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Research paper

Characterization and pharmacokinetic analysis of aerosolized aqueous voriconazole solution

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ABSTRACT

Invasive fungal infections in immunocompromised patients have high mortality rates despite current treatment modalities. This study was designed to evaluate the suitability of an aqueous solution of voriconazole solubilized with sulfobutyl ether-β-cyclodextrin for targeted drug delivery to the lungs via nebulization. A solution was prepared such that the inspired aerosol dose was isotonic with an acceptable mass median aerodynamic diameter of 2.98 μm and a fine particle fraction of 71.7%. Following single and multiple inhaled doses, high voriconazole concentrations were observed within 30 min in the lung tissue and plasma. Drug solubilization with sulfobutyl ether-β-cyclodextrin contributed to the rapid and high drug concentrations in plasma following inhalation. Maximal concentrations in the lung and plasma were 11.0 ± 1.6 μg/g wet lung weight and 7.9 ± 0.68 μg/mL, respectively, following a single inhaled dose with a corresponding tissue/plasma concentration ratio of 1.4 to 1. Following multiple inhaled doses, peak concentrations in lung tissue and plasma were 6.73 ± 3.64 μg/g wet lung weight and 2.32 ± 1.52 μg/mL, respectively. AUC values in lung tissue and plasma were also high. The clinically relevant observed pharmacokinetic parameters of inhaled aqueous solutions of voriconazole suggest that therapeutic outcomes could be benefitted through the use of inhaled voriconazole.

1. Introduction

Invasive fungal infections are increasing in prevalence in immunocompromised patients due to decreased immunity resulting from drug therapy, organ transplantation, and/or various disease states [1]. The distribution of causative organisms for invasive fungal infections has been changing with an increase in the prevalence of *Aspergillus* spp. and other invasive molds [2]. Systemic fungal infections caused by *Aspergillus* spp. are primarily lung infections due to the inhalation of conidia. The resulting infection, Invasive Aspergillosis (IA), is the cause of serious damage to lung tissue due to invasive hyphal growth [3]. Dissemination of IA can also occur to other organ systems, and correlates with a poorer prognosis [4]. Despite the best therapeutic options, mortality rates for IA remain high [4,5].

The primary therapy for the treatment of IA is the systemic administration of voriconazole, and has led to improved patient outcomes compared to other treatments [6,7]. Voriconazole is a triazole antifungal with broad antifungal activity against numerous pathogenic fungi in addition to its activity against *Aspergillus* spp. [8,9]. Voriconazole has also been reported to distribute to the lungs as measured by tissue and epithelial lining fluid concentrations following systemic administration [10,11]. The commercial voriconazole product, Vfend®, is available as an oral tablet or intravenous formulation. The intravenous product is formulated with Captisol®, sulfobutyl ether-β-cyclodextrin, to form a solubilized drug–cyclodextrin complex due to very slight voriconazole solubility in water [12]. Voriconazole has reported side effects of visual disturbances, hepatic toxicity, and dermatologic reactions as well as serious cytochrome P450 mediated drug interactions [8,10]. Adverse events causing discontinuation of therapy occurred in up to 6% of patients, and were primarily due to elevations in liver function tests or rash. Other systemically administered antifungals can be selected as salvage therapy or in patients intolerant to voriconazole, but have the potential for other serious side effects as well as drug interactions [6,13,14].

The potential side effect profile and drug interactions associated with systemic antifungal administration might be reduced by targeting drug delivery to the lungs, the primary site of IA. Targeted lung delivery of antifungals can also lead to high drug

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concentrations at the site of infection to improve clinical outcomes. Two antifungals, amphotericin B and itraconazole, have been inhaled with the reported pharmacokinetic and outcome measures [13,15–23]. Inhaled amphotericin B formulations include drug solubilized with deoxycholate, drug encapsulated in liposomes, and drug–lipid complexed suspensions. Inhaled itraconazole was formulated as crystalline or amorphous nano-particulate suspensions.

Inhaled amphotericin B has a better but non-optimal side effect profile and significantly improved outcomes compared to the systemically administered formulations [13,15,17,23]. However, the pharmacokinetic profiles of inhaled compared to intravenous amphotericin B are substantially different. Lung concentrations of amphotericin B following intravenous administration are initially undetectable followed by low levels despite extensive tissue distribution following multiple doses [24–28]. Inhaled amphotericin B has led to much higher lung tissue concentrations but undetectable plasma levels [16,29,30]. The high drug concentrations in the lung tissue following amphotericin B inhalation was hypothesized to result in significant outcomes in human patients and animal models of IA compared to intravenous drug administration [15,17].

Inhaled nano-particulate itraconazole was also well tolerated with normal histological findings and an absence of inflammatory mediators following a chronic, multi-dose study in animals [22]. The pharmacokinetic profile of different inhaled formulations following a single inhaled dose demonstrated high and prolonged itraconazole concentrations in the lungs with maximal lung levels achieved 30–60 min after the completion of nebulization, while serum concentrations remained low and peaked after 2–5.35 h in animals [20,21,31]. The ratio of lung-to-serum AUC values was 25–50 and C_{max} ratios ranged from approximately 10 to 100, indicating low drug partitioning out of the lungs. Following multiple doses, lung concentrations remained substantially higher than serum concentrations [21]. Inhaled itraconazole demonstrated significantly improved outcomes compared to oral itraconazole and control groups in animal models of IA, and was suggested to be due to sufficient drug concentrations in the lungs to inhibit invasive fungal growth at a fraction of the oral dose [18,19].

