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Bias and Uncertainty of Monte Carlo Simulations with Beta-Lactams

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Introduction

Monte Carlo simulations (MCS) to predict the probability of successful antibiotic treatment became increasingly popular. However, the results of some MCS for beta-lactams might be flawed due to:

A) the use of literature data from non-compartmental analyses (NCA),

B) applying possibly simplified one-compartment models,

C) not assuring the predictive performance of population PK models,

D) not accounting for the uncertainty in PK or MIC distributions, while claiming that antibiotic A reaches significantly higher probabilities of target attainment (PTAs) compared to antibiotic B.

The majority of published papers on MCS with beta-lactams are possibly flawed due to the first 3 or 4 reasons. We are not aware of any systematic studies on the uncertainty of MCS for beta-lactams. Thus, these statistical comparisons (see D) seemed not justified.

Objectives

1) To compare selection criteria for models to be used in MCS.
2) To quantify the influence of model misspecification on the PTAs.
3) To systematically quantify the uncertainty in PTAs.

Methods

We used the PKPD target time above MIC (T>MIC) over a dose interval of ≥40% or ≥70% and calculated the expected value for the PTA against bacteria from 32 MIC distributions from literature.

Selection of the best model for MCS: We compared NONMEM's objective function, diagnostic plots, and visual predictive checks.

Bias due to model misspecification: We simulated the plasma concentration profiles of 48 subjects after a single 30 min infusion based on a 2-compartment model for a typical beta-lactam (terminal half-life 1.8 h). See Figure 1 for procedures applied.

Uncertainty: We used the simulated profiles of these 48 subjects to assess the uncertainty in the results of a MCS as shown in Figure 2.

Software: We used NONMEM V (level 1.1, GloboMax LLC, Hanover, MD, USA) for population PK analyses and simulations, WinNonlin(R) Pro (Version 4.0.1, Pharsight Corporation, USA) for NCA and statistics, and validated Perl scripts for visual predictive checks and non-parametric bootstrap resampling.

Figure 1: Assessing the bias of a MCS due to model misspecification

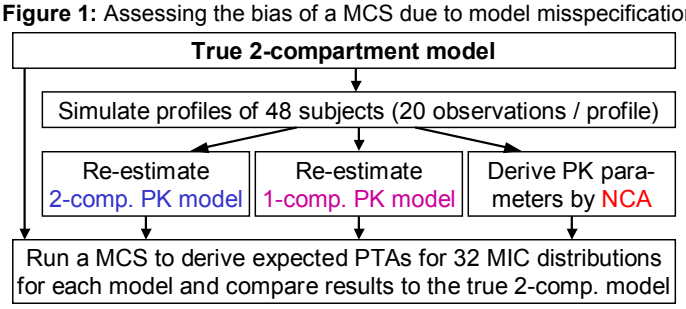
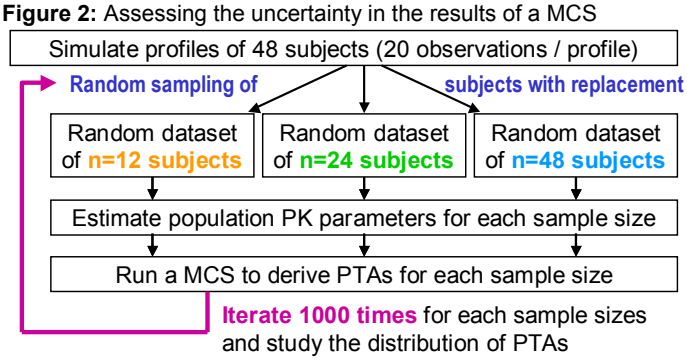


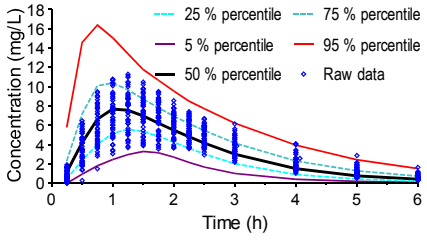
Figure 2: Assessing the uncertainty in the results of a MCS



Results

- Standard diagnostic plots vs visual predictive check (Fig. 3)
- Objective function vs visual predictive check (Fig. 4)
- Bias in MCS results due to model misspecification (Tab. 1)
- Uncertainty in PTA vs MIC profiles (Fig. 5) & expected PTAs (Tab. 2)

Figure 3: Comparison of visual predictive check* and diagnostic plots



*This example was originally presented by Bulitta & Holford at PAGANZ 2005.

