.

authors, to be longer in CSF than in plasma (Washburn et al 1983; Suzuki et al 1989), although others did not observe such a difference (Patamasucon & McCracken 1982). Yet, although steady state was achieved in plasma, the diffusion equilibrium between CSF and plasma may not have been reached by the end of infusions when samples were collected. To investigate this possibility, imipenem was infused for 360 min (instead of 60 min as previously) at an input rate of 792 $\mu g\,min^{-1}$, in 5 rats. The CSF/plasma ratio estimated at the end of these extended infusions was $1{\cdot}5 \pm 0{\cdot}9\%$, which is virtually identical to the value ($1{\cdot}6 \pm 0{\cdot}3\%$) estimated after shorter infusions (60 min) at the same input rate. Although these data do not completely exclude the possibility of CSF acting as a deep compartment, they suggest that the CSF/plasma concentration ratio estimated in this study (intravenous infusion for a duration of 5 plasma half-lives) may be used to compare the extent of CSF diffusion of these two carbapenems.

The CSF diffusion of meropenem was clearly non-linear (Figure 3), which may contribute to its reduced CNS toxicity. As far as this observation can be extrapolated to humans, it could also be responsible for reduced efficacy, as the highest possible concentration achievable in CSF ($C_{CSF,max}$), which according to the model is equal to $1{\cdot}3\,\mu g\,mL^{-1}$, is in the same magnitude as the minimal inhibition concentration (MIC) values of most pathogens responsible for meningitis (Jorgensen et al 1991a; Wieseman et al 1995). Furthermore, it has been suggested that for effective antibacterial therapy in the brain, the C_{CSF} should be 10 times the MIC (Wise 1986). Noticeably, the plasma concentration at which 50% of this maximum CSF concentration is reached, is also within the range frequently encountered in clinical practice ($C_{SS,50} = 75{\cdot}1\,\mu g\,mL^{-1}$). Due to this saturable diffusion, increasing the dose of meropenem, as suggested with other β-lactam antibiotics (Nau et al 1998), may not be efficient for eradicating bacteria with a reduced sensitivity to this antibiotic. However, extreme care is needed in extrapolation to the clinical setting, not only because of possible interspecies differences, but also because these results have been obtained in healthy rats with normal blood–brain and blood–CSF barriers, which may not be the case of patients suffering from diseases such as meningitis. Such diseases may allow increased carbapenem penetration into CSF, leading to greater antibiotic levels (Modai et al 1985; Jacobs et al 1986; Dagan et al 1994).

Different results were obtained with imipenem. Although the CSF diffusion of this compound should eventually become saturated when plasma concentrations increase over a certain value, it may be considered as linear for practical purposes in the wide range of C_{SS} encountered during this study, which probably covers most of the concentrations observed in clinical practice (Buckley et al 1992). Interestingly the mean C_{CSF}/C_{SS} ratio characteristic of imipenem CSF diffusion was 1·6%, which is virtually similar to the ratio between the $C_{CSF,max}$ and $C_{SS,50}$ values estimated for meropenem ($C_{CSF,max}/C_{SS,50} = 1{\cdot}7\%$) which can be assimilated to the C_{CSF}/C_{SS} ratio of this compound at low concentrations, when CSF diffusion is linear. The practically linear CSF diffusion of imipenem is in agreement with data previously published by Suzuki et al (1989). These authors also concluded that cilastatin does not interfere with the pharmacokinetics of imipenem in the central nervous system, confirming previously published data (Washburn et al 1983). It is therefore unlikely that cilastatin, co-administered with imipenem but not with meropenem, could have contributed to the differences observed between the CSF diffusion characteristics of these two carbapenems, in our study.

In conclusion, this study has clearly demonstrated distinct CSF diffusion characteristics between imipenem and meropenem in healthy rats. Although direct extrapolation of these data to the clinical setting is impossible, these new results could partially explain previous observations indicating that meropenem convulsant activity is reduced compared with that of imipenem. However, this would also mean that differences could exist between the two compounds in terms of antibiotic efficacy, due to differences in CSF diffusion characteristics. New investigations using experimental models closer to the clinical situation, such as experimental models of meningitis in rats, should be conducted to complement the present results.

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