PHARMACOKINETICS, PHARMACODYNAMICS AND DRUG METABOLISM

Pharmacokinetics of Itraconazole After Intravenous and Oral Dosing of Itraconazole-Cyclodextrin Formulations

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ABSTRACT: The current research evaluated and compared the efficacy of hydroxybutenyl-β-cyclodextrin (HBenBCD) and hydroxypropyl-β-cyclodextrin (HPBCD) as enhancers of itraconazole solubility and oral bioavailability. At 10 wt% cyclodextrin, 17-fold and 3.8-fold increases in itraconazole aqueous solubility were observed in the presence of HBenBCD and HPBCD, respectively. Significant differences in the dissolution of itraconazole in the presence of these two cyclodextrins were also observed. Itraconazole pharmacokinetics is known to exhibit a significant food effect. However, testing in biorelevant media indicated that no food effects should be observed after oral administration of itraconazole:HBenBCD complexes. Formulations of itraconazole with HBenBCD were prepared and these complexes, along with the commercial forms of itraconazole with and without HPBCD (Sporanox®) were administered to male Sprague–Dawley rats by oral and intravenous routes. Intravenous administration of itraconazole formulated with HBenBCD resulted in a higher AUC relative to Sporanox®. When administered as oral solutions, the itraconazole:HBenBCD formulation provided higher oral bioavailability than the Sporanox® oral solution. When administered as solid formulations, the itraconazole:HBenBCD solid formulation provided a 2× increase in oral bioavailability relative to the Sporanox® solid formulation. No food effects were observed with the itraconazole:HBenBCD solid dosage forms. Drug/metabolite ratios were dependent upon the dosage form. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:3100–3116, 2007

Keywords: hydroxybutenyl-β-cyclodextrin; hydroxypropyl-β-cyclodextrin; itraconazole; hydroxyitraconazole; bioavailability; pharmacokinetics; food; formulations

INTRODUCTION

Fungal infection can be a serious medical problem, particularly as a complicating factor in serious illnesses such as hematological malignancy, HIV infection, and chemotherapy-induced neutropenia. A preferred treatment for cutaneous and

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systemic fungal infections involves administration of antifungal azole compounds. Antifungal azole compounds are structurally diverse and characterized by having imidazole or triazole functionalities. This class includes drugs such as itraconazole, ketoconazole, fluconazole, saperconazole, miconazole, voriconazole, and several others. These compounds generally have low water solubility, which in most cases translates into low bioavailability. This can have a negative impact on efficacy, side effects, inter- and intrapatient variability, and ultimately the utility of the drug.

Itraconazole (Fig. 1) is a broad-spectrum triazole agent available for the treatment of histoplasmosis, blastomycosis, onychomycosis, and amphotericin B-refractory aspergillosis.[1–5] Itraconazole is highly effective *in vitro* against *Candida albicans* and other *Candida* species.[6] The effectiveness of itraconazole is in part due to the fact that hydroxyitraconazole, the main metabolite of itraconazole, also has considerable antifungal activity.[7]

Itraconazole is a weakly basic drug (pK_a *ca.* 3.7) that was found experimentally to have very poor water-solubility (intrinsic solubility, $S_o = 30$ μg/mL). The drug is highly crystalline having a T_m of 170°C and a log*p*-value of 5.66 at pH 8.1.[8] Itraconazole can only be ionized and solubilized in water at very low pH. Itraconazole has limited solubility in organic solvents with CH_2Cl_2 being the preferred solvent. Itraconazole also has limited stability at elevated temperatures and at low pH.

A number of investigators have explored the use of cyclodextrins (CDs) as a means to increase water solubility and bioavailability of antifungal drugs such as itraconazole.[9–13] CDs are cyclic oligomers of glucose, which typically contain 6, 7, or 8 glucose monomers joined by α-1,4 linkages; these oligomers are commonly called α-CD, β-CD, and γ-CD, respectively. Topologically, CDs form a torus that has a hydrophobic interior and a hydrophilic exterior. This allows the CD to be dissolved in water, where it acts as a host molecule and forms inclusion complexes with hydrophobic guest molecules. This feature has led to the use of CDs in pharmaceutical formulations.[14,15] Unmodified CDs, particularly β-CD, are relatively crystalline and have limited aqueous solubility. In parenteral formulations, limited solubility is a very serious issue as renal concentration of the unmodified CD can lead to crystallization of the CD and necrotic damage.[16] Fortunately, the solubility of unmodified CDs in water can be significantly increased by the addition of a small number of substituents to the hydroxyl groups of the anhydroglucose monomers.[17]

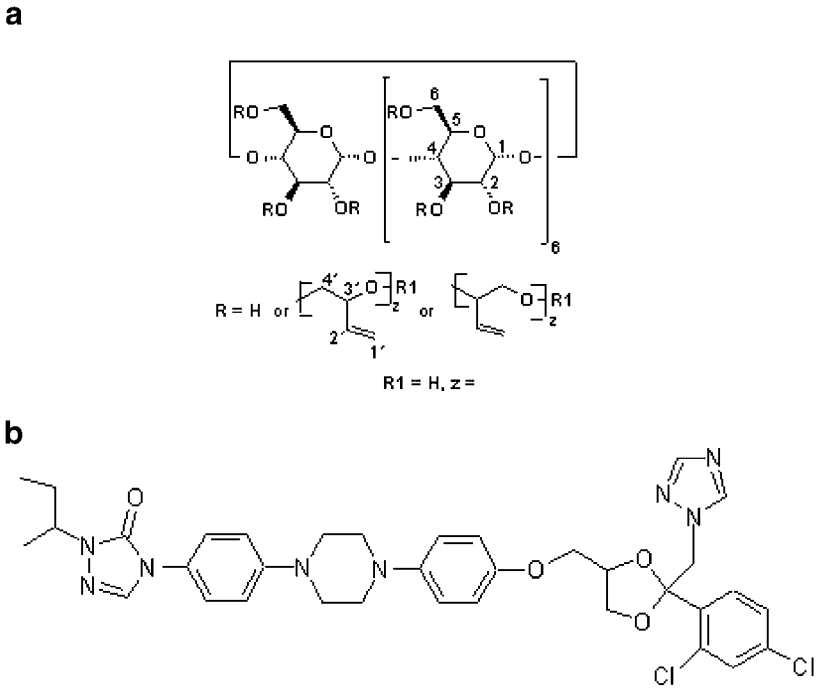

Figure 1. Structures of (a) HBenBCD and (b) itraconazole which were used in this study.