Population pharmacokinetics of isavuconazole based on pharmacogenetics in inmunosuppressed patients-4CPS-239

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Aim and objectives

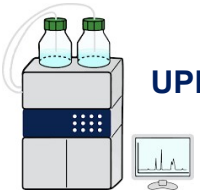
- To develop a population pharmacokinetic model (PopPK) that describes the behavior of isavuconazole in prophylaxis and treatment of invasive fungal infections (IFI) and to evaluate possible factors affecting dosage.

Materials and Methods

- Prospective and multidisciplinary study (June 2020 to January 2022).
- Immunosuppressed patients treated with oral and intravenous isavuconazole as prophylaxis or treatment for IFI.

VARIABLES

- × Demographic
- × Clinical
- × Biochemical
- × Genetic:
  - **Polymorphisms**
  - **Inductors** and **inhibitors**
  - **Degree of saturation** of drug-metabolizing enzymes (*SuperCYPsPred*).



UPLC

Predose concentration

PopPK analysis

- × Nonlinear mixed-effects model NONMEM v7.4 - FOCEI
- × Software R v3.4

Results

PHARMACOKINETIC MODEL

N: 31 patients (10 females)
Hematology (19) and intensive care (12)
Non-wild CYP3A4 (20%)
99 samples
Mean concentration (SD): 1.80 (0.95) µg/mL

- SIngle.-compartment model with first order absorption and elimination.
- Absortion rate: 22.6 h^{-1} (Cojutti et al. 2021)
- Volume of distribution: 147 L
- Apparent clearance (CL/F):

$$CL/F\ (L/h) = 3.54*(ALB/2.9)^{-0.7} *(BS/1.9)^{1.9} *(1+0.8)^{3A4Ind}$$

ALB: serum albumin (g/dL), BS: body surface (m^2),

3A4Ind: presence of inductor drugs for CYP3A4 ALB: albúmin (g/dL)

Interindividual variability for CL/F: 40%

Residual variability for CL/F: 30% (additive) and 0,05 µg/mL (proportional)

Conclusion and relevance

The developed PopPK model adequately characterizes the kinetic behavior of isavuconazole and includes the ALB, BD and the presence of inductors of CYP3A4 parameters that affect its clearance.

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