Efficiency criteria generated by optimal design tools should be evaluated in the light of study objectives

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INTRODUCTION

Scientific experiments need to be properly designed to optimize the quality of the data and the derived information. For a pharmacokinetic (PK) study, this is often referred to the allocation of the sampling times after dosing (sampling schedule). The definition of an optimal sampling schedule is of particular importance when sparse sampling is applied in population PK studies. The objective is typically to define the time points that maximize the accuracy of the model parameters (i.e., minimizes their SE). Among the most popular approaches used for this aim is the D-optimality criteria, in which the aim is to minimize the determinant of the variance–covariance matrix (1). This approach is implemented in available software tools, such as WinPOPT (2).

OBJECTIVES

To assess the efficiency of different pharmacokinetic sampling strategies - logistically constrained or optimal - and to further assess these designs using population analyses of simulated datasets.

METHODS

Population PK model

The pharmacokinetics of an hypothetical compound was described using a 2-compartment open model. The parameters were: k_a $1h^{-1}$, CL 650 L/h, Vc 4500 L, Q 785 L/h, Vp 12800 L; intersubject and residual variabilities were assumed log-normal and proportional, respectively. The compound was assumed to be given every 48 h.

Analyses

Two designs for the collection of plasma samples were considered:

1.{0.5, 2, 4 h after the first dose; predose, 0.5, 2, 4 h at steady state}

2.{1, 6, 12 h after the first dose; predose, 1, 6, 12 h at steady state}.

The two designs were evaluated using the WinPOPT software (2). The same program was used for selecting an optimal sampling schedule.

Simulations

Simulations (n=500) were performed using NONMEM (3) with the above model and parameters; plasma concentrations were extracted at relevant times and used to estimate population/individual parameters, which were compared with the 'true' ones.

RESULTS

Analyses

Output of WinPOPT:

Design 1

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RESULTS
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Method: Evaluate


                                Group 1
Dose:                           10000
Dose Interval:                  48
Number of subjects per group:   20
Number of design points per group: 7
Initial sampling times:         0.5 2 4 47 0.5 2 4
Final sampling times:           0.5 2 4 47 0.5 2 4
Dose numbers:                   1 1 1 13 14 14 14


                                Model 1
Parameters:                     Cl V1 V2 Q KA
Fixed effect parameters:        675 4410 12800 785 0.993
Fixed fixed effects:
Standard errors:                646.9376 2663.6368 54686.2831 1736.8248 0.6413
Standard errors(%):             95.8426 60.3999 427.2366 221.2516 64.5837
Between subject variances:      0.249 0.143 0.419 0.258 0.39
BSV model:                      1 1 1 1 1
Fixed random effects:
Standard errors:                0.093755 0.092371 0.93471 0.20936 0.18021
Standard errors(%):             37.6525 64.595 223.0801 81.1472 46.2065
Residual standard deviations:   0.183 0.01
Fixed residual effects:         2
Standard errors:                0.114913
Standard errors(%):             8.1491
Prior Information Matrix:       No
Fisher Information Matrix:      FIM_model_1.csv
Determinant:                    1.15008e-011
Criterion:                      0.10128
Eigenvalues:                    37.0665 0.00015944 5.7973e-005 3.3332e-010
                                1.1491e-006 4577.246 130.6576 140.5891
                                1.124 33.8268 30.0299


Time taken: 0.668 sec
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Design 2

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RESULTS
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Method: Evaluate


                                Group 1
Dose:                           10000
Dose Interval:                  48
Number of subjects per group:   20
Number of design points per group: 7
Initial sampling times:         1 6 12 47 1 6 12
Final sampling times:           1 6 12 47 1 6 12
Dose numbers:                   1 1 1 13 14 14 14


                                Model 1
Parameters:                     Cl V1 V2 Q KA
Fixed effect parameters:        675 4410 12800 785 0.993
Fixed fixed effects:
Standard errors:                121.2188 5940.9748 4448.1962 598.4457 1.8582
Standard errors(%):             17.9583 134.716 34.7515 76.2351 187.1329
Between subject variances:      0.249 0.143 0.419 0.258 0.39
BSV model:                      1 1 1 1 1
Fixed random effects:
Standard errors:                0.080798 0.14587 0.15604 0.12017 0.29947
Standard errors(%):             32.4491 102.004 37.2406 46.5784 76.7865
Residual standard deviations:   0.183 0.01
Fixed residual effects:         2
Standard errors:                0.017096
Standard errors(%):             9.3422
Prior Information Matrix:       No
Fisher Information Matrix:      FIM_model_1.csv
Determinant:                    4.64894e-009
Criterion:                      0.17478
Eigenvalues:                    29.9461 0.00017175 8.2993e-005 1.8977e-008
                                3.6476e-007 3515.1866 153.1902 105.255
                                9.8715 68.4682 41.0722


Time taken: 0.002 sec
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The Design 2 had an efficiency ("criterion ratio") equal to 170% of Design 1.

