Pharmacokinetics of doripenem in CSF of patients with non-inflamed meninges

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Objectives: To investigate intact blood–brain barrier (BBB) penetration by doripenem and characterize doripenem pharmacokinetics in CSF using a pharmacokinetic model.

Patients and methods: Thirty-eight neurological patients with no active neurological disease or CNS infection received a single 500 mg doripenem dose before pump implantation surgery, or lumbar puncture, for intrathecal baclofen administration. In most cases single CSF and blood samples were collected per patient and analysed for doripenem with HPLC. A two-stage pharmacokinetic analysis was performed to estimate: (i) empirical Bayesian estimates (EBEs) of individual doripenem plasma pharmacokinetic parameters, using plasma doripenem concentrations and literature population priors for a two-compartment model; and (ii) doripenem CSF pharmacokinetic parameters using simulated plasma concentrations from stage (i) as a forcing function. The mean values of the structural model parameters, $k_{CSF}$ (distribution rate constant) and $P_C$ (CSF/plasma partition coefficient), and the residual variability were estimated.

Results: The mean estimates of the parameters were $k_{CSF} = 0.105$ h$^{-1}$ and $P_C = 0.053$, corresponding to mean steady-state doripenem CSF concentrations of 0.20 mg/L and 0.40 mg/L for regimens of 3 × 500 mg daily and 3 × 1000 mg daily, respectively, and a mean equilibrium half-life of 6.6 h. The model was validated internally using a visual predictive check (VPC) and bootstrap. Simulating two dosing scenarios gave doripenem levels in the CSF above or close to the literature MIC values.

Conclusions: The present NONMEM software analysis shows that doripenem crosses intact BBB significantly and suggests that the drug should be further evaluated as a candidate to treat certain CNS infections, since drug penetration through BBB is enhanced by meningeal inflammation.

Keywords: central nervous system, cerebrospinal fluid, blood–brain barrier, non-linear mixed-effects modelling

Introduction

The treatment of CNS infections is difficult due to the variable and/or limited permeability of the various antibiotics across the blood–brain barrier (BBB) that in healthy subjects permits only small-molecule penetration.1,2 In the case of bacterial meningitis, the crucial step of treatment is the prompt initiation of antibiotic therapy, since the rapid sterilization of CSF with antibiotic therapy has been associated with better clinical outcome.3–5 Doripenem is a very promising antimicrobial agent, recently approved by the FDA for the treatment of complicated intra-abdominal infections and complicated urinary tract infections.6 It is a carbapenem antibiotic that exhibits bactericidal action by inhibiting bacterial penicillin-binding proteins and is in vitro active against both Gram-positive and Gram-negative aerobic and anaerobic organisms.7 Doripenem has a broad spectrum of activity, probably wider than that of meropenem, imipenem and ertapenem,7,8,9 being effective against most of the pathogens that cause dangerous nosocomial infections, e.g. *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Streptococcus pneumoniae* etc.7,9 Also, it has a lower epileptogenic potential compared with other carbapenems.7,13 Doripenem retains the
synergistic effect of a carbapenem combined with vancomycin against methicillin-resistant Staphylococcus aureus (MRSA).\textsuperscript{14} Moreover, its \textit{in vitro} effectiveness against many strains of Acinetobacter spp.,\textsuperscript{15} one of the leading causes of post-operative meningitis in neurosurgery,\textsuperscript{16} makes it an agent that deserves serious consideration for possible use in the treatment of certain CNS infections.

No pharmacokinetic data for doripenem in CSF are available. However, we have shown previously that doripenem penetrates the intact human BBB to a small but measurable extent.\textsuperscript{17} The lack of relative pharmacokinetic studies has probably inhibited the study of the clinical effectiveness of doripenem in bacterial meningitis, despite the fact that its broad spectrum of antimicrobial activity would make it a highly promising agent for this indication.

The aim of this study was to investigate the CSF pharmacokinetics of doripenem after intravenous administration to patients with an intact blood–brain barrier using mixed-effects compartmental modelling with the software NONMEM.\textsuperscript{18} In this study, neurological patients intended to undergo surgery for implantation of a pump to allow intrathecal administration of baclofen were enrolled. CSF samples are withdrawn routinely in these patients as a standard of care during pump implantation or lumbar puncture for the baclofen test.

Patients and methods

Pharmacokinetic study design and sample collection

A total of 38 neurological patients suffering from spasticity were enrolled in the study. The cause of spasticity was cerebral palsy, stroke, or multiple sclerosis in a long-standing stable phase. In all cases there was no active neurological disease or CSF infection and the BBB was considered intact. These patients were submitted to the implantation of a pump for the intrathecal administration of baclofen, an anti-spasticity agent, or to a lumbar puncture to test intrathecal infusion of baclofen. This trial infusion was performed in order to ascertain the improvement in spasticity of each patient following baclofen administration (‘baclofen test’). Intrathecal baclofen pump implantation is only offered to those patients with a positive baclofen test. Pre-procedural chemoprophylaxis was deemed necessary since pump implantation entails the permanent insertion of a catheter into the spinal subarachnoid space. Similarly, the baclofen test entails drug infusion into the sub-arachnoid space and carries the theoretical risk of pathogen introduction into the subarachnoid space. Aggressive preoperative broad-spectrum antibiotic prophylaxis is mandatory to reduce the risk of nosocomial meningitis. Therefore doripenem (DORIBAX\textsuperscript{8} 500 mg as a 30 min intravenous infusion prior to first incision) was given to all 38 patients as preoperative/preprocedural prophylaxis, followed by vancomycin (1 g as a 2 h infusion prior to the operation/lumbar puncture). Catheter insertion into the spinal subarachnoid space, or lumbar puncture for the trial intrathecal baclofen infusion, was performed at different time intervals after initiation of antibiotic infusion in each patient. A single CSF sample, but in some cases two samples, was taken from each patient through the catheter to check the patency and the proper placement of the catheter during intrathecal baclofen pump implantation. In the case of the baclofen test, a simple CSF sample was taken at the time of lumbar puncture. Plasma samples were also taken either immediately after the end of drug infusion or at the same sampling time as the CSF sample. CSF and plasma samples were collected 15 min to 11 h after the end of the administration of doripenem.

The study took place at Evangelismos General Hospital. The study protocol and the informed consent form were reviewed and approved by the Institutional Ethics Committee. The study was performed in accordance with good clinical practice guidelines and informed consent was obtained from all patients.

Doripenem assay in plasma and CSF

Sample preparation and methods

\textbf{Plasma samples} Blood samples were gathered into heparinized vacuum tubes (BD Vacutainer\textsuperscript{5}) and centrifuged at 10000 g for 10 min at 4°C. The supernatant (plasma) was collected and mixed with an equal volume of 1 M MOPS buffer solution (Sigma-Aldrich, St Louis, MO, USA) and stored at —70°C until analysed. The same procedure was followed for blank blood samples.

\textbf{CSF samples} Similarly the CSF samples were mixed with an equal volume of 1 M MOPS buffer solution and stored at —70°C until analysis. Plasma samples were processed and quantitatively analysed for doripenem concentration according to the validated method described in Ikeda et al.\textsuperscript{19} The CSF samples were processed similarly with a few minor modifications. Specifically in the latter case, the relevant calibration curves derived were in the concentration range of 50–500 ng/mL because of the very low doripenem concentration expected in CSF samples. Thus the volume of internal standard (IS) meropenem, added because of the very low doripenem concentration expected in CSF samples.

\textbf{Software} Non-linear mixed-effects modelling applying the first-order conditional (FOCE) method implemented in the NONMEM 7.2 software package (ICON, Hanover, MD, USA)\textsuperscript{18} and compiled with gfortran 4.6, was used to develop the pharmacokinetic model and to conduct model-based simulations.

Pharmacokinetic modelling and simulations

A NONMEM pharmacokinetic analysis was carried out in two stages. The first stage used the plasma samples and literature population priors for a two-compartment model\textsuperscript{20} to estimate the empirical Bayesian estimates (EBEs) of the pharmacokinetic parameters of each patient for doripenem in plasma; i.e. population parameters were fixed to the literature values and EBEs were estimated using the POSTHOC option of NONMEM. The structural model was parameterized as CL, V\textsubscript{1}, Q\textsubscript{1} and V\textsubscript{2} using the ADVAN 3 TRANS 4 routine, with the following covariate model:\textsuperscript{20}

\begin{equation}
\text{CL} = \theta_1 \cdot (\text{CRCL}/98)^{b_1}
\end{equation}

