Stochastic Simulations Assist to Improve a Poorly Designed Clinical Study for the CSF Pharmacokinetics of Doripenem

Nalda-Molina[1,2], A. Dokoumetzidis[1], G. Valsami[1]

[1]School of Pharmacy, University of Athens, Greece, [2]School of Pharmacy, University Miguel Hernandez de Elche,Spain

Introduction

Doripenem (DRP), a carbapenem antibiotic, is active in vitro against gram-positive and gram-negative aerobic and anaerobic organisms [1], including pathogens that cause dangerous nosocomial infections, such as *Pseudomonas aeruginosa, Acinetobacter spp, Streptococcus pneumonia* etc. A previous study [2] investigated the cerebrospinal fluid (CSF) pharmacokinetics of doripenem after IV administration to patients, using NONMEM 7.2. Briefly, the model consists of a standard two compartment model (the parameters of which were taken and fixed from the literature), plus a third distribution compartment corresponding to CSF, parameterized in terms of distribution rate constant (Kcsf) and partition coefficient (PC) which were estimated from plasma and CSF data.

However, a limited sampling design (including mostly one sample per patient) and the lack of later samples (after 6 hours) led to a high uncertainty in the parameter estimation.

Purpose

To assess the impact of addiing new patients with improved sampling design to the dataset of a previous study of DRP in the CSF with sampling design problems, by performing stochastic simulations including uncertainty.

Patients and Methods

Previous PK-Study design and dataset

36 neurological patients received a single 500mg DRP dose before baclofen pump implantation surgery. In most cases a single CSF sample was taken from each patient through the catheter to test the pump. Blood samples were also taken either immediately after the end of drug infusion and/or at the same sampling time as the CSF sample. A pharmacokinetic analysis was carried out in two stages: 1) the plasma samples and literature population priors for a two-compartment model [3] were used 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) [3]. The EBE of the PK parameters where used as covariates to estimate the PK parameters of a third distribution compartment corresponding to CSF. 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 [4]. The parameters estimates obtained by this model and the initial dataset are shown in Table 3.

PK-Simulation

5, 15, 30 or 60 patients, with one CSF and plasma sample at 12 hours, were simulated and added to the initial dataset to assess the impact of the addition of new patients with improved sampling design. In order to cover the uncertainty in the non-fixed parameters of the model (k_{CSF} and PC), simulations of three scenarios were performed, corresponding to the 25th, 50th and 75th percentiles of the uncertainty parameter distribution obtained from the bootstrap analysis of the previous NONMEM analysis (Table 1). Then, estimation of k_{CSF} and PC for the 12 datasets obtained (36 patients + 5, 15, 30 or 60 extra-patients, simulated from the 25th, 50th or 75th percentiles) were performed and the results summarized (Table 2).

	Percentile in bootstrap distribution		
	25% (Scenario 1)	50% (Scenario 2)	75% (Scenario 3)
K_{csf} h^{-1}	*0.036*	*0.067*	*0.108*
PC	*0.154*	*0.082*	*0.051*
Residual Error (CV%)	*44.8*	*44.8*	*44.8*

Table 1. Sets of parameters used to simulate 5, 15, 30 and 60 extra-patients that were added to the original dataset. These parameters were obtained from the bootstrap distribution obtained after 1000 runs.

Results

The simulations showed a significant reduction in the RSE of the model parameter estimates, even with only five extra-patients. In fact, including more than 15 extra patients, i.e. 30 or 60, did not have a significant added benefit (Table 2). Also, it is worth to note that the RSE reduction was more pronounced in the 75th percentile scenario, rather than the 50th percentile as one would have expected.

In Figure 1, the VPC plots built with the parameters of the three simulated scenarios are shown together with the dataset. It can be observed that the VPC plots are very similar up to the final point (at 6 hours) of the initial dataset (green circles). After 6 hours, the difference in the VPC becomes more apparent due to the fact that initial dataset does not cover this region, hence the large uncertainty in the parameter estimates.

Based on the simulations and VPC results, new patients were included in the study, with one CSF sample per patient collected at 12 hours after the start of drug infusion (red circles, Figure 1). However, the number of new patients that were included at the end was only two because of a limited time frame. The final analysis of the full dataset (5) showed a reduction of the estimates standard error by 75% approximately (Table 3) even with only two extra samples. Moreover, the new parameter estimates were close to the 75th percentile scenario rather than the 50th, in accordance with the results of the simulations. In the VPC plots of Figure 1, the two extra-patients (red circles) give the additional information needed to discriminate between the three scenarios, and clearly favor the third one.

	Nº extra-patients	K^*_{csf}	PC*
Scenario 1	*60*	*0.0335 (38%)*	*0.153 (29%)*
	30	*0.0423 (33%)*	*0.123 (25%)*
	15	*0.0398 (41%)*	*0.13 (33%)*
	5	*0.0275 (65%)*	*0.185 (55%)*
Scenario 2	*60*	*0.0577 (22%)*	*0.0914 (13%)*
	30	*0.0722 (19%)*	*0.0744 (11%)*
	15	*0.0551 (31%)*	*0.0955 (24%)*
	5	*0.0476 (64%)*	*0.109 (57%)*
Scenario 3	*60*	*0.112 (11%)*	*0.0502 (5%)*
	30	*0.113 (14%)*	*0.0498 (8%)*
	15	*0.109 (15%)*	*0.0517 (9%)*
	5	*0.106 (25%)*	*0.0528 (19%)*

*Expressed as mean values (RSE%)

Table 2. Mean values estimation of K_{csf} and PC, after adding 60, 30, 15 or 5 simulated extra-patients (according to the specifications of the three scenarios), to the initial dataset.