Output of WinPOPT: Optimal design

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RESULTS
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Method: Simulated Annealing


                                Group 1
Dose:                           10000
Dose Interval:                  48
Number of subjects per group:   20
Number of design points per group: 7
Initial sampling times:         0.5 2 4 47 0.5 2 4
Final sampling times:           3.07 8.76 22 2.97 0.231 48 2.97
Dose numbers:                   1 1 1 13 14 14 14


                                Model 1
Parameters:                     Cl V1 V2 Q KA
Fixed effect parameters:        675 4410 12800 785 0.993
Fixed fixed effects:
Standard errors:                76.3011 481.6304 1992.5227 103.4364 0.17071
Standard errors(%):             11.3039 10.9213 15.5666 13.1766 17.191
Between subject variances:      0.249 0.143 0.419 0.258 0.39
BSV model:                      1 1 1 1 1
Fixed random effects:
Standard errors:                0.080814 0.068287 0.15328 0.10597 0.16919
Standard errors(%):             32.4553 47.753 36.5822 41.0736 43.3828
Residual standard deviations:   0.183 0.01
Fixed residual effects:         2
Standard errors:                0.01958
Standard errors(%):             10.6992
Prior Information Matrix:       No
Fisher Information Matrix:      FIM_model_1.csv
Determinant:                    8.34774e-006
Criterion:                      0.3454
Eigenvalues:                    38.3025 0.00017181 9.6599e-005 4.3049e-006
                                2.5188e-007 2782.8791 153.1175 214.9695
                                89.0173 34.8915 42.5685


Time taken: 1 mins 49.6 secs
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With this number of samples the identified optimal design was: {3, 9, 22 h post-dose in Cycle 1 Day 1 and pre-dose, 0.2, 3, 3 h post-dose in Cycle 2 Day 1}. The optimal design had an efficiency equal to 336% of Design 1.

When the optimization was focused on CL and Vc only (while other parameters were fixed), Design 2 and optimal design were 30% and 345% more efficient than Design 1, respectively.

Simulations

In spite of more uncertainty in the parameter estimates, the non-optimal designs provided population and individual parameters in reasonable agreement with the true values in all cases.

Population clearance in particular was estimated with low bias (-6%) also with the least efficient schedule. Bias for Vc was generally higher, but still within 20%; larger bias were observed for k_a and IIV.

RESULTS – CONT'D

Simulations - cont'd

% Bias of population parameters

Parameters	KA	CL	V2	V3	Q
	1/h	L/h	L	L	L/h
true values					
THETA	1.00	698	4520	12000	789
OMEGA	1.37	0.220	0.161	0.290	0.237
Design 1					
THETA	0.877	657	4020	10200	949
OMEGA	0.676	0.184	0.178	0.244	0.21
% bias theta	-12.0	-5.874	-11.1	-15.0	20.3
% bias omega	-50.7	-13.6	10.6	-15.9	-13.1
Design 2					
THETA	0.782	696	5350	12900	705
OMEGA	1.48	0.211	0.143	0.366	0.31
% bias theta	-21.6	-0.287	18.4	7.50	-10.6
% bias omega	8.03	-0.939	-11.2	26.2	30.0
optimal design					
THETA	1.91	688	5340	11800	737
OMEGA	1.23	0.108	0.317	0.283	1.19
% bias theta	91.6	-1.43	18.1	-1.67	-6.59
% bias omega	-10.2	-50.9	96.9	-2.41	402

Summary statistics of % bias of individual parameters

	percentile	KA	CL	V2	V3	Q
Design 1	10th	-49.7	-26.1	-39.6	-57.5	-27.1
	50th	-13.9	-1.5	-13.3	-13.4	23.6
	90th	42.4	28.4	31.0	60.0	123
Design 2	10th	-35.4	-15.8	-23.8	-39.7	-47.4
	50th	16.7	2.85	12.2	3.22	-7.56
	90th	103	29	66	71	54
optimal design	10th	-19.3	-14.5	-24.8	-40.9	-42.1
	50th	40.7	2.87	12.9	-1.73	-9.03
	90th	149	25.7	74.3	59.0	57.6

CONCLUSIONS

The minimization of the uncertainty around parameters can be an aim of the design of a study (e.g., in pediatric PK studies). However, when accurate individual PK parameters have to be used in a sequential PKPD approach, bias should be also considered. The available optimality sampling design tools are useful in exploring the precision given a sampling schedule and proposing schedules to be assessed using simulations.

References and acknowledgements

(1) Aarons L & Ogungbenro K. Basic Clin Pharmacol Toxicol, 106, 250–255

(2) Thanks to S Duffull and the WinPOPT team. WinPOPT is freely available at http://www.winpopt.com/

(3) Beal S et al. NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA.