A real time optimal design for model discrimination and parameter estimation for itraconazole

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Introduction

- Approximately 10% of patients who have cystic fibrosis (CF) develop allergic bronchopulmonary aspergillosis – an allergic reaction to antigens on the surface of the pathogen
- Itraconazole is one of the drugs of choice for the treatment of *Aspergillosis* spp infections.
- At present very little is known about the pharmacokinetics of itraconazole in patients with CF – but limited information support the use of higher doses than other patient groups
- Itraconazole has an active metabolite (hydroxyitraconazole)

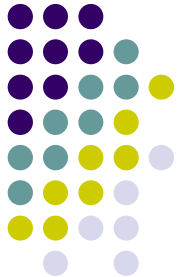
Capsule or solution?

- Both a capsule and solution are available – standard treatment involves the capsule only.
- Limited data suggest that the solution provides a considerably greater rate and extent of absorption than the capsule
- Also… the solution does not appear to be affected by the presence of food (cf the capsule)
- The most appropriate dosing of the solution in patients with CF has not been determined…

Aim

- To choose an experimental design (set of elementary designs) for model selection and efficient estimation of relevant parameters for itraconazole and hydroxyitraconazole

Prior information

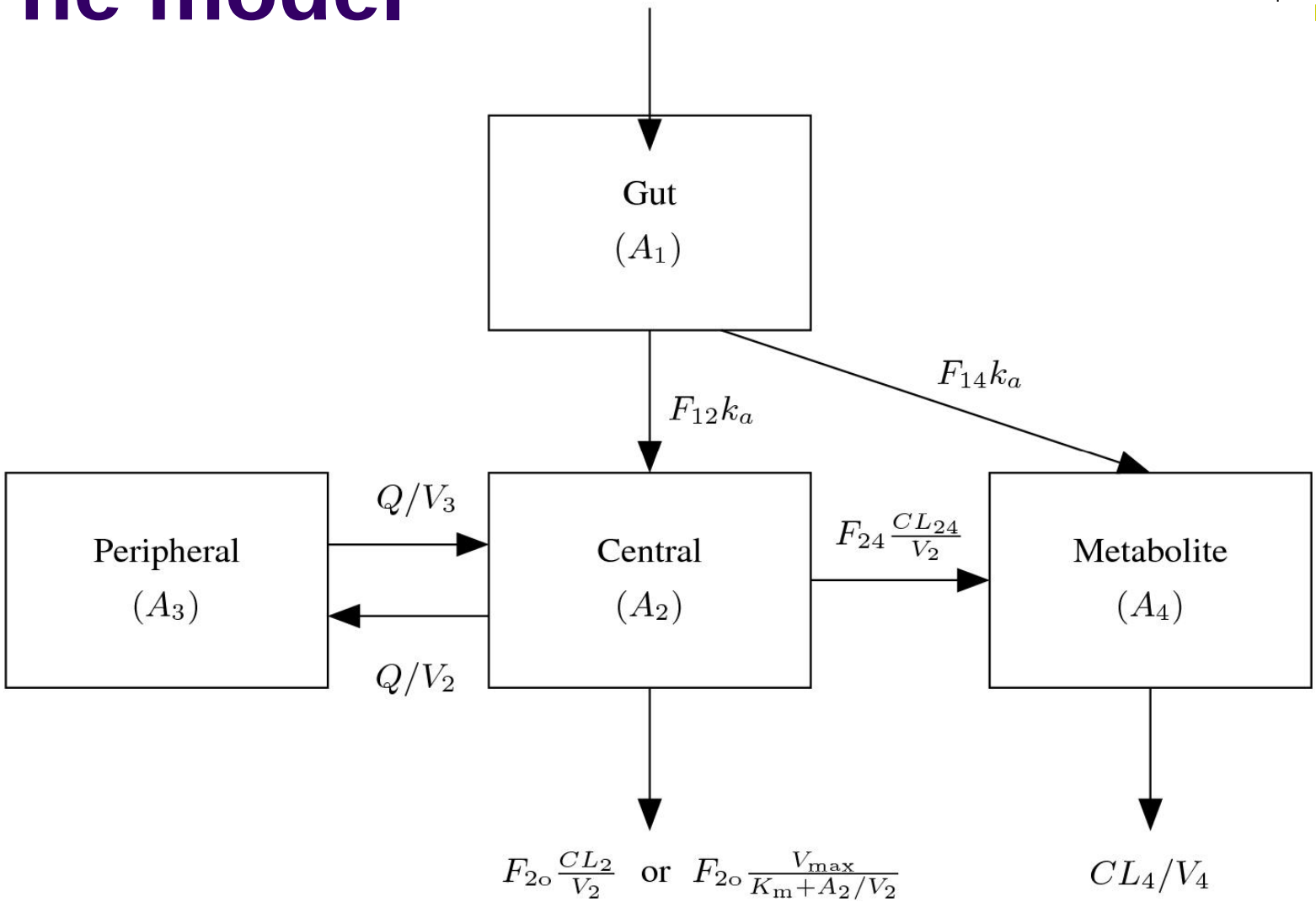


- Data were available from 4 studies of itraconazole and 1 described both itraconazole and hydroxyitraconazole
  - Koks et al. Ther Drug Monit 2003;25:229-233
  - Barone et al. Antimicrob Agents Chemother. 1993;778-784
  - FDA web site (x 2 documents)
- The model for itraconazole and hydroxyitraconazole were described by 2 linked compartmental models
- Data from Barone et al., suggested that the elimination of itraconazole from the central compartment was non-linear (this has been supported in other studies)

Clinical application

- A maximum of 30 patients are to be recruited
- A maximum of 4 samples per patient per occasion
- The study would be a single dose cross-over with capsule 200 mg followed by solution 200 mg
- A minimum washout period of 72 hours would be observed

The model



The ODE's

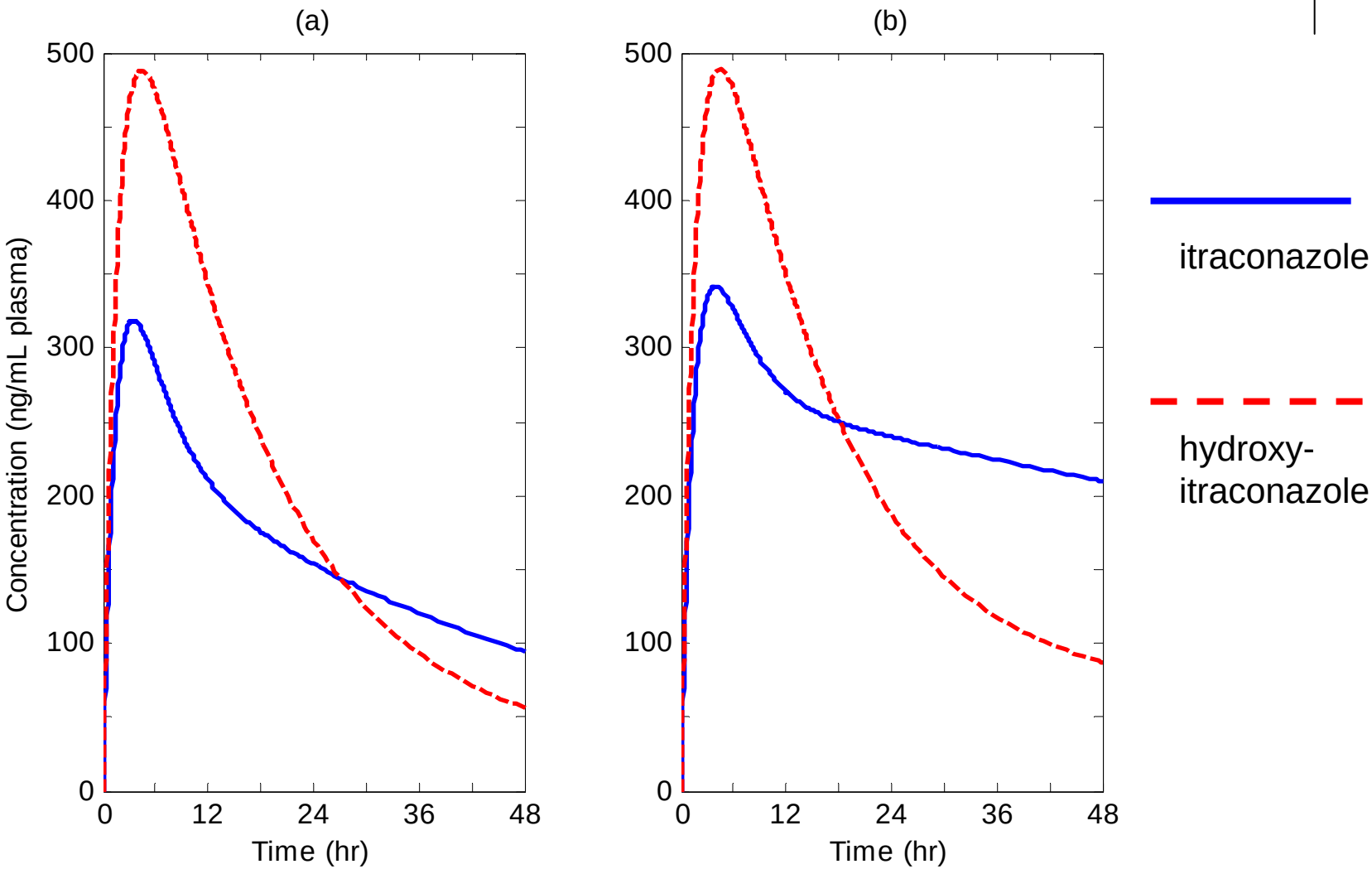
$$\frac{\mathrm{d}A_1(t)}{\mathrm{d}t} = -F_{12}k_aA_1(t) - F_{14}k_aA_1(t) \tag{1}$$

