Pharmacokinetics of doripenem in cerebrospinal fluid

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Introduction

Doripenem (DRP) is a carbapenem antibiotic that exhibits bactericidal action by inhibiting bacterial penicillin-binding proteins. It is active in vitro against both gram-positive and gram-negative aerobic and anaerobic organisms [1] and is including pathogens that cause dangerous nosocomial infections, such as *Pseudomonas aeruginosa, Acinetobacter spp, Streptococcus pneumonia* etc. A review of the literature found no data on the penetration of the blood-brain barrier by DRP in humans.

Purpose

To investigate the blood-brain barrier penetration of DRP and to characterize its pharmacokinetics in cerebrospinal fluid (CSF), using a model developed by NONMEM.

Methods

Analytical procedures

44 neurological patients received a single 500 mg prophylactic dose of DRP at various times before surgery for implantation of a pump for intrathecal administration of baclofen or after lumbar puncture for the trial intrathecal infusion of baclofen. Patients had neither active neurological disease nor infection of the CNS. A single CSF sample was collected from each patient through the intrathecal catheter to check the proper placement of the catheter. All CSF samples were transferred on ice after the addition of an equal volume of buffer (MOPS 1 M), to prevent drug degradation and stored at -70°C. In some cases two samples of CSF per patient were collected, as well as one blood sample. Samples were analyzed using an HPLC method [2] and DRP concentrations were quantified.

Modeling

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 [3] to estimate the Empirical Bayesian Estimates (EBE) of the PK parameters of each patient for DRP in plasma. The structural model was parameterized as (CL, V1, Q2, V2) with the following covariate model [3].

$$CL = \theta1 * (CRCL/98)^{\theta5}$$
$$V1 = \theta2 * (WT/73)^{\theta6}$$
$$Q2 = \theta3 * (WT/73)^{\theta7}$$
$$V2 = \theta4 * (CRCL/98)^{\theta8} * (WT/73)^{\theta9} * (AGE/40)^{\theta10}$$

The EBE of the PK parameters where used as covariates to estimate the PK parameters of a third distribution compartment corresponding to CSF [4]. The structural parameters included in the model were the rate constant, k_{CSF}, and the partition coefficient (*PC*), corresponding to the ratio of the CSF over the plasma concentration at steady state.

$$\frac{dC_{CSF}(t)}{dt} = k_{CSF}(C_1(t) \cdot PC - C_{CSF}(t)) \qquad (1)$$

Where C_1 is the plasma concentration and C_{CSF} is the concentration of the CSF.

Results

Model development

The results of this study showed that doripenem penetrates, to a small but measurable extent, the intact blood brain barrier. 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} (θ11) and *PC* (θ12) and the interindividual variability for *PC* (Ω5) were estimated together with their standard errors, while the residual variability for CSF (σ2) was fixed to the corresponding plasma value (σ1). The estimates for the mean of the parameters are presented on Table 1. These values correspond to a mean steady state CSF concentration of 0.22 mg/L for a 1500 mg daily dose and a mean half-life time to equilibrium of 6.3 hours.

Table 1: The estimates for the mean of the parameters that were taken from literature (θ1-θ10) and θ11, θ12 that were estimated by the model that was developed.

Parameters	Estimates	% SE	BSV	Estimates	% SE
θ1	13.6	-	Ω1	0.0370	-
θ2	11.6	-	Ω2	0.0349	-
θ3	4.74	-	Ω3	0.1730	-
θ4	6.04	-	Ω4	0.0924	-
θ5	0.659	-	-	-	-
θ6	0.596	-	-	-	-
θ7	1.06	-	-	-	-
θ8	0.417	-	-	-	-
θ9	0.840	-	-	-	-
θ10	0.307	-	-	-	-
kCSF (θ11)	0.1120	8.28	-	-	-
PC (θ12)	0.0508	3.18	Ω5	0.317	7.75
σ1, σ2	17 %	-	-	-	-

The Visual Predictive Check (VPC) for plasma and CSF model, is illustrated in Figures 1a and 1b, respectively.

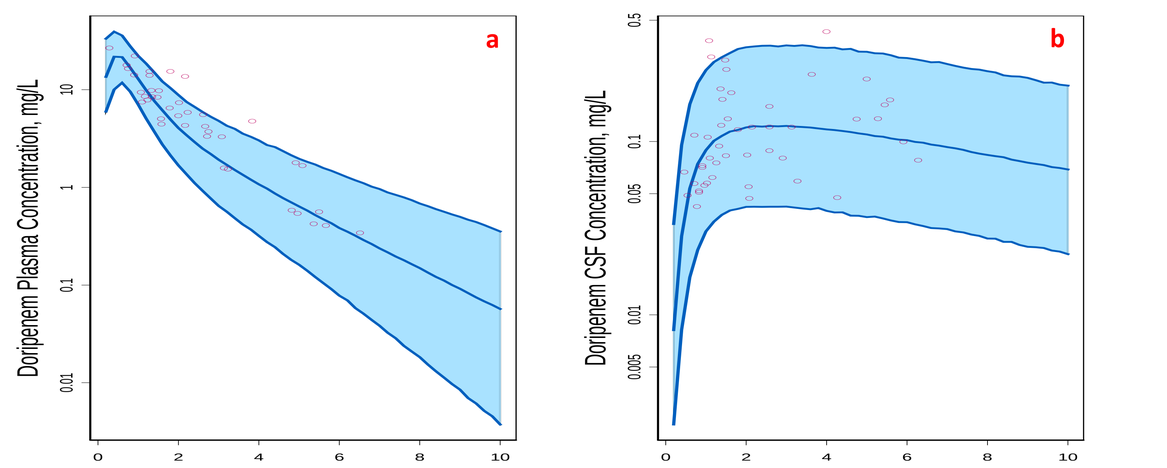

Figure 1: a) VPC for plasma model and **b)** VPC for the developed CSF model. Lines correspond to 5, 50 and 95% percentiles.

Simulations

Simulations were performed for two dosage regimens of DRP: a) 3x500 mg and b) 3x1000 mg, daily for 4 days (Fig. 2a and 2b, respectively). The pharmacodynamic index predictive of in vivo efficacy for the carbapenems, including DRP, is %T>MIC (the cumulative percentage of a 24h period that drug concentration exceeds MIC at steady state PK conditions), where %T>MIC between 30% to 50% is generally considered the range necessary to achieve bacteriostatic to bactericidal activity. For the second dose, 39% of patients maintained DRP concentrations above MIC_{90}=0.5 mg/L (e.g. *Pseudomonas aeruginosa*) and 79% of patients maintained DRP concentrations above MIC_{90} =0.25 mg/L (e.g. *Streptococcus pneumoniae*) for 40%T (Fig. 2b).

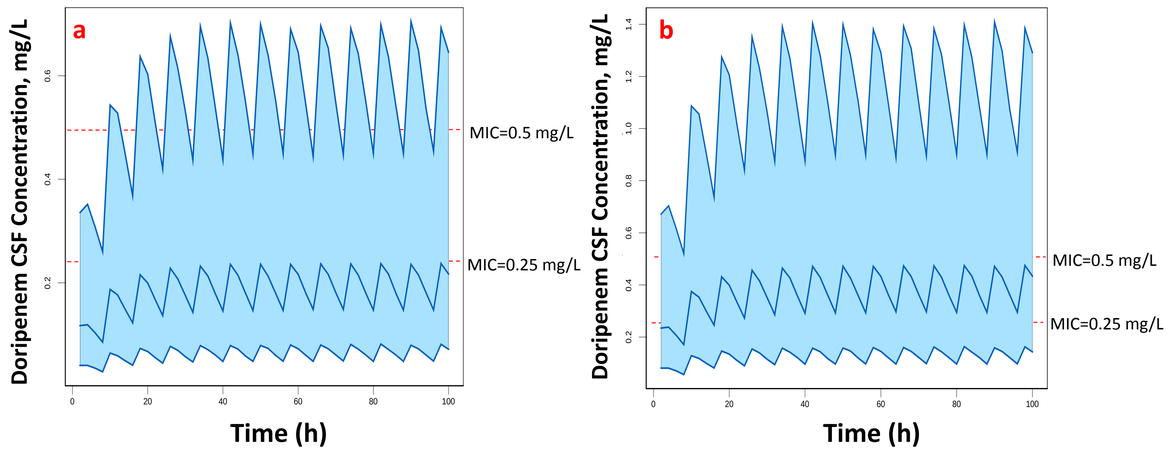

Figure 2: 90% Prediction intervals for a) 3x500 mg of DRP daily and b) 3x1000 mg of DRP daily.

Conclusions

The present NONMEM analysis of DRP CSF data shows that DRP crosses the BBB significantly even in healthy non-inflamed meninges and therefore may be appropriate to treat certain CNS infections. Since meningeal inflammation increases the permeability of BBB higher DRP steady state CSF concentration are expected under inflammation conditions.

References

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