Successful validation of a model-informed precision dosing instrument for meropenem in critically ill patients, the DoseCalculator, against NONMEM®

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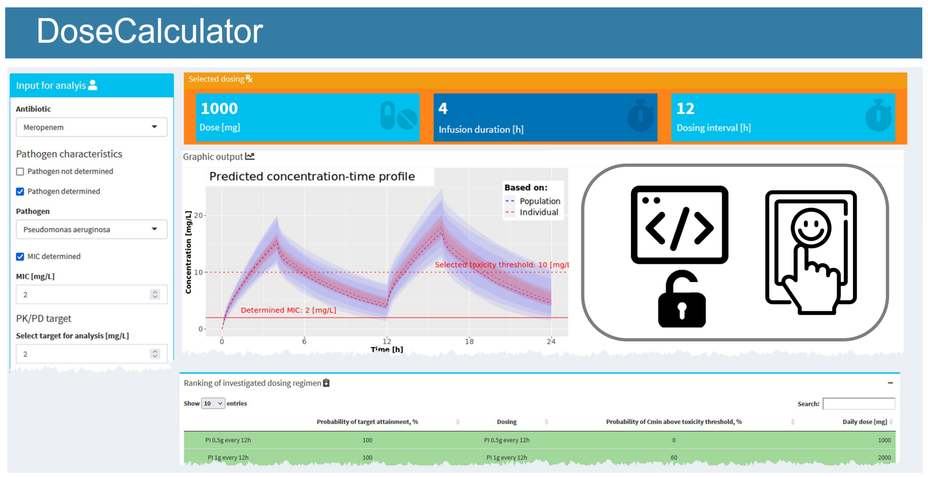
Background and Objectives



MIPD instrument
- **Meropenem** therapy
- **Critically ill** patients

TDMxR

Figure 1: Graphical user interface of the model-informed precision dosing (MIPD) instrument 'DoseCalculator' for dosing optimisation of meropenem in critically ill patients[1,2,3,4].

Academic/industry standard NONMEM®

Objective:
Validation of DoseCalculator incorporated TDMxR algorithm against NONMEM for (i) Estimation of **maximum *a posteriori* (MAP)** parameters, (ii) **Simulations with MAP** parameters & **posterior distribution#**

Methods

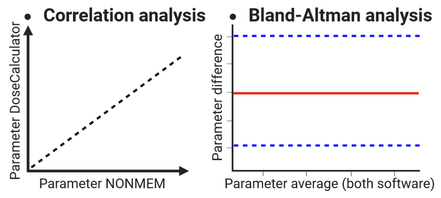
Clinical data set[5]
- $n_{patients}$=53
- $n_{samples}$=181

NONMEM®

DoseCalculator

MAP parameter estimation

TDMxR::
estimate.map()

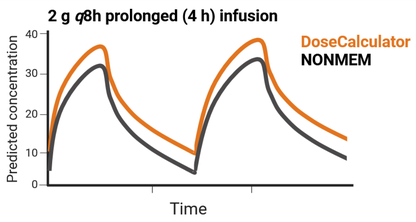


rBIAS<±10% 6,7
MARE <10%
rRMSE ↓
for MAP parameter CL, V1, V2

$ESTIMATION
MAXEVAL=0

C(t) simulation with MAP parameter & **posterior distribution#**

TDMxR::
simulate.scenario (type= "ind_var_vcov")



rBIAS <±20% 7,8,9
MARE <20%
rRMSE ↓
for $P_{0.05}$ $P_{0.50}$,$P_{0.95}$ of predicted concentration

