A comparison of two model-based approaches to investigating covariate effects on the dose-exposure relationship in a Phase III context

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Background

- In Phase III, where large populations are often exposed to chronic treatment, it is typical to attempt to identify covariates which explain variability in the dose exposure relationship
- Typically, this type of analysis is performed using sparse data (3-4 observations per visit) over a relatively long period (6-12 months)
- Gold standard method is compartmental analysis using nonlinear mixed-effects (NLME)
- Searching for covariate relationships in this manner can be extremely time-consuming
- Investigation of methods which allow more rapid, but nevertheless adequately sensitive identification of covariate effects are warranted

Objective

- Compare the NLME method with a linear mixed-effects (LME) approach in terms of their respective abilities to adequately elucidate relevant covariate relationships on exposure in a subject-rich but observation-poor context
- Methods will be compared in terms of sensitivity, accuracy, precision, and analytical time

Methods

Design

- A design corresponding to a typical Phase III confirmatory trial was used for simulation
- PK samples were simulated at 4 visits over a period of 6 months – on Day 1, Day 14, Day 84 and Day 182
- PK samples were simulated at nominal times of 1.5 h, 4 h and 23.5 h
- 400 patients were included
- Dosing was 600 µg once daily

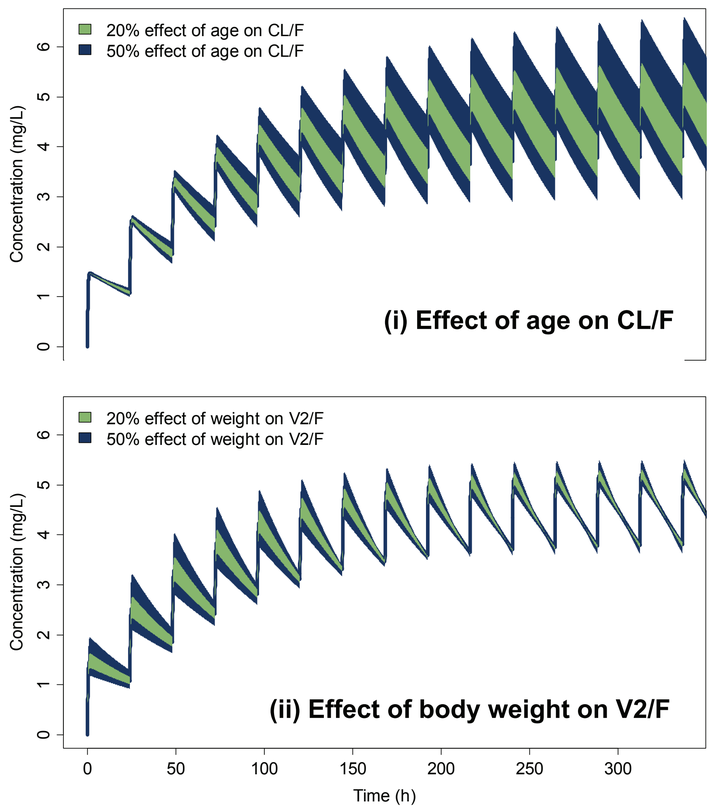
Simulation Model

- Fictitious compound with low clearance, high volume and consequently high accumulation (approximately five-fold)
- One-compartment model with linear absorption and elimination (Table 1)
- Covariate effects on CL/F and V2/F (between 5% and 50% on model parameters, *over the range of values studied* (20-80 y for age, and 40-120 kg for body weight)) – Figure 1 (5% effect not shown)

Table 1. *Base simulation model*

Parameter	Typical value	Variability
Apparent clearance (CL/F, L/h)	5.50	40%
Apparent central volume of distribution (V2/F, L)	400	40%
Absorption rate constant (ka, /h)	4.00	50%
Proportional residual error (σ^2, variance)	0.09	–

Figure 1. *Covariate effects*



Simulation and analysis

- Each scenario simulated 1000 times using SSE tool in Perl-speaks-NONMEM (PsN)
- Each replicate was analyzed using two discrete approaches
  - NLME analysis of all the simulated data in a given scenario using a compartmental model implemented in NONMEM VI 2.0 (4800 observations per model fit)
  - LME analysis of observed *steady-state* peaks and pre-dose troughs *only*, as implemented in nlme package of R 2.8.1 (1200 observations per model fit)
- Results assessed in terms of peak and trough concentrations (observed or predicted)

Results

Table 2. *Power to detect ALL covariate effects simultaneously (%) using both approaches. For LME, expressed as troughs [peaks]*

Weight on V2/F		Age on CL/F 0%		Age on CL/F 20%		Age on CL/F 50%	
0%		LME	–	LME	30.2 [30.0]	LME	96.7 [94.3]
		Log LME	–	Log LME	29.1 [26.6]	Log LME	94.2 [90.5]
		NLME 5	–	NLME 5	72.8	NLME 5	99.8
		NLME 0.1	–	NLME 0.1	46.9	NLME 0.1	97.6
20%		LME	5.50 [5.90]	LME	2.20 [1.80]	LME	5.40 [6.10]
		Log LME	6.70 [6.50]	Log LME	2.20 [2.00]	Log LME	6.10 [6.10]
		NLME 5	47.0	NLME 5	28.5	NLME 5	61.0
		NLME 0.1	13.5	NLME 0.1	5.10	NLME 0.1	31.2
50%		LME	6.20 [12.0]	LME	2.40 [4.30]	LME	5.40 [6.10]
		Log LME	8.60 [11.7]	Log LME	3.30 [4.20]	Log LME	6.10 [6.10]
		NLME 5	94.6	NLME 5	41.4	NLME 5	85.2
		NLME 0.1	73.7	NLME 0.1	13.0	NLME 0.1	65.6

