Prediction of subtherapeutic tigecycline plasma levels by model-based Bayesian individualization

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Objectives

The aim of this study was the investigation of optimal sampling schedules for estimating posthoc clearance of the bacteriostatic antibacterial agent, tigecycline, and subsequently the assessment of their performance, in terms of predicting response as early as possible, in the treatment of complicated skin and skin-structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs).

Methods

A dataset of 1000 subjects, generated in MATLAB, was used to evaluate a total of 95558 combinations of 4 sampling times per individual, classified in 4 cases, based on practical considerations (Table 1).

Table 1. Classification of time combinations

case	description	comb.	t_1	t_2	t_3	t_4
1	2 samples up to 48 h, at different doses, 2 up to 60 h	20592	[12-24]	[25-48]	[49-60]	[49-60]
2	2 samples early, 2 up to 48 h	41580	[1-12]	[1-12]	[13-48]	[13-48]
3	1 sample per dose up to 48 h	20736	[1-12]	[13-24]	[25-36]	[37-48]
4	All possible times between 48 to 72 h	12650	[48-72]	[48-72]	[48-72]	[48-72]

For each combination, concentration-time data were simulated in NONMEM 7.3 from a literature two-compartment population PK model [3] and the empirical Bayes estimates of the PK parameters were estimated. The dosage regimen applied, was a loading IV bolus dose of 100 mg followed by 50 mg infusions over 1 h, every 12 h. In the population model, systemic clearance (CL) was a function of body weight in kg (WT), creatinine clearance in ml/min (CLCR) and gender (G, male=1, female=0):

$$CL_j(liters/h) = 15.7 \cdot (CLCR_j/88.3)^{0.250} + 0.0943 \cdot (WT_j - 80) + 3.23 \cdot G_j$$

Tigecycline follows linear kinetics and the AUC_{24}/MIC ratio is the PK-PD index predictive of efficacy with breakpoints (BP) of 17.9 (cSSSIs) [1] and 6.96 (cIAIs) [2]. Thus, the main focus was on CL, from which the AUC_{24} was calculated as Dose/CL. The absolute relative mean prediction error (|MPE%|) and the 90th percentile of the |MPE%| of the AUC_{24} as measures of bias, the relative root mean square prediction error (RMSE%) of the AUC_{24} as a measure of precision and the ETA shrinkage of CL as a measure of informativeness, were computed and regarded as optimality criteria. Moreover, the D-optimality criterion, i.e. the determinant of the Fisher information matrix (FIM) of the typical individual was maximized.

The assessment of predictive performance of the time combinations was based on metrics derived from the confusion matrices (Table 2) corresponding to each MIC of interest [4] for both cSSSIs and cIAIs. The positive status corresponds to subtherapeutic plasma levels. Specifically, accuracy (ACC), sensitivity (TPR), specificity (TNR) and the Matthews correlation coefficient (MCC) were calculated.

Table 2. Confusion matrix of the method

	$(AUC_{24}/MIC)_{est}$<BP	$(AUC_{24}/MIC)_{est}$>BP
$(AUC_{24}/MIC)_{sim}$<BP	true positives	false negatives
$(AUC_{24}/MIC)_{sim}$>BP	false positives	true negatives

Results

According to the statistical optimality criteria considered, the sampling schemes that gave optimal estimations of posthoc clearance, hence of the AUC_{24}/MIC ratio, are presented in Table 3. The results of Table 3, based on calculating the bias in estimating clearance were different to the ones derived from the maximization of the determinant of the FIM, indicating that the FIM method may not be reliable for this task.

Table 3. Optimal sampling schemes for each case

case	optimal scheme (h)	|MPE%|	|MPE%| 90th prc	RMSE%	ETA shr CL
1	13, 48, 59, 60	10.78	22.22	13.53	7.29
2	1, 12, 47, 48	11.65	23.36	14.63	7.48
3	1, 24, 36, 48	11.81	25.18	14.87	9.65
4	**61, 64, 71, 72**	9.87	21.50	12.53	7.61
overall range		9.87-22.03	20.57-45.78	12.52-28.46	7.25-35.38

The predictive performance of the optimal sampling schemes appeared to vary across the MIC range and alternate between the two therapeutic indications. Tables 4 and 5 show the results for two representative MICs in the case of cSSSIs and cIAIs respectively. Overall, the predictive performance of the selected schemes was considered satisfactory.

Table 4. Assessment of predictive performance for MIC=0.25 and 0.5 (cSSSIs)

scheme (h)	13, 48, 59, 60		1, 12, 47, 48		1, 24, 36, 48		61, 64, 71, 72	
MIC (mg/L)	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.5
ACC	0.913	0.943	0.896	0.938	0.886	0.936	0.904	0.948
TPR	0.918	0.991	0.909	0.991	0.895	0.988	0.898	0.988
TNR	0.910	0.542	0.889	0.495	0.881	0.495	0.907	0.617
MCC	0.814	0.664	0.781	0.628	0.759	0.616	0.794	0.701

Table 5. Assessment of predictive performance for MIC=0.5 and 1 (cIAIs)

scheme (h)	13, 48, 59, 60		1, 12, 47, 48		1, 24, 36, 48		61, 64, 71, 72	
MIC (mg/L)	0.5	1	0.5	1	0.5	1	0.5	1
ACC	0.940	0.917	0.941	0.895	0.934	0.912	0.950	0.921
TPR	0.839	0.966	0.845	0.961	0.857	0.962	0.901	0.961
TNR	0.959	0.752	0.959	0.674	0.949	0.743	0.959	0.787
MCC	0.783	0.757	0.787	0.688	0.769	0.743	0.825	0.771

According to the calculations of the AUC_{24}/MIC for the simulated data, for all the subjects, therapeutic plasma levels were achieved for MICs equal to or less than 0.25 mg/L (cSSSIs) and 0.5 mg/L (cIAIs). Moreover, therapeutic plasma levels were not achieved for MICs equal to or greater than 1 mg/L (cSSSIs) and 2 mg/L (cIAIs), confirming the results of a recent study [4].

Conclusions

The results of an optimality study for tigecycline, are presented, but the methodology can be expanded to other agents of this kind. The optimization of antibacterial dosing can be used to prevent an upsurge in antimicrobial resistance as well as to improve clinical response.

References

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