$$\frac{\mathrm{d}A_2(t)}{\mathrm{d}t} = F_{12}k_aA_1(t) + \frac{Q}{V_3}A_3(t) - \frac{Q}{V_2}A_2(t) - F_{24}\frac{CL_{24}}{V_2}A_2(t) + \begin{cases} -F_{2o}\frac{CL_2}{V_2}A_2(t) & \text{Model 1} \\ -F_{2o}\frac{V_{\max}}{K_m + A_2(t)/V_2}A_2(t) & \text{Model 2} \end{cases} \tag{2}$$

$$\frac{\mathrm{d}A_3(t)}{\mathrm{d}t} = \frac{Q}{V_2}A_2(t) - \frac{Q}{V_3}A_3(t) \tag{3}$$

$$\frac{\mathrm{d}A_4(t)}{\mathrm{d}t} = F_{14}k_aA_1(t) + F_{24}\frac{CL_{24}}{V_2}A_2(t) - \frac{CL_4}{V_4}A_4(t) \tag{4}$$

PK profiles


(a)
(b)
Concentration (ng/mL plasma)
500
400
300
200
100
0
0
12
24
36
48
Time (hr)
itraconazole
hydroxy-
itraconazole

Design – the information matrix

- The information matrix was the same as that provided by Retout et al and was assumed to take the form:

$$M_F(\psi, \xi_q) \approx \frac{1}{2}\begin{bmatrix} A(E,V) & C(E,V) \\ C^T(E,V) & B(E,V) \end{bmatrix}$$

where ψ is a vector of population parameters (fixed and variance of the random effects), ξ_q is the q^{th} elementary design and $C(E, V)$ is a matrix of zeros

Retout et al., Stat Med 2002;21:2623-2639

Design – multiple responses
(parent & metabolite)

- Multiple responses (that conform to the same likelihood) for fixed effects model has been described by summing the information matrices over the responses (Draper and Hunter):

$$M_F(\boldsymbol{\theta},\boldsymbol{\xi}) = \sum_{a=1}^{r}\sum_{b=1}^{r}\sigma^{ab}F_a^T F_b$$

