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Characterization of Isavuconazole Serum Concentrations with Various Administration Routes in a Hospitalized Cohort

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Abstract

Background: Patients with invasive fungal infections are often critically ill and immunosuppressed with multiple comorbidities that may impact drug absorption and exposure. This study sought to characterize isavuconazole serum concentrations (ISCs) in a cohort of real-world hospitalized patients when administered by intravenous (IV) solution, enterally as intact capsules, or via tube as opened capsule contents.

Methods: This retrospective cohort analysis included all hospitalized patients who received isavuconazole as prophylaxis or treatment between September 2017 and September 2018 and had therapeutic drug monitoring performed. For patients receiving isavuconazole by tube, the capsules were opened and contents were diluted with 10-30 mL of sterile water. Administration was per package insert for intact capsules and IV solution. ISCs were obtained as part of routine care and were quantified by high-performance liquid chromatography. An appropriate trough was defined as within 4 hours of the next scheduled dose. Currently, there is a lack of correlation between isavuconazole exposure and efficacy or toxicity; thus, ISCs were compared between administration routes.

Results: 93 ISCs were obtained during 65 encounters from 55 unique patients. The majority of patients were post-transplant (69.1%) and death occurred during 12 (18.5%) encounters. ISCs based on different characteristics of the cohort are shown in Table 1. All ISC assessments were detectable, median 2.3 mg/dL (Q1: 1.5 mg/dL, Q3: 3.3 mg/dL). Administration via tube achieved similar ISCs compared with IV therapy (1.6 mg/dL vs. 1.9 mg/dL, respectively). However, administration of intact capsules resulted in higher median ISCs, 3 mg/dL (Q1: 1.9 mg/dL, Q3: 4.1 mg/dL). All 14 patients with administration via tube were post-transplant, which was not shown to have a significant impact on ISC (median, transplant 2.2 mg/dL vs. non-transplant 2.7 mg/dL).

Conclusion: ISCs were detectable in all patients regardless of transplant status or location at the time of ISC assessment. Administration of isavuconazole via an enteral feeding tube achieved comparable serum concentrations compared with FDA-approved routes of administration and may represent an important alternative for select patients.

Background

- Invasive fungal infections (IFIs) are associated with high rates of adverse outcomes and often coexist with comorbidities that may impact oral drug absorption and antimicrobial exposure
- Isavuconazole was FDA approved, for invasive aspergillosis and mucormycosis, as a capsule and intravenous (IV) solution with recommendations against manipulation of the oral capsule
- Due to the prolonged duration required for management of IFIs and the complications and costs associated with IV therapy, an oral formulation for patients unable to swallow capsules is desired
- This study characterized isavuconazole serum concentrations (ISCs) in a cohort of real-world hospitalized patients after administration via IV solution, enterally as intact capsules, or tube (VT) as opened capsule contents

Methods

- Retrospective cohort analysis of patients admitted to a tertiary academic medical center
- Patients received isavuconazole as prophylaxis or treatment between 09/2017 and 09/2018 with therapeutic drug monitoring
- Tube administration was performed by opening capsule contents and diluting the drug with 10-30 mL of sterile water, other administration was performed per package insert
- ISCs were obtained as part of routine care and were quantified by high-performance liquid chromatography
- An appropriate trough was defined as within 4 hours of the next scheduled dose

Table 1. Baseline Characteristics

Characteristic	Value
Age (median)	54 years (IQR 42-64)
Sex, female	29 (52.7%)
Weight (kg)	67 (IQR 58-78.5)
Mean BMI kg/m^2	24.4 kg/m^2
Transplant status	
Any type	38 (69.1%)
Bone marrow transplant	10 (18.2%)
Solid organ transplant	
Heart	3 (5.5%)
Lung	22 (40%)
Lung/kidney	3 (5.5%)

Results

- 93 ISCs were obtained during 65 encounters from 55 unique patients
- All patients had detectable ISCs
- Median overall ISC was 2.3 mg/dL (Interquartile range [IQR] 1.5-3.3)
- Transplant status (69.1%) did not have a significant effect on ISCs (Table 2)
- Trough vs. non-trough ISCs resulted in similar values (Table 2)
- Non-intensive care unit patient location, prophylaxis indication, and enteral administration of intact capsules resulted in higher exposures, likely reflecting clinical stability
- All VT administration occurred in post-transplant patients and was given via gastric (11, 78.6%) and jejunum tubes (3, 21.4%) with concomitant enteral feedings
- VT ISCs were similar to IV but lower than enteral capsules possibly reflecting clinical stability

Table 2. Characterization of Isavuconazole Concentrations[a]

Characteristic	Frequency (n = 93 serum concentrations)	Isavuconazole Serum Concentration (mg/dL)
Concentration		
< 4 hours of next dose	80 (86)	2.3 (1.5-3.4)
≥ 4 hours of next dose	13 (14)	3.0 (1.9-3.3)
Duration of therapy at assessment		
Day < 10	28 (30.1)	2.2 (1.3-3)
Day 10-30	35 (37.6)	1.9 (1.4-3)
Prolonged (prior to admission)	30 (32.3)	3.1 (1.9-5.2)
Primary route of administration		
Intravenous	34 (36.6)	1.9 (1.3-2.8)
By mouth	45 (48.4)	3.0 (1.9-4.1)
Via tube	14 (15.1)	1.6 (1.3-2.5)
Transplant status		
Yes	71 (76.3)	2.2 (1.5-3.5)
No	22 (23.7)	2.7 (1.5-3.3)
Treatment purpose		
Prophylaxis	26 (28)	3.0 (2.0-5.2)
Treatment	67 (72)	2.0 (1.4-3.2)
Location during assessment		
Floor	65 (69.9)	2.7 (1.8-3.7)
Intensive care unit	28 (30.1)	1.9 (1.3-2.5)
Type of dosing received		
Load only	3 (3.2)	3.3 (3.2-4.5)
Load and maintenance	25 (26.9)	2.0 (1.3-2.7)
Maintenance	65 (69.9)	2.5 (1.6-3.7)

[a]Data are reported in n (%) or median (IQR)

Conclusions

- ISCs were detectable in all patients regardless of transplant status or patient location at the time of assessment
- Isavuconazole administered via tube resulted in comparable serum concentrations compared with FDA-approved routes of administration
- Further research is needed to investigate and establish safety and efficacy concentration thresholds

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