A D-optimal designed population pharmacokinetic study of itraconazole capsules and solution in adults with cystic fibrosis

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Background

- Itraconazole, a triazole oral antifungal (capsules, oral solution) is a highly lipophilic drug with variable absorption and one bioactive metabolite: hydroxy-itraconazole.
- Used for Allergic Bronchopulmonary Aspergillosis in cystic fibrosis (CF).
- TDM target used is: $C_{min,ss}$ = 0.5 - 2.0 mg/L of itraconazole.(1)
- The influence of altered gastric physiology associated with CF on the pharmacokinetics (PK) of itraconazole and its metabolite has not been previously evaluated.

Aim

- To estimate the population (pop) PK parameters for itraconazole and its active metabolite in adult CF patients, in particular the relative bioavailability of the parent after administration of both capsule and solution formulation.
- To assess the performance of the optimal design.

Study Design

- Cross-over, single dose (200 mg itraconazole of each formulation) study with 30 patients and a maximum of 4 samples per occasion per patient.
- The sampling times for the population model were optimized previously using POPT v.2.0. (2)
- The developed optimal design was able to: (Figure1)
  - Discriminate between 2 competing models: linear/non-linear elimination
  - Combine capsules and solution response

	Capsule		Solution	
Group	**Optimal time (h:min)**	**Optimal Window (h:min)**	**Optimal time (h:min)**	**Optimal Window (h:min)**
1	1:14	0:06 – 3:00	0:17	0:06 – 1:00
	8:56	7:00 – 10:00	3:55	3:00 – 3:30
	25:49	24:00 – 27:00	3:56	3:30 – 4:00
	51:45	50:00 – 53:00	3:56	4:00 – 4:30
2	6:13	5:00 – 8:00	0:18	0:06 – 1:00
	9:50	8:00 – 11:00	4:06	3:00 – 4:00
	29:29	28:00 – 29:30	4:06	4:00 – 5:00
	29:29	29:30 – 31:00	72:00	69:00 – 72:00
3	8:08	7:00 – 10:00	0:17	0:06 – 1:00
	28:00	26:30 – 29:30	4:22	3:00 – 6:00
	72:00	69:00 – 70:30	27:08	26:00 – 29:00
	72:00	70:30 – 72:00	72:00	69:00 – 72:00

Table I: Optimal sampling time and windows after administration of itraconazole capsules and solution for 3 groups of patients.

Results

Patients and Samples

- 241 blood samples were collected from 30 patients (Table II).
- 94% of samples were taken within the optimal sampling windows
- Samples were analyzed by HPLC.(3)
- 46% of the itraconazole and 28% of the hydroxy-itraconazole concentrations were below the limit of detection (LOD= 0.04mg/L).

Demographic Data	**Mean (Range)**
Number of patients	30
Sex (M/F)	18 / 12
Age (y)	26.1 (16 – 61)
Weight (kg)	60.7 (46 – 86)
Height (cm)	168.6 (149.0 – 186.0)
Lean Body Weight (kg)	47.8 (35.8 – 64.2)
Dose (mg/kg)	3.4 (2.3 – 4.3)
Number of co-medications per patient	13.7 (7 – 21)

Table II: Demographic data of patients

Model

- 2-compartment model with 1st order absorption rate and 1st order formation rate to metabolite
- F_{pm} fixed to 1
- No evidence of nonlinear elimination of itraconazole found.

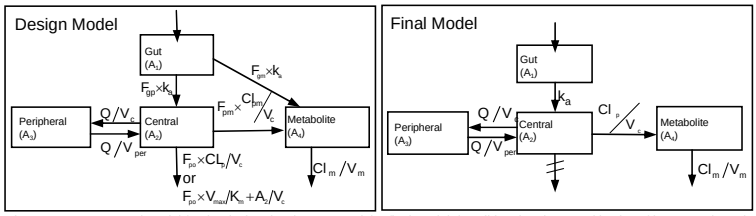

Figure I: Compartmental model for the design development and the final model describing the pharmacokinetics of itraconazole and hydroxy-itraconazole. g=gut, p=parent, m=metabolite, o=out, c=central, per=peripheral.

Population Pharmacokinetics

- PK of itraconazole and hydroxy-itraconazole was modelled simultaneously using NONMEM, ADVAN 5 and FOCE with interaction.
- The relative bioavailability for itraconazole capsules was 82% compared to the solution.
- Between-subject variability ranged from 22 to 106%.
- None of the screened covariates (weight, age, sex, influence of proton-pump-inhibitors as co-medication) explained some of the inter-patient variability on Cl_2, V_2 or F_{rel}.

Accounting for data below the LOD(4)

- Method 1: all BLOD values are discarded
- Method 5: all BLOD values = 1/2 LOD (= Final Model)
- Method 6: 1st BLOD values = 1/2 LOD, all subsequent BLOD discarded
- Method 4: all BLOD values kept, then the contribution of the expectation of each BLOD concentration to the likelihood was estimated
- Parameter estimates, their standard errors and the residual error of these 4 models were compared (Table III).

	Method 1		**Method 5 = Final Model**		**Method 6**		**Method 4**	
Method Description	BLOD=discard		BLOD=1/2LOD		1st BLOD=1/2LOD, others discarded		BLOD=censored, -2LL function	
Pharmacokinetic Parameters (Mean (RSE%))								
Cl_2 (L*h^{-1})	23.2	(20.3)	31.5	(14.0)	30.7	(11.5)	29.8	
V_2 (L)	74.3	(42.7)	56.7	(33.9)	72.4	(28.7)	132	
$k_{a\ cap}$ (h^{-1})	0.021	(21.9)	0.032	(46.7)	0.041	(38.0)	0.029	
$k_{a\ os}$ (h^{-1})	0.132	(30.5)	0.125	(44.2)	0.138	(31.3)	0.168	
F_{rel}	1.61	(19.1)	0.817	(23.5)	0.722	(21.3)	0.751	
Q (L*h^{-1})	83.3	(20.9)	71.3	(35.3)	79.9	(20.7)	71.3c	
V_{per} (L)	2660	(25.3)	2090	(35.0)	1610	(25.3)	2090c	
Cl_4 (L*h^{-1})	14.9	(20.1)	18.3	(12.9)	18.0	(10.6)	15.4	
V_4 (L)	3.98	(45.5)	2.67	(49.8)	2.83	(42.4)	4.75	
t_{lag} (h)	0.30	(2.66)	0.32	(1.68)	0.30	(1.93)	0.29	
Between subject variability (CV % (RSE%))								
BSV Cl_2	49.6	(83.3)	22.1	(75.2)	15.6	(94.3)	26.6	
BSV V_2	96.0	(64.1)	77.3	(48.5)	67.9	(51.1)	183.0	
BSV $k_{a\ cap}$	62.4	(54.1)	91.9	(33.5)	102.0	(28.3)	66.6	
BSV $k_{a\ sol}$	126.9	(25.3)	106.3	(31.4)	110.5	(47.7)	90.6	
BSV F_{rel}	37.9	(53.3)	62.3	(24.7)	63.2	(28.3)	40.1	
Residual variability (CV % (RSE%))								
Itraconazole (Additive error)	30.2	(27.5)	40.8	(16.6)	45.0	(12.7)	83.2 (0.0084)	
Hydroxy-itraconazole (Additive error)	34.0	(11.9)	47.9	(12.7)	46.8	(12.9)	33.7 (0.0511)	

Table III: Summary of estimated parameters and relative standard error (RSE %) from four different methods evaluating datasets with data below the limit of detection (BLOD). c=fixed, -2LL= -2Loglikelihood

Simulations

- From the final model 2,000 Monte Carlo simulations were performed to assess which dosing regimen would provide target success for most patients.
- Under a dose of 500 mg twice daily 87% of patients with the solution and 63% with the capsules would achieve the therapeutic target.
- NNT =4: for every 4 patients treated with the solution one additional patient will achieve target success compared to capsule but at an additional cost of AUD$ 220 per day.

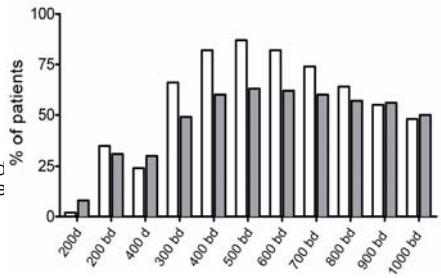

Figure II: The graph shows the percentage of patients achieving the therapeutic target range ($C_{min,ss}$ = 0.5-2 mg/L) with different dosing schedules. bd = twice daily, d = once daily, white bars = solution, grey bars = capsules.

Conclusions

- The prospective application of an optimal design was found to be successful.
- As shown, the optimal sparse design was able to provide precise parameter estimates (Table III) and the final model had the same structure as one of the models considered in the design (Figure I).
- The sampling windows were sufficient to provide flexible sampling and still efficient enough to support a standard model building strategy.
- Compared to healthy volunteers(5,6) lower itraconazole and metabolite concentrations were found in these CF patients, likely due to reduced absolute bioavailability caused by disease-influenced GI tract changes.
- Higher doses of itraconazole are required to achieve the target for both oral formulations.
- To incorporate missing data, using the simple Beal method 5 provided comparable results to the more complex but theoretically better Beal method 4 (integration method).

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