- Where F is a vector of first partial derivatives of the response to the fixed effects parameters (θ)
- We extended this form to include fixed and random effects and simplified its computation by using only a single common residual variance

Draper and Hunter. Biometrika 1966;53:525-533

Design – competing models
(linear, non-linear, capsule, solution)

- Estimation
  - A compound criterion has been described for estimating parameters over a number of competing models (Atkinson & Cox)

$$P(\boldsymbol{\psi}^1, \boldsymbol{\psi}^2, \boldsymbol{\Xi}) = \left| M_F^1(\boldsymbol{\psi}^1, \boldsymbol{\Xi}) \right|^{1/p1} \left| M_F^2(\boldsymbol{\psi}^2, \boldsymbol{\Xi}) \right|^{1/p2}$$

- Discrimination
  - T-optimality has been described by Atkinson & Fedorov – but is highly computationally intensive and difficult to implement
  - Waterhouse et al showed that the compound design worked well for discrimination for some models – this was used here

Atkinson & Cox. J R Stat Soc Ser B 1974;36:321-348
Atkinson & Fedorov. Biometrika 1975; 62:57-70
Waterhouse et al. Research Report 106: Centre for Statistics, UQ

Execution of optimization

- The design was simplified by assuming that:
  - capsules and solution only differed in terms of the rate and extent of absorption,
  - the non-linear and linear models differed only in terms of elimination from the central compartment and all other parameters were common.
- Imposed design constraints meant that CL_{24}, V_3 and Q were not able to be estimated (and were fixed)
- The design was optimized using **`POPT.m`** with a simulated annealing algorithm (taking 7 days)

Design

Group (q)	N_q	Capsule		Solution	
		Elementary design ξ_q^c (hrs:mins)	Sampling window (hrs)	Elementary design ξ_q^s (hrs:mins)	Sampling window (hrs)
1	10	1:14	0.1 → 3.0	0:17	0.1 → 1.0
		8:56	7.0 → 10.0	3:55	3.0 → 3.5
		25:49	24.0 → 27.0	3:56	3.5 → 4.0
		51:45	50.0 → 53.0	3:56	4.0 → 4.5
2	10	6:13	5.0 → 8.0	0:18	0.1 → 1.0
		9:50	8.0 → 11.0	4:06	3.0 → 4.0
		29:29	28.0 → 29.5	4:06	4.0 → 5.0
		29:29	29.5 → 31.0	72:00	69.0 → 72.0
3	10	8:08	7.0 → 10.0	0:17	0.1 → 1.0
		28:00	26.5 → 29.5	4:22	3.0 → 6.0
		72:00	69.0 → 70.5	27:08	26.0 → 29.0
		72:00	70.5 → 72.0	72:00	69.0 → 72.0

Design evaluation

- The compound optimal design was 96.4 and 95.9% as efficient as the optimal design for either linear or non-linear model alone
- Simulation - 100 data sets were simulated under the optimal design from each model and both models fitted to the data using NONMEM (FOCEI)
  - In 100% of data sets the NONMEM run converged successfully
  - In 74% of the data sets simulated under the linear model, the correct model was preferred
  - In 100% of the data sets simulated under the nonlinear model, the correct model was preferred
  - The standard error estimates from **`POPT.m`** were close to the empirical standard deviation of parameter estimates from the NONMEM estimation runs, except for ka and ω_{ka} which differed by 2-fold

Discussion

- Optimal design procedures can be undertaken under the constraints imposed by time and clinical considerations
- Designs may be optimized over relatively complex model features including:
  - Multiple competing models
  - Models that can be defined only as ODEs
  - Models that involve multiple response types
- The compound design criterion appears to perform well for model discrimination and is relatively efficient for estimation
- Joint design windows can be computed efficiently – to produce clinically meaningful designs
- Optimality is a real alternative to simulation for designing popPK and popPKPD studies

We await the results of the actual study…