\begin{equation}
V_1 = \theta_2 \cdot (WT/73)^{b_2}
\end{equation}

\begin{equation}
Q_2 = \theta_3 \cdot (WT/73)^{b_3}
\end{equation}

\begin{equation}
V_2 = \theta_4 \cdot (CRCL/98)^{b_4} \cdot (WT/73)^{b_5} \cdot (\text{AGE}/40)^{b_6}
\end{equation}

where CL is the clearance (L/h), V\textsubscript{1} is the central volume of distribution (L), Q\textsubscript{2} is the inter-compartmental clearance (L/h) and V\textsubscript{2} is the volume of distribution of the peripheral compartment (L), while CRCL, WT and AGE...
are the creatinine clearance (mL/min), the body weight (kg) and age (years), respectively, of each patient. Furthermore, inter-individual variability (IIV) was considered for parameters $CL$, $V_1$, $Q_2$, and $V_2$ and inter-occasion variability (IOV) for parameters $CL$, $V_1$, and $V_2$ (Table 1). The pharmacokinetic parameters of the CSF compartment were estimated. The structural parameters included in the model were the CSF distribution rate constant ($k_{CSF}$) and the partition coefficient ($PC$) corresponding to the ratio of the CSF over the plasma doripenem concentration at steady state. An exponential residual model was used for plasma and CSF concentrations. The differential equation system describing the distribution of drug into the third compartment was described as follows:

$$\frac{dC_{CSF}(t)}{dt} = k_{CSF}(C_{plasma}(t) \cdot PC - C_{CSF}(t)), \quad (5)$$

where $C_{plasma}$ is the simulated plasma doripenem concentration and $C_{CSF}$ is the concentration of doripenem in the CSF. The ADVAN6 subroutine was used to implement equation (5) in NONMEM.

Parameters $PC$ and $k_{CSF}$ can be used to calculate the mean steady-state CSF concentration $C_{SSCSF}$ for a given daily dose and the mean half-life time to equilibrium, $t_{1/2}$, from the following equations:

$$C_{SSCSF} = C_{SSplasma} \cdot PC = \frac{(\text{Daily Dose})/24}{CL} \times PC \quad (6)$$

$$t_{1/2} = \frac{\ln 2}{k_{CSF}} \quad (7)$$

**Model selection criteria**

The improvement of the fit obtained for each model was assessed in several ways. First, the resulting NONMEM-generated minimum value of the objective function (MVOF) was used to perform the likelihood ratio test. This test is based on the change in the MVOF ($\Delta$MVOF), which is equal (up to a constant) to minus twice the log-likelihood of the data and is asymptotically distributed like $\chi^2$, with the degrees of freedom equal to the number of parameters added to the model. $\Delta$MVOFs of $-10.83$ or $-12.12$ were required to reach statistical significance at $P \leq 0.0010$ or $P \leq 0.0005$ for the inclusion or exclusion, respectively, of one fixed effect in nested models. These stringent statistical criteria were used to avoid the inclusion of weak and clinically not relevant effects. In addition, the improvement of the fit was assessed through the reduction of the IIV and residual variability, the precision in parameter estimates, and the examination of diagnostic plots.

**Pharmacokinetic model qualification**

A non-parametric bootstrap analysis was performed as an internal model validation technique using the package Wings for NONMEM. A new replication of the original dataset (a bootstrap sample) was obtained by $N$ random draws of individual data (with replacement) from the dataset. The final population pharmacokinetic model was re-fitted to each new dataset and this process was repeated 1000 times with different random draws. The stability of the final model was evaluated by comparing the final model parameter estimates with the mean and 95% CIs of the non-parametric bootstrap replicates of the final model. If the parameter estimates fell into the 95% CI obtained from the bootstrap analysis the model was considered unbiased.

In addition, a visual predictive check (VPC) was performed using the technique described by Yano et al. The parameter estimates obtained by fitting the population pharmacokinetic model to the final model were used to simulate the population pharmacokinetic profile of doripenem in plasma and in CSF. A non-parametric 90% prediction interval around the median plasma and CSF concentration was constructed to quantify the variability in the model predictions and to visually compare with the observed concentrations.

**Pharmacokinetic simulations**

Using the full pharmacokinetic model, with plasma parameters fixed to the literature values and CSF parameters obtained in the developed model, Monte Carlo simulations were performed and an 80% prediction interval was built. A simulated 4 day therapy of 500 and 1000 mg of doripenem administered every $8\ h$ was considered, while resulting CSF concentrations were compared with the observed concentrations.

**Results**

Doripenem plasma and CSF concentration versus time data taken from 46 interventions (drug administrations on different occasions) in 38 neurological patients enrolled in the present study are shown in Figure 1. In total, 41 plasma samples were included in the analysis from 34 patients. No plasma samples were available for 4 of the 38 patients in the study. A single plasma sample was extracted on each occasion. Furthermore, a total of 49 CSF samples were included in the analysis from 38 patients. One CSF sample per occasion was taken except on three occasions, where two samples were taken. These data are strong evidence that doripenem enters the CSF to a considerable extent in patients with non-inflamed meninges (Figure 1). The studied population was all Caucasian, with a mean weight and age of 76 kg and 37 years old, respectively, and a mean creatinine clearance of 128 mL/min.

**Pharmacokinetic modelling**

A NONMEM analysis was performed and the final model was chosen as the one giving the lowest value of the objective function. The mean values of $k_{CSF}$ and $PC$ were estimated along with...
their standard errors, while the residual variability for CSF ($\sigma_2^2$) was considered to be the only variance component and was also estimated. The estimates for the means of the parameters are presented in Table 2. These values correspond to a mean steady-state CSF concentration of $C_{SSCSF} = 0.20$ mg/L for a 1500 mg daily dose calculated from equation (6) and a mean half-life time to equilibrium of $t_{1/2} = 6.6$ h calculated from equation (7).

### Model qualification

Figure 1 displays the observed versus predicted plots for plasma (Figure 1a) and CSF (Figure 1b) doripenem concentrations, which showed a normal random scatter around the identity line and indicated the absence of significant bias.

The results of the VPC performed on the plasma and CSF concentrations are presented in Figure 1(c) and Figure 1(d), respectively. In this figure, the 5th, 50th and 95th percentiles of the model-based prediction for plasma and CSF concentrations are presented together with the observed plasma and CSF

### Table 2. Parameter estimates with standard error (SE) expressed as percentage coefficient of variation (CV%), and bootstrap analysis of the final population pharmacokinetic model for the distribution of doripenem into the CSF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original dataset fit estimate</th>
<th>Non-parametric bootstrap fit estimate</th>
<th>SE CV%</th>
<th>SE CV%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{CSF}$ (per h)</td>
<td>0.105</td>
<td>0.101</td>
<td>30.4</td>
<td>34.8</td>
<td>0.026 - 0.161</td>
</tr>
<tr>
<td>$PC$</td>
<td>0.053</td>
<td>0.067</td>
<td>22.8</td>
<td>77.4</td>
<td>0.039 - 0.177</td>
</tr>
<tr>
<td>Error $\sigma_2$ (CV%)</td>
<td>44.8</td>
<td>44.0</td>
<td>19.7</td>
<td>19.6</td>
<td>34.8 - 51.8</td>
</tr>
</tbody>
</table>

Figure 1. Observed versus predicted plots for (a) plasma and (b) CSF doripenem concentrations. (c) Doripenem concentration in plasma and (d) CSF after administration of 500 mg as a 30 min intravenous infusion to 38 neurological patients together with the VPC for the plasma model and VPC for the developed CSF model. Lines correspond to 5th, 50th and 95th percentiles (from bottom to top).
concentrations. Figure 1(c) is evidence that the selected model from the literature describes well the doripenem plasma concentration and can be used as a forcing function for the open loop CSF model (equation 5). Figure 1(d) is evidence that the model developed for the CSF is appropriate to describe the time course of doripenem concentrations in the CSF.

Non-parametric bootstrap analysis and posterior predictive check were used to qualify the model developed. The analysis of the bootstrap replicates is given in Table 2. The mean estimates for the final model were found to be similar to the mean 1000 bootstrap replicates, and were contained within the 95% CIs obtained from the bootstrap analysis, suggesting the absence of bias in the NONMEM parameter estimates. The precision of the NONMEM parameter estimates was also in good accordance with the standard errors obtained by bootstrap analysis (Table 2).

