The feasibility of model-based exposure calculations in preclinical toxicology

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Objectives

An important part of drug development involves the establishment of safe drug exposure levels in humans. Preclinical experiments often use an empirical non-compartmental approach for the calculation of drug exposure (AUC & Cmax). This has several limitations including the difficulty to characterise variability and extrapolate to clinical exposure levels. Pharmacokinetic (PK) modelling can address these shortcomings, however, the use of sparse blood sampling that is often required in these experiments calls into question the feasibility of implementing a model-based approach.
The aims of this work are:

- To evaluate the precision of PK parameters for a variety of hypothetical compounds in standard toxicity studies.
- To evaluate the precision of the derived secondary parameter (AUC & Cmax) in these studies.
- To assess the sensitivity of parameter precision to reduced designs involving fewer samples and animals.

Methods

I) Experimental design

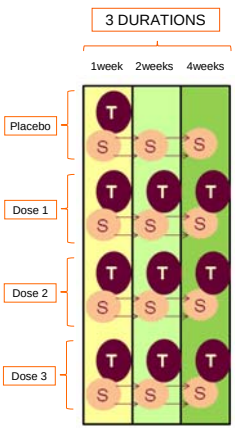

Figure 1: General toxicology set-up.

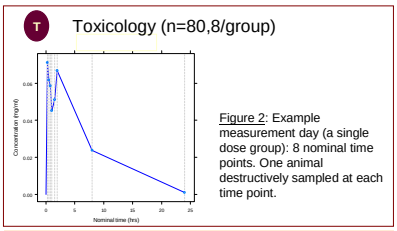

Figure 2: Example measurement day (a single dose group): 8 nominal time points. One animal destructively sampled at each time point.

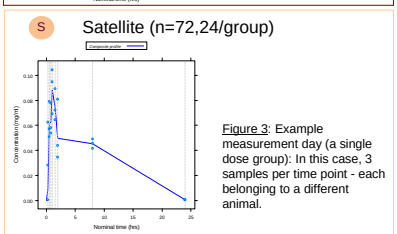

Figure 3: Example measurement day (a single dose group): In this case, 3 samples per time point - each belonging to a different animal.

II) Population PK

- Drug disposition described by 3 model types.
- Permutations of parameter values resulting in 9 different hypothetical drugs (i.e. scenarios) per model.
- 3 sampling schemes:
  - 3 animals/sample point
  - 2 animals/sample point
  - 1 animal /sample point

- The covariance matrix derived from the expected Fisher Information Matrix (FIM) was used to determine parameter precision. Calculations were performed in PopED.
- The FIM-based approach is proposed as alternative to lengthy simulation/re-estimation for the calculation of expected parameter precision.
- Computation of secondary PK parameters (AUC & Cmax) was obtained by simulation using NONMEM VI ($PRIOR).
- Secondary parameter precision was compared across designs for all hypothetical drugs.

Results

- All primary PK parameters were estimated with a CV%< 20% in all scenarios, except for the peripheral compartment rate constants (K12 and K21), which showed precision < 50% in all scenarios (data not shown) .
- Secondary PK parameters had an expected CV%< 35% for AUC and < 25% for Cmax for all scenarios. Therefore, precision obtained in three different models for 9 different drugs was acceptable.
- In all scenarios tested, a reduction in the number of animals by one third and two thirds yielded no significant loss in expected precision.

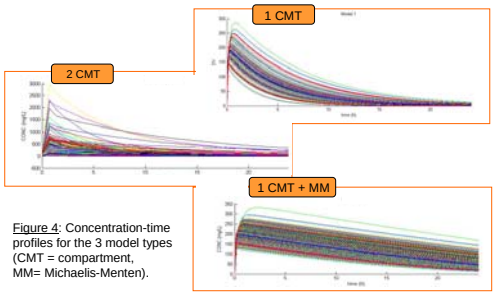

Figure 4: Concentration-time profiles for the 3 model types (CMT = compartment, MM= Michaelis-Menten).

SCENARIO	Ka (h^{-1})	V (L)	Cl ($L\ h^{-1}$)
1(unaltered)	14.82	0.049	0.100
2	-	-	50% ↑
3	-	50% ↑	50% ↓
4	-	50% ↓	50% ↑
5	-	50% ↓	50% ↓
6	80% ↓	50% ↑	50% ↑
7	80% ↓	50% ↑	50% ↓
8	80% ↓	50% ↓	50% ↑
9	80% ↓	50% ↓	50% ↓

Table 1: Permutations in parameter values.

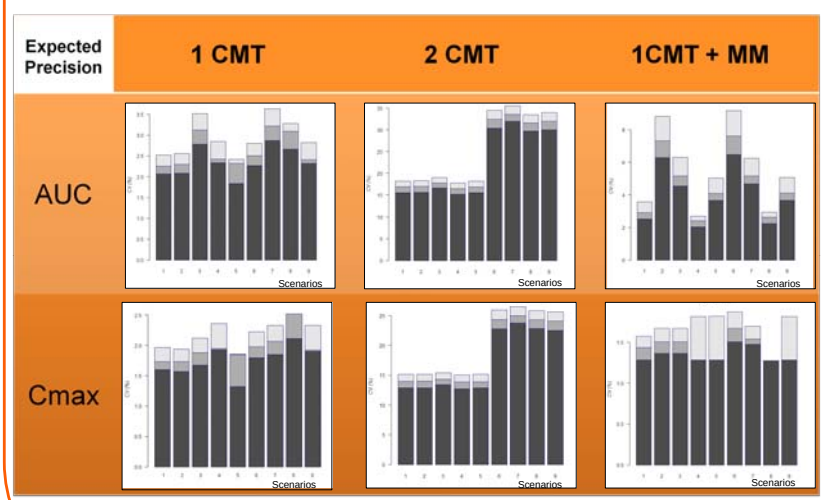

Table 2: Expected precision (expressed in %CV) obtained for secondary parameter estimates for all 9 scenarios per model type.

3 animals per sample time
2 animals per sample time
1 animal per sample time

Conclusions

- ✓ Population PK parameters characterising nonlinear kinetics and peripheral tissue distribution can be estimated without changes to existing general toxicity study protocols.
- ✓ Low precision in the estimates of Michaelis-Menten constant and peripheral compartment distribution do not significantly affect expected precision of the secondary parameters of interest.
- ✓ Significant reductions to the numbers of animals/samples may be possible if analysis is performed using a model-based approach.