The drug titration paradox in the presence of intra-individual variation: can we estimate the true concentration-effect relationship?

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Background: drug titration paradox

The drug titration paradox arises when higher drug concentrations are paradoxically associated with poorer efficacy outcomes, due to the titration of the drug dose to achieve a desired effect [1]. In situations where there is inter-individual variability in the pharmacodynamic outcome, the sickest patients receive higher doses, resulting in elevated drug concentrations.

Inter-individual variability + titration design

- Drug titration paradox at **population level**
- Unbiased estimate of concentration-effect relationship can still be obtained using non-linear mixed effects models [2]

Intra-individual variability + titration design **(this poster)**

- Drug titration paradox at **both population and individual level.**
- **Unknown** if data can support unbiased estimation of concentration-effect relationship [3].

Results: simulated drug titration paradox

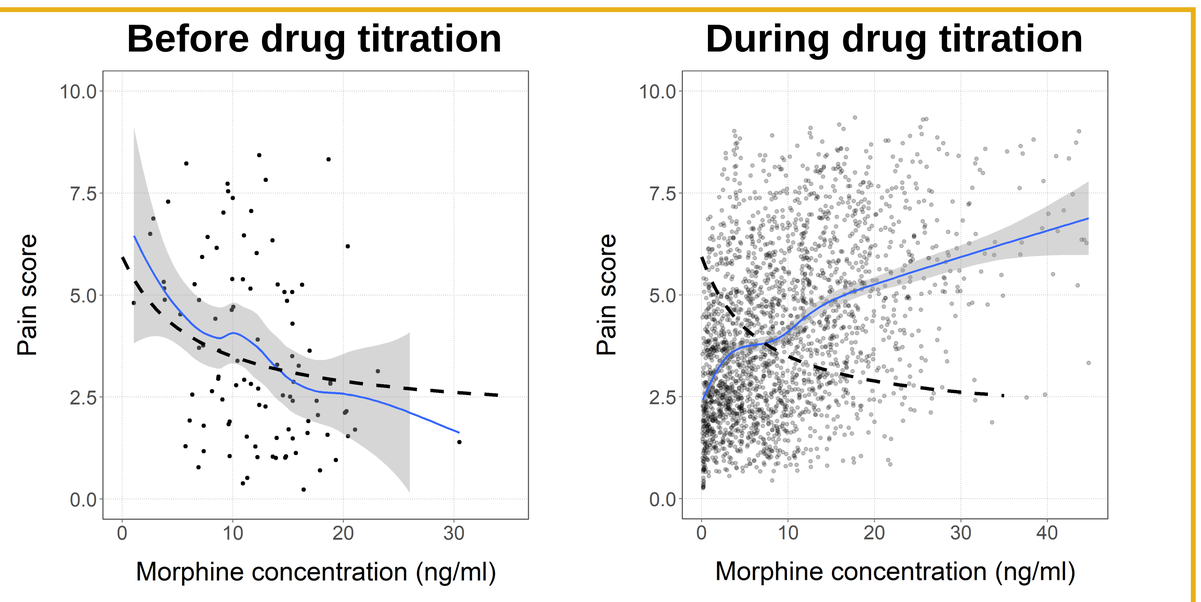

Figure 1. Comparison of concentration-pain relationship before titration (left plot, at time=2 hours) and after titration (right plot, at time=4-48 hours). Dashed line shows the average 'true' concentration-effect relationship, while the blue lines and grey areas show LOESS smoothers (and 95% CI) through the simulated observations (circles).

Figure 1 and 2 illustrate how the titration design in combination with intra-individual variability results in the drug titration paradox on **both population and individual level.**

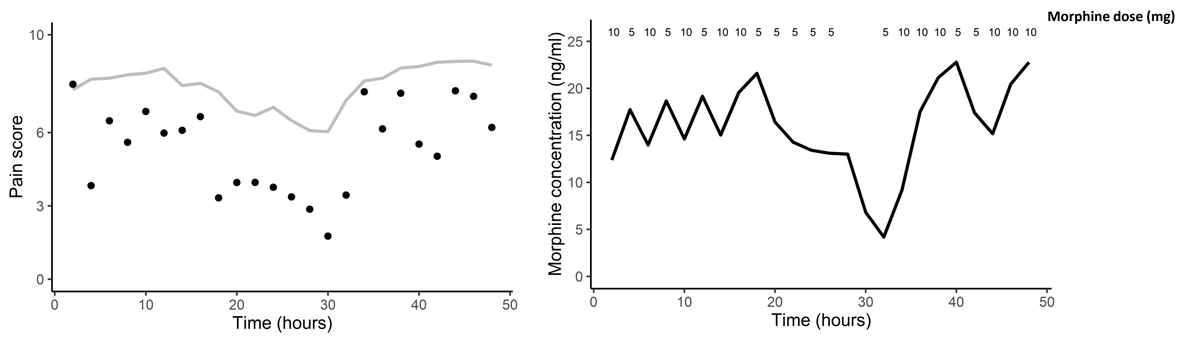

Figure 2. Illustration of drug titration paradox at the individual level for a single subject, where the **periods with high pain scores** (0-16 hours and 34-48 hours) are also the **periods with the highest morphine concentrations**. Left: shows the baseline pain as grey line (which has intraindividual variability) and the simulated pain scores upon morphine treatment as black circles. Right: Simulated morphine concentration (black line) over time as a result of the starting dose and additional bolus doses (depicted in the upper part of the plot).

Objectives

Evaluate bias in estimated concentration-effect relationship for a simulated morphine titration study with substantial intra-individual variability in pain levels for analysis approaches that use stochastic differential equations (SDEs) or inter-occasion variability (IOV) or neither.

Results: evaluation of parameter estimates

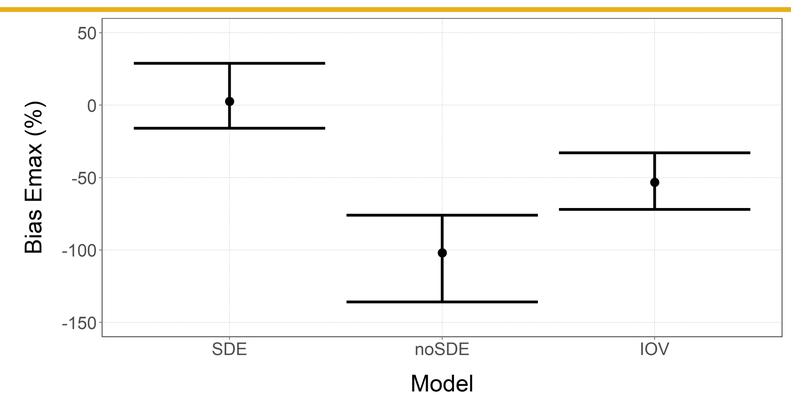

Figure 3. Visualization of the bias in the estimated Emax parameter (compared to the true value of 2 on logit scale) for the three different re-estimation approaches. Shown are the median bias (circle) and the 90% interval (error bars) in the N=100 simulated datasets. SDE, "true" model which uses SDE to characterize the intra-individual variability of baseline pain; noSDE, model without SDE; IOV, model without SDE, but with inter-occasion variability.

Estimating with the "true" model (i.e., including SDE) resulted in median biases of 8.3% and 2.6% for PD parameters EC50 and EMAX, respectively. The misspecified models resulted in biased parameter estimates, especially for Emax (Figure 3). The model without SDE had substantial bias in the Emax, with estimates often close to 0 (median bias -101.9%), resulting in a reversed direction of the drug effect in 56/100 datasets. The addition of IOV to this model mitigated this to some extent, but substantial bias persisted (median bias for Emax -53.3%).

Conclusion

Even in the presence of **strong intra-individual variability and drug titration**, models that adequately characterize the intra-individual variability (e.g. such as the model with SDE) can still obtain an **unbiased estimate** of the **concentration-effect relationship**.

This study underscores the critical importance of appropriately characterizing intra-individual variability in titration studies:

- Misspecified models yielded significantly biased estimates of the drug effect and even occasionally a **reversal of the direction of the drug effect** (i.e., higher drug concentrations are associated with more pain).
- Biased estimates of drug effects could lead to incorrectly concluding a lack of efficacy for promising drugs

Methods

Simulation design

- Simulated 100 datasets, each containing 100 patients
- Pain scores (ranging 0-10) simulated every 2 hours over 48 hours.
- Starting dose: bolus 5 mg morphine (irrespective of pain) at time=0.
- Morphine titration design based on pain scores
  - Pain score <3: no additional morphine.
  - Pain scores 3-6, 5 mg morphine bolus.
  - Pain scores >6, 10 mg morphine bolus.
- A published population PK model for morphine was used to simulate morphine concentrations over time based on individual doses [4].
- The morphine concentration-pain relationship: direct effect Emax model with interindividual variability on baseline pain, EC50 (typical value = 10 ng/ml), and Emax. Intra-individual variability in disease severity (i.e., baseline pain) was simulated as Brownian motion.

Parameter re-estimation

Three model fitting approaches were applied in NONMEM 7.5.1 to each dataset:

- The "true" PKPD model using stochastic differential equations (SDE) with an Extended Kalman Filter to characterize intra-individual variations of the baseline pain [5].
- Additionally, two misspecified models were tested:
  - Omitting SDE completely
  - Omitting SDE and adding inter-occasion variability (IOV), with each occasion lasting 12 hours.

Bias evaluation

Bias for each simulated datasets was calculated by comparing the parameter estimates for EC50 and Emax against the true values.

[1] Schnider et al. Clin Pharmacol Ther (2021) 110:401-408.
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[3] Schnider et al. Br J Anaesth (2022) 129:861-867.
[4] Ahlers et al. Anesth Analges (2015) 121:1261-1273.
[5] Tornøe et al. Pharmaceut Res (2005) 22:1247-1258.