Model simulations

Simulations were performed for two dosage regimens of doripenem: (i) $3 \times 500$ mg daily and (ii) $3 \times 1000$ mg daily for 4 days using the mean values of the model parameters. The results are shown in Figure 2, where the accumulation pattern of doripenem for the 4 day treatment is plotted for the two doses. The horizontal lines in all plots correspond to MIC$_{90}$ values of 0.25 mg/L and 0.50 mg/L, respectively.

Discussion

The present study undertakes the initiative to examine the penetration of doripenem through the intact BBB and describe its pharmacokinetics in the CSF of patients with no active neurological disease using mixed-effects compartmental modelling. Patients were submitted to the neurosurgery clinic of Evangelismos General Hospital either for the implantation of a pump for the intrathecal administration of baclofen or for the baclofen test. The danger of post-operative meningitis makes aggressive chemoprophylaxis necessary, a decision made by the surgeon following consultation with the hospital Infectious Disease Department. Doripenem was selected on this basis, in addition to vancomycin, which represents the standard of care. The risk of meningitis, the frail health of many of these patients and the incidence of nosocomial infections by strains highly susceptible to doripenem justified the chosen chemoprophylaxis regimen, which under other circumstances might have been considered excessive. Moreover, single-dose chemoprophylaxis is highly unlikely to lead to the development of resistant strains.

A major problem when trying to estimate drug pharmacokinetics in the CSF of patients with non-inflamed meninges is the limited number of samples that can be withdrawn from each patient. However, the construction of CSF concentration versus time profiles requires multiple CSF sampling. This is feasible in patients that actually have CNS infections, since a drain or shunt can enable pharmacokinetic sampling. However,
multiple CSF sampling is not feasible in patients with non-inflamed meninges, for both medical and ethical reasons. Nevertheless, this problem can be overcome by CSF sampling at different times in different patients, as was the case in the present study.

The results of the present pharmacokinetic study show that doripenem penetrates non-inflamed meninges to a considerable extent. Doripenem levels in CSF after single-dose administration of 500 mg ranged from 0.05 to 0.50 mg/L, depending on the time of CSF sampling after the end of drug infusion (Figure 1), while the respective plasma levels were measured between 0.2 and 22 mg/L for the same time interval. These results confirm our preliminary results based on measurements from five neurological patients with non-inflamed meninges, where doripenem was found to enter the CSF to a measurable extent.

Since only one plasma sample per subject was available, the shrinkage of the EBEs of the pharmacokinetic parameters in plasma was calculated. The shrinkage values for $CL$, $V_1$, $V_2$, and $V_3$ were 32%, 38%, 74% and 76%, respectively. These values are high, as expected from the limited sampling. High shrinkage values indicate EBEs biased towards the population mean, which could affect the estimates of the CSF parameters. However, CL and $V_1$ corresponding to the central compartment, which drives the CSF kinetics (equation 5), are marginally close to 30%, which is a limit often considered acceptable.

The non-invasive design of this clinical study allowed only a limited number of samples per subject (mostly just one). The fact that only one sample per subject was available for almost all patients dictated a single variability component be included in the model. Thus no IVV was estimated, but instead all patients dictated a single variability component be included in the model. Thus no IVV was estimated, but instead all patients dictated a single variability component be included in the model. This uncertainty is consistent with the bootstrap analysis and is a result of the lack of later samples. However, despite the uncertainty, the parameter estimates provided in Table 2, which correspond to a mean steady-state CSF concentration of 0.20 mg/L for a $3 \times 500$ mg daily dose and a mean half-life time to equilibrium of 6.6 h, can provide useful quantitative information about the kinetics of the penetration of doripenem in the CSF.

Using the daily dosage regimens of $3 \times 500$ mg and $3 \times 1000$ mg, simulations were performed, which are shown in Figure 2, and demonstrate pharmacokinetic levels in the CSF corresponding to potential clinical use. The calculated steady-state concentrations of doripenem in the CSF (equation 6) are comparable to the target MIC$_{90}$ values in healthy meninges, i.e. 0.20 mg/L for the $3 \times 500$ mg daily dose and 0.40 mg/L for the $3 \times 1000$ mg daily dose. The pharmacodynamic index predictive of in vivo efficacy for carbapenems, including doripenem, is $T_{\text{MIC}}$, the cumulative percentage of a 24 h period that drug concentration exceeds the MIC at steady-state pharmacokinetic conditions. A range of $T_{\text{MIC}}$ values of 30%–50% is generally considered necessary to achieve bacteriostatic to bactericidal activity. According to the simulations (Figure 2) for a doripenem dose equal to $3 \times 500$ mg, the median of predicted doripenem CSF levels corresponding to a typical subject would remain slightly below MIC$_{90}=0.25$ mg/L ($S.\ pneumoniae$), whereas with a dose of $3 \times 1000$ mg a typical subject would be well above MIC$_{90}=0.25$ mg/L, but still below MIC$_{90}=0.50$ mg/L ($P.\ aeruginosa$). Also, for the higher dose, the prediction interval of 80% indicates that the probability of a patient having drug levels below MIC$_{90}=0.25$ mg/L is small (close to the lower 10th percentile), while there is a significant probability (but <50%) that the levels are above MIC$_{90}=0.50$ mg/L. Given that these simulated levels correspond to non-inflamed meninges, doripenem penetration in CSF is expected to be enhanced under inflammation conditions. It should be noted that all simulations were built under the assumption of linear kinetics of elimination and disposition. However, more studies need to be carried out to verify this assumption or quantify departures from it.

A comparison of MICS for different bacteria with this CSF value (Figure 2) indicated that doripenem may be useful in the treatment of CNS infections, taking into account that drug penetration through the BBB may be significantly more extensive when meningeal inflammation is present. CSF is protected from free exposure to administered drugs by BBB, which under healthy conditions permits penetration of small molecules and prevents the entry of more complex molecules into the CSF. However, permeation of more complex drugs across the blood–CSF barrier (B-CSF-B) is enhanced by inflamed meninges, due to acidosis in the CSF compartment and a consequent increase in the plasma–CSF pH gradient that enables penetration into the CSF of molecules that are ionized at normal pH. In addition, the low plasma protein binding of doripenem may also facilitate drug entry into the CSF. Pharmacokinetic studies in patients with inflamed meninges would provide more information about doripenem’s pharmacokinetics in CSF and may strengthen the results of the present study by supporting the hypothesis that the in vitro broad-spectrum activity of doripenem correlates with high effectiveness in the treatment of nosocomial meningitis. Clinical studies with other carbapenems such as meropenem and imipenem have shown that these agents can be successfully used for the empirical treatment of serious nosocomial bacterial infections caused by susceptible pathogens. Fluid and tissue concentrations of imipenem are comparable to the values of β-lactam antibiotics, with the exception of relatively less penetration into CSF compared with third-generation cephalosporins. On the other hand, meropenem penetrates well into most body fluids and tissues, including CSF, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. Meropenem is approved by the FDA for the treatment of CNS infections in combination with vancomycin. However, a warning regarding potential seizures while on meropenem was published by the FDA in 2008. Therefore the results of the present study in conjunction with the lower epileptogenic potential of doripenem compared with meropenem and other carbapenems make doripenem an agent that deserves serious consideration for possible use in the treatment of
certain CNS infections. This suggestion is supported by the successful treatment of ventriculitis due to imipenem- and meropenem-resistant P. aeruginosa with doripenem and tobramycin that was reported recently and the results of the recent study of Stuki et al., where doripenem was found equal to or slightly more efficacious when used as monotherapy for the treatment of experimental meningitis due to Gram-negative microorganisms. However, more studies in patients with active CNS infection should be performed in order to confirm and strengthen the results of the present study.

Conclusions
A non-invasive clinical study allowing a limited number of samples per subject (in most cases just one) was carried out on patients having an intact BBB, aiming to elucidate the pharmacokinetics of doripenem in CSF. The present NONMEM analysis of doripenem CSF data shows that doripenem enters the CSF significantly, even in healthy non-inflamed meninges. The parameter estimates, which correspond to a mean steady-state CSF concentration of 0.20 mg/L and 0.40 mg/L for a 3 × 500 mg and a 3 × 1000 mg daily dose, respectively, and a mean half-life time to equilibrium of 6.6 h, can provide useful quantitative information about the kinetics of the penetration of doripenem into the CSF. The calculated steady-state concentrations correspond to efficacious doripenem levels for most patients. Thus doripenem may be considered for further evaluation as a candidate to treat certain CNS infections, also taking into account that higher doripenem steady-state CSF concentrations are expected under inflamed conditions, since meningeal inflammation is known to increase the permeability of both the BBB and B-CSF-B.

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Transparency declarations
None to declare.

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