LME=linear mixed effects, ordinal; log LME=LME, log-transformed both sides; NLME 5=NLME, $p < 0.05$; NLME 0.01=NLME, $p < 0.01$. For LME: troughs [peaks]

Power to detect covariate effects

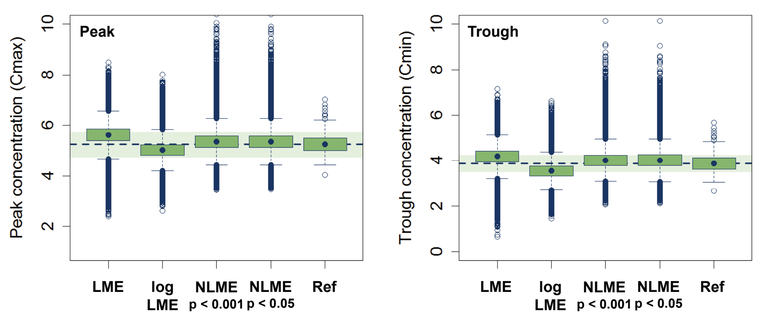
- NMLE was most sensitive method, but also used much more data
- Clinically relevant effect (50%) on CL/F detected by LME with almost the same power
- Power of LME to detect effects on V2/F (at steady state) virtually zero in simulated scenario

Table 3. *Bias (mean error, %) and precision (RMSE, %) of steady-state peak and trough concentration estimates produced by each method*

Weight on V2/F		Age on CL/F 0%		Age on CL/F 20%		Age on CL/F 50%	
0%		Key: Bias (ME, %) / Precision (RMSE, %)		LME	7.13 [6.70] / 8.45 [7.56]	LME	7.05 [6.70] / 8.24 [7.51]
				Log LME	-8.87 [-4.47] / 9.90 [5.60]	Log LME	-8.92 [-4.51] / 9.70 [5.59]
				NLME 5	3.55 [1.89] / 5.51 [3.62]	NLME 5	3.52 [1.87] / 5.49 [3.60]
				NLME 0.1	3.54 [1.88] / 5.79 [3.85]	NLME 0.1	3.52 [1.87] / 5.60 [3.69]
20%		LME	7.10 [6.68] / 7.71 [7.12]	LME	7.14 [6.71] / 8.60 [7.67]	LME	7.05 [6.66] / 8.39 [7.63]
		Log LME	-8.92 [-4.49] / 9.34 [5.01]	Log LME	-8.86 [-4.46] / 10.0 [5.71]	Log LME	-8.91 [-4.50] / 9.82 [5.70]
		NLME 5	3.51 [1.86] / 4.48 [2.74]	NLME 5	3.44 [1.79] / 5.68 [3.74]	NLME 5	3.00 [1.49] / 8.84 [6.29]
		NLME 0.1	3.50 [1.84] / 4.47 [2.73]	NLME 0.1	3.40 [1.74] / 5.81 [3.86]	NLME 0.1	2.72 [1.28] / 10.3 [7.40]
50%		LME	7.09 [6.69] / 7.79 [7.23]	LME	7.15 [6.72] / 8.69 [7.76]	LME	7.17 [6.57] / 8.55 [7.60]
		Log LME	-8.94 [-4.48] / 9.44 [5.13]	Log LME	-8.88 [-4.45] / 10.1 [5.80]	Log LME	-8.81 [-4.58] / 9.80 [5.82]
		NLME 5	3.56 [1.88] / 4.51 [2.75]	NLME 5	3.58 [1.84] / 5.47 [3.53]	NLME 5	3.48 [1.82] / 5.91 [3.94]
		NLME 0.1	3.56 [1.88] / 4.55 [2.79]	NLME 0.1	3.56 [1.78] / 5.64 [3.66]	NLME 0.1	3.30 [1.68] / 7.29 [5.06]

LME=linear mixed effects, ordinal; log LME=LME, log-transformed both sides; NLME 5=NLME, $p < 0.05$; NLME 0.1=NLME, $p < 0.001$. Numbers expressed as troughs [peaks]

Figure 2. *Illustrative example of results (50% age effect on CL/F)*



Bias and precision in peaks, troughs

- Though the LME method was generally more biased and less precise, overall performance was comparable (Table 3, Figure 2)

Analytical time

- LME was > 15-fold faster in this example

Conclusions

- The LME method may be a more efficient method for elucidating PK covariate effects of clinical interest (i.e. influencing dosing recommendations) using sparse Phase III steady-state exposure data in large numbers of patients
- NLME remains the gold standard but LME is orders of magnitude faster and allows more efficient screening of the covariate space
- Simulation studies, such as the one carried out here are recommended prior to implementation on specific scenarios

Next Steps

- The usefulness of the LME approach will be examined in the context of
  - low- and moderately-accumulating drugs
  - more complex PK models
  - correlations between covariate effects
  - more recent LME implementations
  - alternative residual error models

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