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Background and Aims

The population approach is a powerful tool to estimate pharmacokinetic (PK) parameters and to identify between- and within-subject variability from sparse sampling data. However, designing a population PK study is not straightforward. Poorly designed studies may fail to answer research questions. Optimal design methods have been increasingly used in the last decade to suggest the design structure, sampling times and sampling windows. The drawback of these methods is that the results depend on prior information (PK models and parameters).

The aims of this study are

- to use optimal design methods to develop designs for future population PK studies of oral ciprofloxacin in malnourished children
- to investigate the impact of different prior information on the optimal design results

Methods

Program and input information

Optimal designs were developed using the population Fisher information matrix (FIM) implemented in the PopDes program, version 4.0 [1]. The structural model, PK parameters and variability were obtained from a previous study [2]. Briefly, a total of 52 severely malnourished children were assigned to one of three groups according to sampling times. All patients received oral ciprofloxacin 10 mg/kg every 12 hours and up to 4 samples was taken from each patient. The structural model was one compartment with first order absorption and a lag. The final population PK model is summarised below:

$$\begin{aligned} \text{TVCL (L/h)} &= 42.7(\text{L/h/70 kg}) \times (\text{WT}/70)^{0.75} \times (1 + 0.0368 * (\text{NA} - 136)) \\ &\quad \times (1 - 0.283 * (\text{HIGH})) \\ \text{TVV (L)} &= 372 (\text{L}/70 \text{ kg}) \times (\text{WT}/70) \times (1 + 0.0291 * (\text{NA} - 136)) \\ \text{TVKA} &= 2.97 \text{ h}^{-1} \\ \text{ALAG} &= 0.742 \text{ h} \end{aligned}$$

WT is body weight, NA is sodium concentration and HIGH is high mortality risk (1 if patient has high risk, otherwise 0). Between-subject variability for CL, V and Ka were 38.1%, 43% and 102%, respectively. The combined additive (0.0273 mg/L) and proportional (18.3%) error model was used for residual variability.

Design evaluation and optimisation

To account for the covariates in the model, the population FIM was approximated using two approaches: (i) Monte Carlo Integration and (ii) Using the individual values of covariates. The practical constraints are showed in Table 1. Design optimisations were performed using the Exact design and Time interval options. A modified Fedorov exchange algorithm with a grid size of 0.25 was used.

Table 1 Design variables

Design variable	Practical constraints
Total number of subjects	52
Number of subgroups	1,2,3
Number of subjects in each subgroup	
- 1 group	52
- 2 groups	26/26, 31/21, 39/13, 42/10
- 3 groups	17/18/17
Number of samples	3,4,5

Impact of other prior information

Study I: Ciprofloxacin 20-30 mg/kg IV/PO was given to treat a range of infections (sepsis, diarrhoea, CF). A two compartment model with first order absorption and a lag was used. The final model included age, weight and the presence of CF [3].

Study II: Ten patients with CF received ciprofloxacin 10 mg/kg by 30-min infusion followed by oral administration. The final model was a two compartment with first order absorption and no lag. Weight was included in the CL, V1 and V2 models [4].

Other investigations

- The importance of sampling times after the second dose.
- The total number of subjects (the minimal number of subjects with % CV ≤ 10 for all parameters was considered optimal).

Results

Table 2 Design evaluation results

Method	NONMEM	Individual covariates	Distribution of covariates
Determinant	-	9.9 x 10 ³⁵	1.5 x 10 ³⁶
Criterion	-	251	258
% CV			
Ka	44.4	36.9	37.7
CL	7.3	6.5	6.3
Vd	7.2	6.1	7.1
Lag	18.7	16.1	16.3
ω ² _{Ka}	57.1	40.0	40.0
ω ² _{CL}	20.3	24.0	24.1
ω ² _{Vd}	24.4	26.2	26.3
Proportional	30.0	25.0	24.6
Additive	103.3	206.9	158.7

Table 3 Design optimisation results

Properties	3 samples			4 samples		5 samples
Group number	1	2	3	1	2	1
Optimal sampling times (sampling windows) (h)	0.75 (0.75-0.79)	1.00 (0.90-1.10)	2.00 (1.50-2.50)	0.75 (0.75-0.79)	1.00 (0.90-1.10)	0.75 (0.75-0.79)
	1.00 (0.90-1.10)	2.25 (2.00-2.50)	3.25 (3.00-3.50)	1.00 (0.90-1.10)	1.50 (1.25-1.75)	1.00 (0.90-1.10)
	12.00 (11.0-12.0)	12.00 (11.0-12.0)	12.00 (11.0-12.0)	2.75 (2.50-3.00)	3.25 (3.22-3.50)	1.50 (1.25-1.75)
				12.00 (11.0-12.0)	12.00 (11.0-12.0)	3.25 (3.00-3.5)
						12.00 (11.0-12.0)
Determinant	2.9 x 10 ⁴⁰			1.7 x 10 ⁴⁵		3.2 x 10 ⁴⁴
Criterion	498			762		927
Efficiency	193			295		359

Criterion is the determinant to the power of 1 over the number of parameters in the model
Sampling windows calculated with a minimum of 80% efficiency relative to fixed sampling times are in parentheses