For this model, the
1) DV vs. IPRED,
2) WRES vs. IPRED, &
3) WRES vs. TIME
plots all showed no bias or trend at all.

The DV vs. PRED and RES vs. TIME plot showed "some" bias.

Figure 4: Visual predictive check vs. NONMEM's objective function

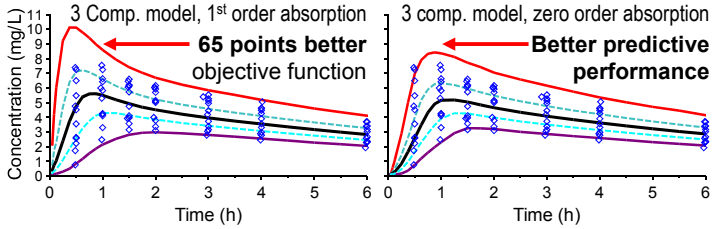


Table 1: Bias due to model misspecification for 32 MIC distributions and two PKPD targets (n=64 in total) [median (range)]

Expected PTA for the true model	Re-estimated 2 comp. model	Re-estimated 1 comp. model	NCA, based on Vz and CL
90-100% (n=12)	0.0% (-0.2 to 0.3%)	**-6.9%** (-38.5 to -1.2%)	**1.8%** (0.6 to 6.2%)
80-90% (n=12)	0.0% (-0.1 to 0.3%)	**-9.4%** (-40.0 to -4.7%)	**4.9%** (3.1 to 7.6%)
65-80% (n=15)	-0.1% (-0.6 to 0.2%)	**-22.1%** (-38.3 to -5.9%)	**7.8%** (4.1 to 15.5%)
50-65% (n=14)	-0.2% (-0.6 to 0.2%)	**-25.8%** (-38.6 to -5.0%)	**8.6%** (4.5 to 22.9%)
< 50% (n=11)	-0.2% (-1.0 to -0.1%)	**-17.5%** (-26.1 to -4.4%)	**9.5%** (4.8 to 24.9%)

Figure 5: Uncertainty in PTA vs MIC profiles for n=12 or n=48 subjects

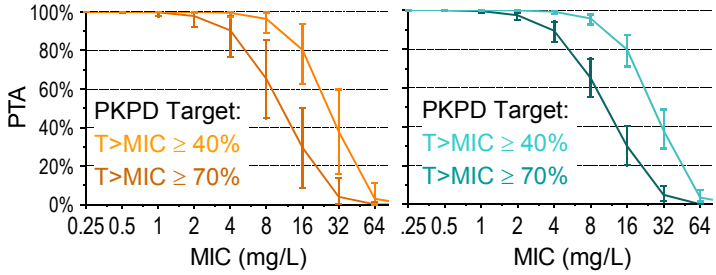


Table 2: Effect of uncertainty in PK parameters and in MIC distribution (PD) on 90% confidence intervals for the expected PTAs

Uncertainty in PK	Uncertainty in PD	Expected PTAs: median (5%-95% percentile) *E. coli*	*P. aeruginosa*	MSSA
Yes	No	93% (90-95%)	67% (60-72%)	65% (53-77%)
No	Yes	92% (86-95%)	62% (53-70%)	56% (52-60%)
Yes	Yes	93% (88-97%)	67% (56-76%)	65% (52-78%)

Values shown for PK datasets with 24 subjects and MIC distributions with 50 isolates.

Conclusions

1) Visual predictive checks should always be performed to qualify a population PK model for MCS.
2) Model misspecification can severely bias the predicted PTAs.
3) Uncertainty in PK parameters and in MIC distribution needs to be considered for a statistical comparison of predicted PTAs.
4) A full population PK model e.g. with non-parametric bootstrapping is required for a sound statistical comparison of PTAs and expected PTAs for bacteria from specific MIC distributions. Such a comparison should be based on individual concentration vs. time raw data.