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: $C_{\text{min,ss}} > 0.5$ 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

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

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\(^2\), leukemia and BMT\(^3\) patients.
- Allometric scaled model

Pharmacokinetic Parameters Mean (BSV CV %)
- $C_{\text{Itra}}(\text{F})(\text{L}^\cdot\text{h}^{-1})$ 35.5 (68.8)\(^\text{TVCL}= \theta_1\cdot(WT/70)^{0.75}\)
- $V_{\text{Itra}}(\text{F})(\text{L})$ 672 (75.8)\(^\text{TVV}= \theta_2\cdot(WT/70)\)
- $C_{\text{M}}(\text{F}+\text{F}_{\text{M}})(\text{F})(\text{L}^\cdot\text{h}^{-1})$ 10.6 (73.4)
- $V_M/(\text{F}+\text{F}_{\text{M}})(\text{L})$ 5.29
- $F_{\text{oral}}$ (capsules/oral solution) 0.55 (61.1)
- $k_{\text{cap}}$ (h\(^{-1}\)) 0.09
- $t_{\text{lag}}$ (h) 0.96
- $t_{\text{lag}}$ (h) 12.5
- $RUV_{\text{oral}} / RUV_{\text{M}} (\text{CV} \%)$ 49.9 / 47.1

References

No difference between CF and BMT was found, FrM was fixed to 1. Correlation between $C_{\text{Itra}}(\text{F})$ and $V_{\text{Itra}}(\text{F})$ was 0.69.