Implementation and validation of a pharmacokinetic model for Bayesian therapeutic drug monitoring of daptomycin in patients with bone and joint infection

J Heitzmann[a], R Bricca[b], S Roux[b], MC Gagnieu[a], A Becker[b], A Conrad[b], F Valour[b,c], F Laurent[c], C Triffault-Fillit[b], C Chidiac[b,c], T Ferry[b,c], S Goutelle[a,d].
[a]Hospices Civils de Lyon, Service de Pharmacie/Pharmacologie; [b]Hospices Civils de Lyon, Service des Maladies Infectieuses et Tropicales; [c]INSERM U1111, International Center for Research in Infectiology (CIRI), Université Lyon 1; [d]UMR CNRS 5558, LBBE, Université Lyon 1, Lyon, France

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Introduction

Off-label therapy of bone and joint infections (BJI)

Antibacterial effect correlates with AUC/MIC[1,2]

Daptomycine

A lipopeptide antibiotic

Muscular toxicity correlates with high trough[1,2]

Objectives

→ To **implement** and **validate** a pharmacokinetic (PK) model for Bayesian therapeutic drug monitoring (TDM) of daptomycin.

→ To **assess** the dosage requirements of Daptomycin in patients with BJI.

1. Safdar et al. Antimicrob Agents Chemother. 2004 Jan;48(1):63-8 2. Bhavnani et al. Clin Infect Dis. 2010 Jun 15;50(12)

Material and methods

Re-analysis of a published dataset from 81 patients [3]

Getting a nonparametric model with Pmetrics

Model implementation in the BesDose™ software[4]

External validation of the model (n = 94 patients)

Predictive performance of the model was assessed by mean error (ME) and mean absolute percent error (MAPE) of individual predictions.

→ **Evaluation of dosage requirements**: the nonparametric model was used to estimate the AUC at the first TDM occasion and calculate the dose required to achieve the AUC target (≥ 666 mg.h/L) and the Cmin target (< 24 mg/L) in each individual patient.

3. Bricca et al. J Antimicrob Chemother 2019 Apr;74(4):1012-1020 4. Neely et al. Ther Drug Monit. 2012 Aug;34(4):467-76

Results

A two-compartment model, including the influence of creatine clearance (Clcr) and body weight (BW) :

- **Learning dataset** : 81 patients
  → ME of -0.7 ± 4.3 mg/L, MAPE of 6.3 ± 8.1 %
- **Validation dataset** : 94 patients
  → ME = -0.18 ± 5.29 mg/L, MAPE = 7.9 ± 34.7%

Variables	Value
Sex	40 Females (42,5%)
Age (years)	62 ± 17
BW (kg)	76 ± 18
CLcr (ml/min)	103 ± 56
Concentrations per patient for external validation with BestDose™	2.8 ± 0.5
Initial dose (mg/kg/24h)	7.6 ± 1.3
Mean AUC at the steady-state on the first TDM occasion (mg.h/L)	957 ± 386

Table 1 : Characteristics of the 94 patients in the validation dataset (mean ± SD or %)

23% Of patients showing underexposure (AUC < 666 mg.h/L)

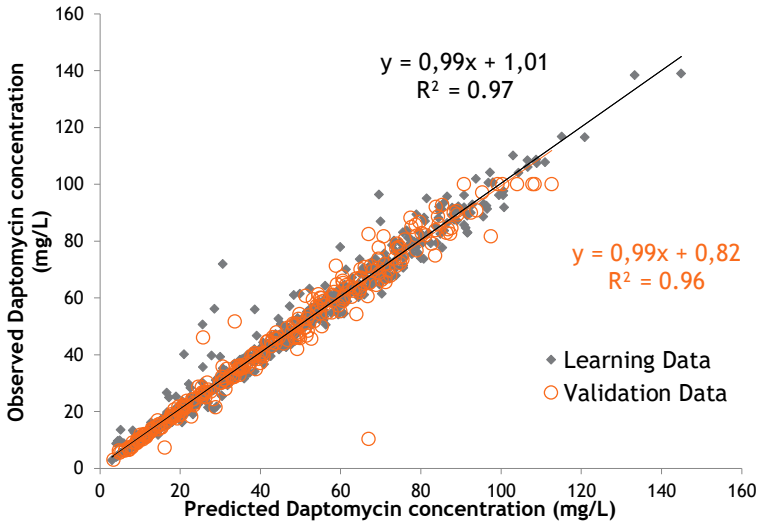

Figure 1 : Observed versus predicted daptomycin plasma concentrations

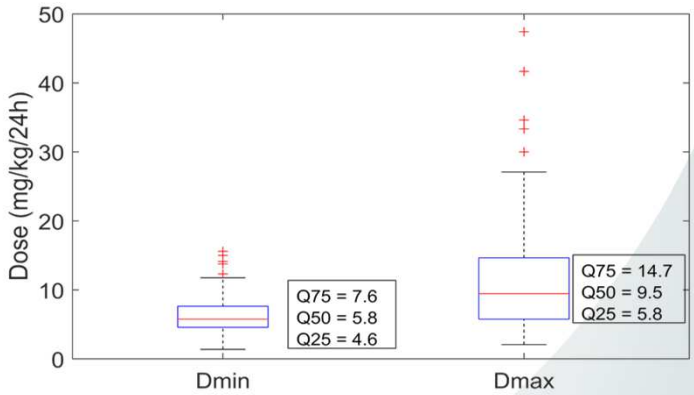

Figure 2 : Box plot of model-based minimal (Dmin) et maximal (Dmax) effective dose of daptomycine

Discussion / Conclusion

→ Our results suggest that **daptomycin dosing can be optimized in patients with BJI**, as a significant proportion of patients are underexposed, while others may have low dosage requirements.

→ Bayesian TDM may be valuable and our PK model is now **validated for this use**.