Variance-Covariance matrix from **.phi file**

Results

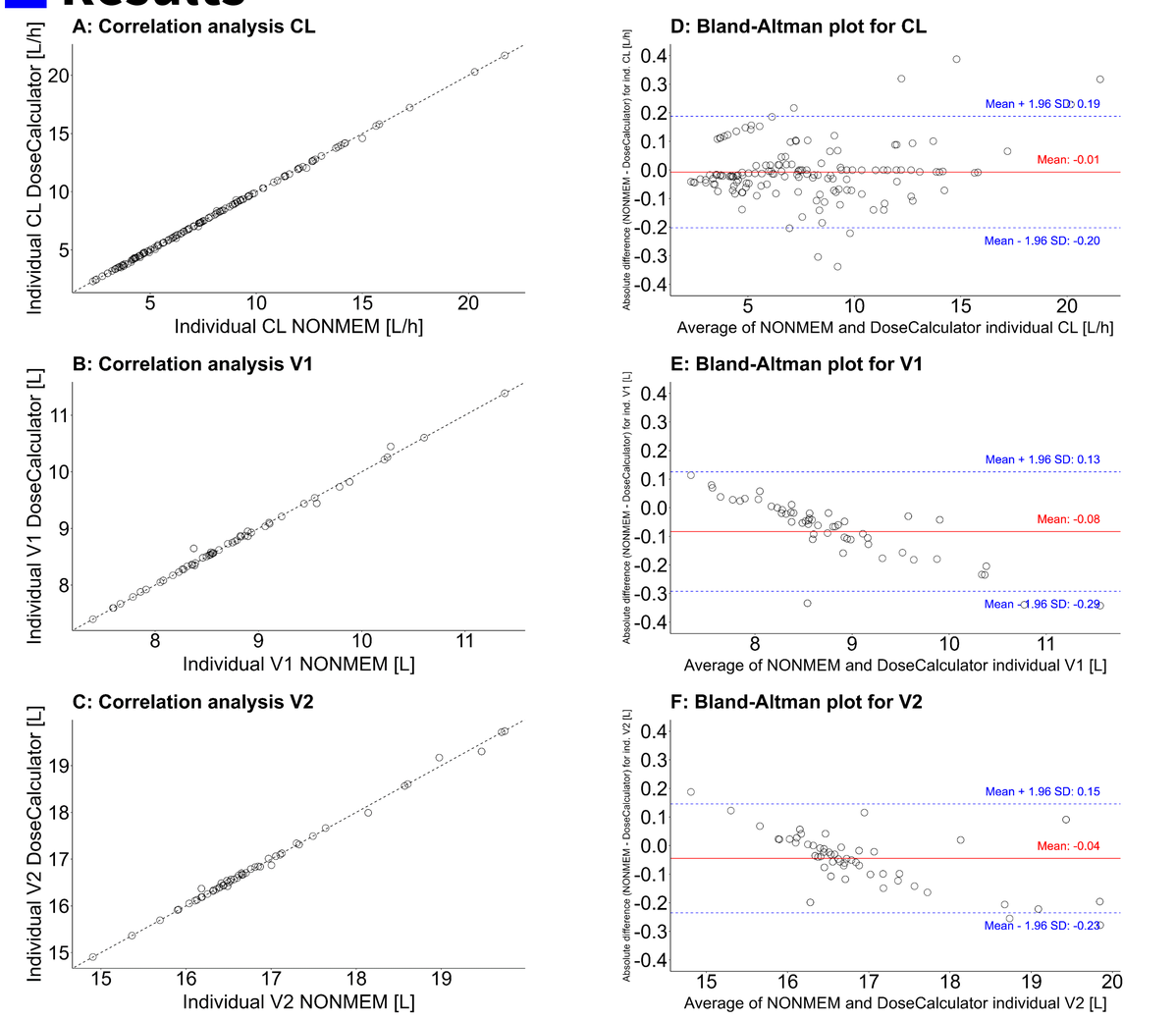


Figure 2: Comparative graphical diagrams of maximum *a posteriori* Bayesian estimation results from 53 critically ill patients derived from DoseCalculator incorporated TDMxR algorithm versus NONMEM. Left panel: Correlation analysis plots of individually predicted PK parameters CL (A), V1 (B) and V2 (C). Dashed line: line of identity. Right panel: Bland-Altman plots for CL (D), V1 (E) and V2 (F) demonstrating absolute differences in each parameter (NONMEM - DoseCalculator) against average values derived from both methods, respectively. Solid red line: mean discrepancy; blue dashed lines: limits of agreement (mean ± 1.96 standard deviations).

Table 1: rBIAS, MARE and rRMSE for the individual maximum *a posteriori* (MAP) parameters CL, V1, V2 obtained from the DoseCalculator and the NONMEM (reference) after MAP estimation in the DoseCalculator and NONMEM (reference)

MAP parameter	rBIAS (%)	MARE (%)	rRMSE (%)
CL	-0.294	0.0674	1.07
V1	0.191	0.272	0.990
V2	0.0168	0.201	0.517