	Original dataset		Original dataset + 2 extra-patients	
	Dataset Fit	BS results	Dataset Fit	BS results
K_{csf} h^{-1}	*0.0532 (113%)*	*0.0800 (69.0%)*	*0.105 (30.4%)*	*0.101 (34.8%)*
PC	*0.0986 (101%)*	*0.124 (108%)*	*0.0534 (22.8%)*	*0.0668 (77.4%)*
Res. Error (CV%)	*44.8 (21.4%)*	*44.9 (19.4%)*	*44.8 (19.7%)*	*44.0 (19.6%)*

*Expressed as mean values (RSE%)

Table 3. Mean values estimation of K_{csf} and PC of the initial and the new datasets, where two new patients with longer sample times were added. The bootstrap results of each analysis are also shown.

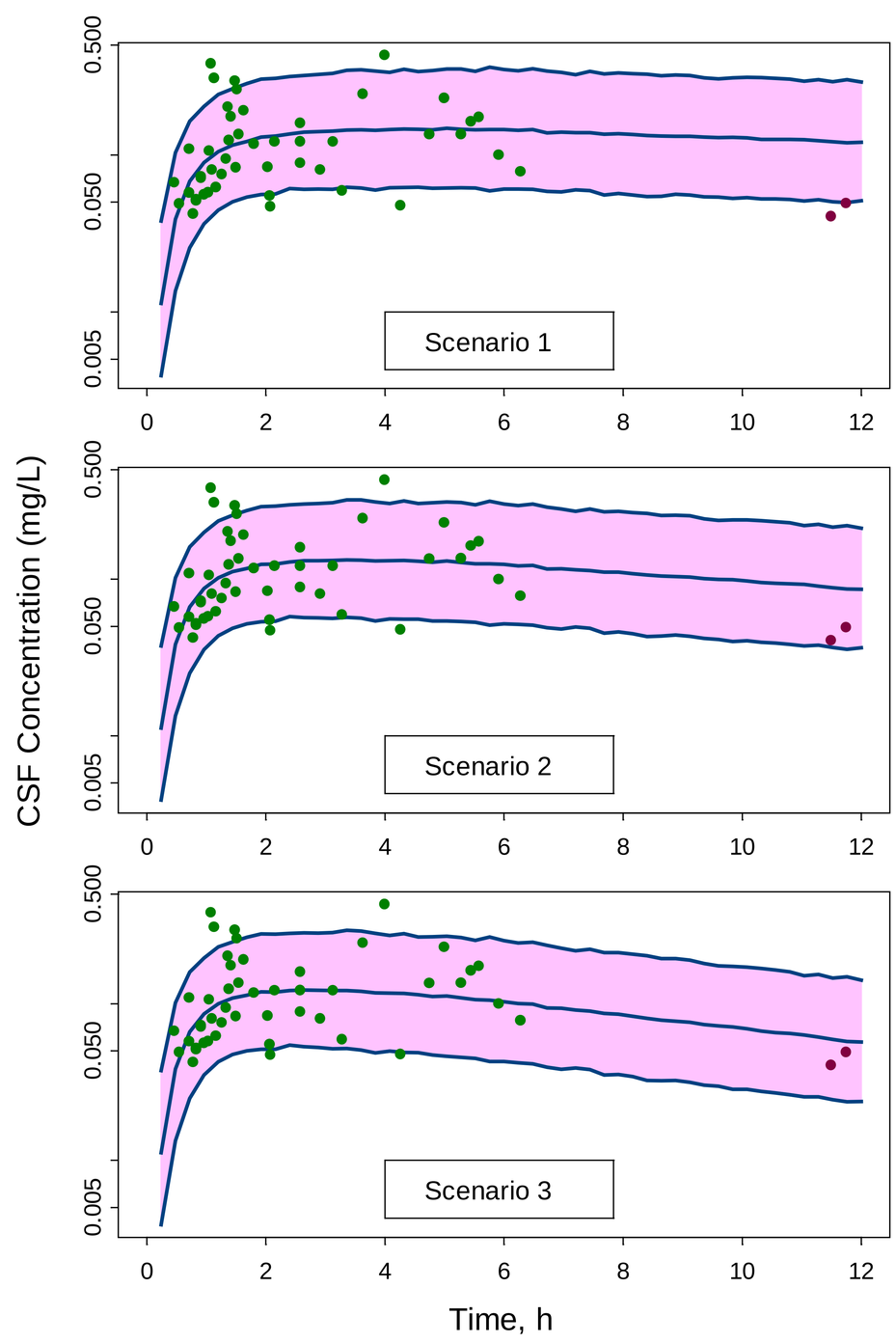

Figure 1. Visual Predictive Check plots (90%) built with the parameters of the three simulated scenarios, before the new patients were added to the dataset. Green dots represent the initial dataset, while red dots represent the two new patients.

Conclusions

Stochastic simulations are useful to improve the clinical study design, and inform about the impact of new patients, and new sampling times, even when the original estimates are biased.

References

[1] Matthews J. and Lancaster J. *Clin. Therapeut.*; 31:42-63 (2009).
[2] Charkoftaki, G. et al. Poster Communication, *AAPS Annual Meeting,* New Orleans (2011).
[3] Nandy et al, *Antimicrob Agents Chemother*. 54:2354-9 (2010).
[4] Anderson et al, *Br J Clin Pharmacol.* 46:237-43 (1998).
[5] Nalda-Molina et al, *J Antimicrob Chemother*. (2012) [ahead of print]