Lower Pediatric Oral Bioavailability of Voriconazole is Not Due to Lower Intestinal Bile Salt Concentration in Children

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Purpose

Voriconazole is a second-generation triazole antifungal agent with potent activity against a broad spectrum of clinically significant fungal pathogens, including Aspergillus, Candida, Cryptococcus neoformans, and certain less common molds. It is used for treating life-threatening fungal infections in children, especially in immunocompromised patients, and is marketed as Vfend (Pfizer, New York, NY). Voriconazole has an absolute bioavailability (BA) of ~96% in adults, whereas in children of 2-11 years of age, its BA is only ~45-65%. Also, children exhibit ~3-fold higher voriconazole clearance compared to adults.1

Voriconazole is cleared predominantly via oxidative metabolism by cytochrome P450 (CYP) 3A4, CYP2C19, flavin-containing monooxygenases (FMO) and, to a lesser extent, CYP2C9. The two major metabolites of voriconazole are N-oxide and hydroxymethyl voriconazole (Fig 1).2

Methods

Ex Vivo Permeation Studies of Voriconazole:

Absorptive transport of voriconazole was measured across mouse intestinal tissue in an Ussing-type diffusion chamber. The apical side of tissue segments was exposed for 3 hours to voriconazole (1mM) dissolved in Krebs-Bicarbonate Ringer buffer (control) or Fasted-State Simulated Intestinal Fluid (FaSSIF) containing 1mM (pediatric) or 3mM (adult) bile salts. Basolateral (receiver) and apical (donor) solutions and tissue lysates were analyzed for voriconazole and its N-oxide metabolite with high-performance liquid chromatography / UV detection (HPLC-UV), using diclofenac sodium as an internal standard.

Voriconazole and Voriconazole N-oxide Analysis:

HPLC-UV detection was employed to quantify voriconazole and its major metabolite, voriconazole N-oxide. An agilent 1100 HPLC system (Agilent Technologies, Santa Clara, CA) and a Nova-Pak C18 column (150 × 3.9 mm, 4 μm) were used to separate the samples. Analytes were eluted from the column with a linear gradient of mobile phase A/B (v/v) starting at 90:10 at 0 minutes to 15:85 at 10 minutes at a 0.6 mL/min flow rate. Mobile phase A consisted of 5 mM ammonium acetate with 0.1% formic acid and mobile phase B consisted of acetonitrile with 0.1% formic acid. The retention time was 5.5 minutes for voriconazole, 6.2 minutes for diclofenac sodium and 4.8 minutes for the voriconazole N-oxide. Peak areas were measured at 265 nm for diclofenac sodium and voriconazole N-oxide, and at 254 nm for voriconazole.

Results

Voriconazole absorptive transport rate was ~3-fold greater in FaSSIF media containing 1mM or 3mM bile salts compared to that observed with control KBR media. Voriconazole is BCS class II drug with low solubility due to lipophilic nature.

Bile salts solubilize the drug which leads to increased rate of transport in FaSSIF media. Concentration (1mm and 3mm) of bile salts had no effect on voriconazole absorptive transport.

Conclusions

- As anticipated, bile salts increase the transport rate of voriconazole across mouse intestinal epithelium, presumably by increasing its solubility.

- However, our observation that reducing bile salt concentration from 3 mM (adult intestinal concentration) to 1 mM (pediatric intestinal concentration) does not affect voriconazole permeability suggests that the lower oral bioavailability of voriconazole in children compared to adults is not due to differences in intestinal fluid composition.

- Our results support the predictions of the PBPK model developed in our laboratory3 that intestinal first-pass metabolism likely contributes to lower oral bioavailability of voriconazole in children compared to adults.

References