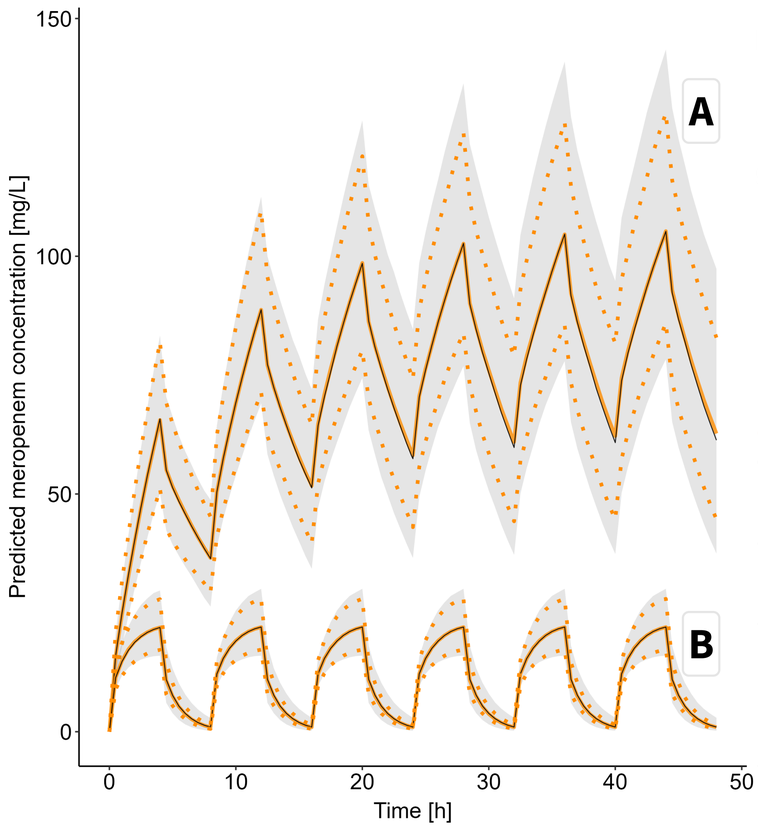


Figure 3: Comparative visualisation of *a posteriori* predicted meropenem concentrations over time in NONMEM and the DoseCalculator for 2 exemplary patients with $CLCR_{CG}$ of (A) 21 mL/min and (B) 408 mL/min and a total number of (A) two and (B) four meropenem samples considered in the Bayesian estimation.

Table 2: rBIAS, MARE and rRMSE for 5th , 50th and 95th percentile of predicted *a posteriori* meropenem concentrations obtained from the DoseCalculator and NONMEM (reference).

Prediction percentile	rBIAS (%)	MARE (%)	rRMSE (%)
$P_{0.05}$	18.2	9.68	25.0
$P_{0.50}$	0.145	0.188	0.452
$P_{0.95}$	-12.8	11.4	14.6

Discussion and Conclusions

- **Acceptance criteria met** with **high agreement in graphical analyses** (correlation analysis, Bland-Altman analysis, C(t) simulation plots) between **DoseCalculator incorporated TDMxR algorithm** compared to **NONMEM** for:
  - **MAP parameter estimation**
  - **Individual C(t) simulations (MAP parameter & posterior distribution#)**
- Higher deviations for $P_{0.05}$ and $P_{0.95}$ due to DoseCalculator using full variance-covariance matrix, whereas diagonal elements of ETC matrix used within NONMEM
- **MAP estimation and Bayesian simulation results of DoseCalculator incorporated TDMxR algorithm successfully validated against NONMEM**

Steps towards clinical implementation

DoseCalculator
- ✔ Internal evaluation of integrated PK model[3,4]
- ✔ Clinical benefit simulation study (PK/PD target attainment improvement, daily dose reduction)[2]
- ✔ Real-world evaluations (sampling time uncertainties, impact of integration of different eGFR formula values)
- ✔ Development of implementation concept[2]
- Clinical validation of Bayesian framework
- Evaluation for patients undergoing extracorporeal methods

References
[1] Wicha et al., Int. J. Antimicrob. Agents (2015)
[2] Weber et al., ECCMID (2023)
[3] Weinelt et al., Pharmaceutics (2021)
[4] Ehmann et al., Int. J. Antimicrob. Agents (2019)
[5] Weinelt et al., Antibiot. (2022)
[6] Le Louedec et al., CPT Pharmacometrics Syst. Pharmacol. (2021)
[7] Cunio et al., Clin. Microbiol. Infect. (2021)
[8] Sheiner and Beal, J. Pharmacokinet. Biopharm. (1981)
[9] Sheiner et al., Clin. Pharmacol. Ther. (1979)

[#] approximated by variance-covariance matrix of individual ETAs

Abbreviations

CL	Clearance
$CLCR_{CG}$	Creatinine clearance based on Cockcroft-Gault
eGFR	Estimated glomerular filtration rate
ETC:	Variance-Covariance matrix of the individual ETA values
IIV	Interindividual variability
MAP	Maximum *a posteriori*
MARE	Median absolute relative error
MIPD:	Model-informed precision dosing
P	Percentile
PD	Pharmacodynamic
PK	Pharmacokinetic
q8h	Every 8 h
rBIAS	Relative bias
rRMSE	Relative root mean squared error
TDM	Therapeutic Drug Monitoring
V1	Volume of distribution central compartment
V2	Volume of distribution peripheral compartment

Equations

$$\text{rBias},\% = 1/N \sum_{1}^{i}\left(\frac{\theta_{i,DoseCalculator} - \theta_{i,NONMEM}}{\theta_{i,NONMEM}}\right) \times 100\%$$

$$MARE,\% = median\left(\left|\frac{\theta_{i,DoseCalculator} - \theta_{i,NONMEM}}{\theta_{i,NONMEM}}\right|\right) \times 100\%$$

$$\text{rRMSE},\% = \sqrt{\frac{1}{N}\sum_{1}^{i}\frac{\left(\theta_{i,DoseCalculator} - \theta_{i,NONMEM}\right)^2}{\left(\theta_{i,NONMEM}\right)^2}} \times 100\%$$

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Poster PDF

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