A Population Pharmacokinetic Study of Oral Itraconazole in Cystic Fibrosis and Bone Marrow Transplant Children

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Background

- Itraconazole, a triazole oral antifungal (capsules, oral solution) is a highly lipophilic weak base with variable absorption.
- It has one bioactive metabolite: hydroxy-itraconazole.
- Used for treatment of Allergic Bronchopulmonary Aspergillosis in cystic fibrosis (CF) and for prophylaxis in bone marrow transplant (BMT) patients.
- TDM target used is: $C_{min,ss}$ > 0.5 and < 2.0 mg/L of itraconazole.(1)

AIM

- To develop a populations pharmacokinetic (popPK) model for itraconazole and its active metabolite hydroxy-itraconazole to improve dosage regimens.

Study Design

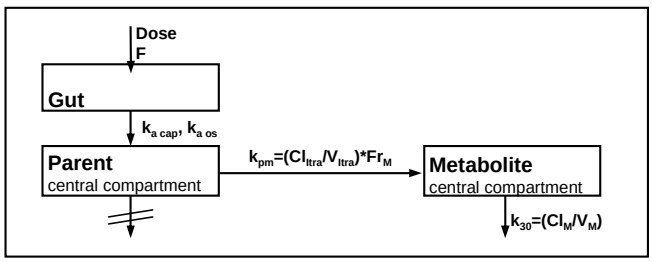
- Patients swapped from capsules to oral solution for 3 doses.
- Minimum of 4 finger-prick samples per patient.

Results

- **Demographics and data**
  - 229 blood samples from 49 patients
  - Median dose: 5.4 mg/kg (1.5 -12.5 mg/kg)
  - Median itraconazole concentration: 0.26 mg/L
  - Median hydroxy-itraconazole concentration: 0.53 mg/L

Characteristics	Numbers [median (range)]	
Disease (CF/BMT)	29/20	
Gender (F/M)	19/30	
Age (y)	8	(0.4 - 30) (5 CF adults)
Weight (kg)	29.3	(6.8 - 83.5)
Co-medications per patient	12.5	(3 - 27)

- **Model**



Pharmacokinetic Parameters	Mean	(BSV CV%)
Cl_{Itra}/F (L*h^{-1})	35.5	(68.8) TVCL= θ_1*(WT/70)**0.75
V_{Itra}/F (L)	672	(75.8) TVV = θ_2*(WT/70)
$Cl_M/(F*Fr_M)$ (L*h^{-1})	10.6	(73.4)
$V_M/(F*Fr_M)$ (L)	5.29	
F_{rel} (capsules/oral solution)	0.55	(61.1)
$k_{a\ cap}$ (h^{-1})	0.09	
$k_{a\ os}$ (h^{-1})	0.96	
t_{lag} (h)	0.31	
RUV_{Itra} / RUV_M (CV %)	49.9 / 47.1	

No difference between CF and BMT was found, Fr_M was fixed to 1, Correlation between Cl_{Itra}/F and V_{Itra}/F was 0.69

References

1. Buchkowsky S, Patrtovi N, Ensom M. Ther Drug Monit 2005;27:322-333.
2. Conway SP, Etherington C, Peckham DG, et al. J Antimicrob Chemoth 2004;53:841-847.
3. Poirier J-M, Berlioz F, Isnard F, et al. Therapie 1996;51:163-167.

Simulations

- Monte Carlo simulations (n=1,000) for several doses were performed to assess new dosing strategies

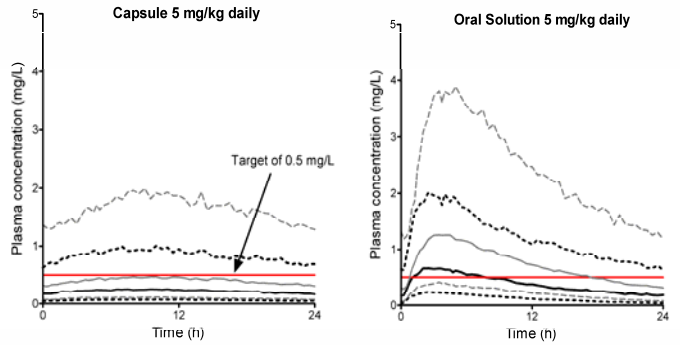


Figure 1: Simulation of the current dosing regimen. Panels shows the median itraconazole (black) and hydroxy-itraconazole (grey) plasma concentrations at steady-state for both capsule and oral solution formulation respectively including the 10-90% percentile range (broken lines). The target concentration is illustrated as a red line.

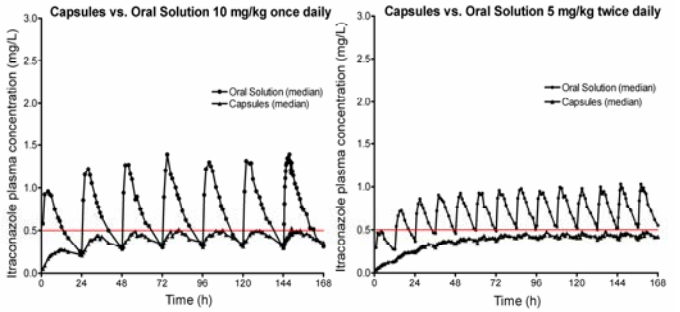


Figure 2: Simulated median plasma concentration-time profile of itraconazole over 7 days of 10 mg/kg once daily and 5 mg/kg twice daily after either the capsule (triangle) or the oral solution (round) formulation. The target concentration is illustrated as a red line.

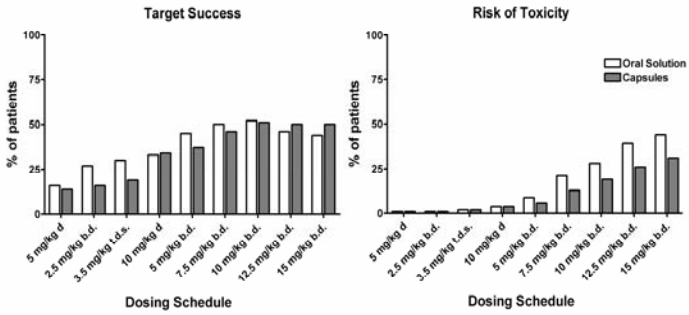


Figure 3: Chance of patients achieving the therapeutic target range for itraconazole ($C_{min,ss}$ = 0.5-2 mg/L) with different dosing schedules and percent of patients at risk of toxicity at these doses. b.d. = twice daily, d = once daily, t.d.s. = three times daily

Conclusions

- With current dosing regimen (5 mg/kg once daily) less than 20% of patients will achieve the target concentration (Figure 1,3).
- Twice daily dosing preferable over daily dosing (Figure 2).
- 7.5-10 mg/kg of solution and 10-12.5 mg/kg of capsules twice daily would provide most patients with target success (Figure 3).
- High inter-patient variability confirmed previous data in CF(2), leukaemia and BMT(3) patients.
- Allometric scaled model