Table 4 Study designs optimised using information from other populations

Properties	3 samples			4 samples		5 samples
Group number	1	2	3	1	2	1
Study I						
Optimal sampling times (h)	0.50	0.50	0.50	0.50	0.50	0.50
	1.25	3.25	1.00	1.00	1.00	1.00
	12.00	12.00	12.00	3.50	3.50	3.50
				12.00	12.00	12.00
Study II						
Optimal sampling times (h)	0.25	0.25	0.25	0.25	0.25	0.25
	12.00	0.25	1.00	0.25	1.25	1.25
	12.00	12.00	12.00	7.25	12.00	1.25
				12.00	12.00	12.00
						12.00

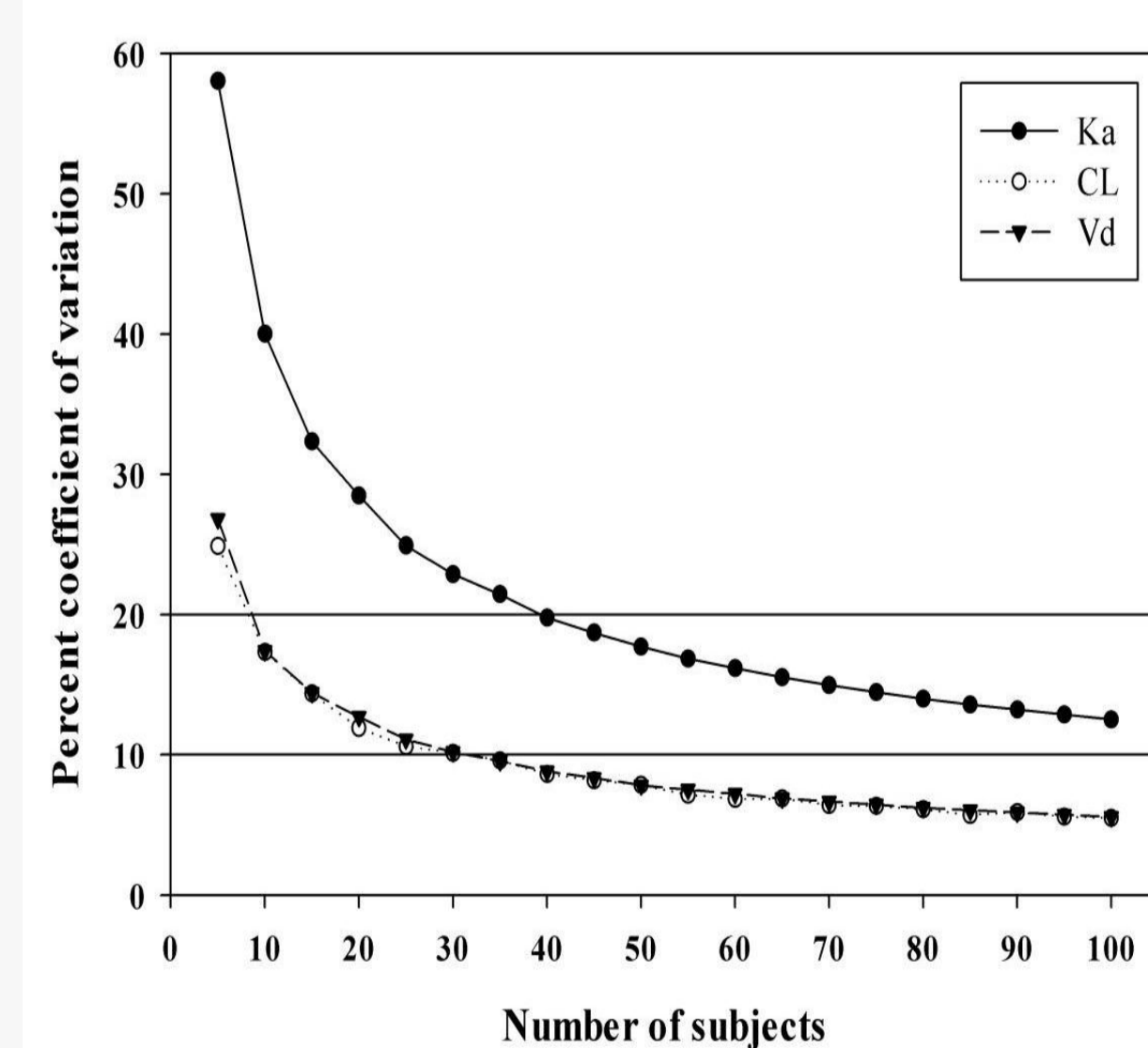


Figure 1 Estimated % CV for 3-sample study design

- 5 samples: 1 group (n = 25)
- 4 samples: 2 groups (n = 40 in total)
- 3 samples: 3 groups (n = 40 in total; %CV for Ka remains above 10 even if the number of subjects is increased to 100. A higher cut-off point of 20% was used)
- Samples taken after the first dose contain adequate information to estimate all PK parameters. An additional sample after the second dose is not necessary

Conclusion

Optimal study designs and sampling windows have been developed for future PK studies in malnourished children. Since the optimal designs depended on the prior information, prior knowledge of drug concentration-time profiles should be used with optimal design methods when designing population PK studies.

References

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