Both inhaled amphotericin B and inhaled particulate itraconazole demonstrated substantial drug retention in the lungs, improved survival in the animal models of IA, and suggested positive clinical outcomes were associated with favorable lung pharmacokinetic profiles. Gavalda and colleagues reported an improved survival in an animal model of IA when both inhaled and intravenous antifungal were administered concurrently compared to inhaled or intravenous drug administered separately [15]. This report suggests near-therapeutic plasma concentrations combined with very high concentrations of antifungal in the lung could improve patient outcomes. However, neither inhaled amphotericin B nor inhaled itraconazole produces blood concentrations that are close to therapeutic levels. Therefore, targeted delivery of an antifungal to the lungs with distribution to the blood producing high drug concentrations in both lung tissue and blood can potentially improve clinical outcomes and be a significant improvement in antifungal therapeutic options.

The poor distribution of amphotericin B and itraconazole to the systemic circulation following inhalation could be due, in part, to the very low aqueous solubilities of these compounds. Inhalation of a solubilized antifungal, the voriconazole–cyclodextrin inclusion complex as Vfend® IV, could lead to better lung concentrations than reported following systemic drug administration as well as systemic drug distribution. In this study, it is hypothesized that an aqueous solution of voriconazole solubilized with sulfobutyl ether-β-cyclodextrin, when inhaled as a single dose, would produce high lung drug concentrations as well as allow rapid distribution from the lungs to the plasma. Furthermore, following multiple doses, inhaled voriconazole solutions would also produce elevated and consistent trough concentrations in lungs and plasma. Although solubilized voriconazole should distribute to the systemic circulation following inhalation, reductions in the incidence of hepatotoxicity, visual abnormalities, and dermatologic reactions could still occur due to a lower drug burden and dose sparing compared to systemic drug administration.

2. Materials and methods

2.1. Materials

Vfend® IV (Pfizer Inc., New York, NY, USA), voriconazole, and sulfobutyl ether-β-cyclodextrin, Captisol® were generously supplied by CyDex Pharmaceuticals, Inc. (Lenexa, KS). Sterile water for injection (SWFI) (Hospira, Inc.) and normal saline were purchased from Cardinal Health (Dublin, OH). Sodium tetraborate decahydrate, boric acid, and sodium acetate trihydrate were purchased from Sigma–Aldrich, Inc. (St. Louis, MO). Acetic acid was purchased from Sigma–Aldrich Laborchemikalien GmbH (Seelze, Germany). HPLC grade ethyl acetate was purchased from Spectrum Chemical Manuf. Corp. (Gardena, CA). HPLC grade acetonitrile was purchased from Fisher Scientific (Fair Lawn, NJ). HPLC grade methanol was purchased from EMD Chemicals Inc. (Gibbstown, NJ). Water was obtained from an in-house Milli-Q UV Plus water purification system from the Millipore Corp. (Billerica, MA).

2.2. Characterization of in vitro properties of voriconazole solutions

Vfend® IV was reconstituted with SWFI as instructed in the prescribing information to a 10 mg/mL voriconazole concentration, which also contained sulfobutyl ether-β-cyclodextrin at 160 mg/mL. Additional dilutions were prepared with SWFI to voriconazole concentrations from 2.5 mg/mL to 10 mg/mL. The osmolality of voriconazole solutions was tested (n = 10 per concentration) using a μOsmette Micro Osmometer (Precision Systems Inc., Natick, MA). The pH of the 6.25 mg/mL voriconazole dilution was determined using an Orion 350 PerpHecT® Advanced Benchtop pH Meter (Thermo Fisher Scientific, Waltham, MA).

2.3. Particle size analysis using a cascade impactor

Voriconazole solutions were diluted to 6.25 mg/mL voriconazole and aerosolized using an Aeroneb® Pro micro pump nebulizer (Nektar Therapeutics, San Carlos, CA) for 20 min. Aerodynamic droplet size distributions were determined using a USP Apparatus 1 non-viable eight-stage cascade impactor (Thermo-Anderson, Symrna, GA) to quantify total emitted dose (TED) from the nebulizer output, mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and percentage droplets with an aerodynamic diameter less than 4.7 μm (defined as the percentage fine particle fraction or FPF). The characterization of aerodynamic droplet size distribution was conducted through modifications to the guidelines described in USP 30 Section 601: Aerosols, Nasal Sprays, Metered-dose Inhalers, and Dry Powder Inhalers [32].

2.4. Single-dose pharmacokinetic analysis

Male outbred ICR (Institute for Cancer Research) mice were purchased from Harlan Sprague Dawley, Inc. (Indianapolis, IN) and housed with free access to water and food. Prior to dosing, mice were acclimatized to the nose-only dosing animal restraints. Mice received a single inhaled dose of 5 mL aqueous voriconazole solution at 6.25 mg/mL voriconazole using a nose-only dosing apparatus with a drug exposure time of 20 min. Single-dose pharmacokinetic profiles were determined in two groups of mice: