Drug Metabolism and Pharmacokinetics 30 (2015) 400–409

Contents lists available at ScienceDirect

Drug Metabolism and Pharmacokinetics

journal homepage: http://www.journals.elsevier.com/drug-metabolism-and-pharmacokinetics

Regular article

Pharmacokinetic evaluation of liposomal amphotericin B (L-AMB) in patients with invasive fungal infection: Population approach in Japanese pediatrics

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ARTICLE INFO

Article history:
Received 9 January 2015
Received in revised form
16 July 2015
Accepted 13 August 2015
Available online 28 August 2015

Keywords:
Liposomal amphotericin B
Invasive fungal infection
Population pharmacokinetics
Pediatric patients
PK exposures
Adverse drug reaction
Clinical laboratory test values

ABSTRACT

The pharmacokinetic characteristics of liposomal amphotericin B (L-AMB; AmBisome®) in patients with invasive fungal infection were investigated. A population pharmacokinetic (PK) model in Japanese pediatric patients was developed based on 159 serum amphotericin B (AMPH-B) concentrations obtained in a post-marketing clinical study. The subjects were 39 patients with a mean age of 8.4 years (SD 4.5) and mean body weight of 27.1 kg (SD 14.1). A two-compartment PK model with zero-order input and first-order elimination was fitted to serum AMPH-B concentrations for L-AMB doses of 1.0, 2.5, and 5.0 mg/kg/day. Body weight showed significant correlations with PK parameters, such as clearance (CL) and distribution volume of the central compartment (V_c). The predicted C_{max}/dose and $AUC_{0\text{-}24}$/dose in Japanese pediatric patients were similar to those in non-Japanese pediatric patients and Japanese adult patients. Extremely large increases in C_{trough} compared with predicted values were observed in some Japanese pediatric patients, but no relationships with demographic characteristics, clinical laboratory test values, or representative adverse drug reaction (decreased potassium) were found. The population PK parameters in this study are useful for simulating PK profiles of L-AMB and will be helpful for PK exposure comparisons among different populations and in investigations of pharmacokinetic–pharmacodynamic characteristics in patients.

Chemical compounds: Amphotericin B Deoxycholate (PubChem CID:23668620); amphotericin B (PubChem CID:5280965); 3-nitrophenol (PubChem CID:11137); methanol (PubChem CID:887).

1. Introduction

Invasive fungal infection causes morbidity and mortality among patients with acute leukemia and receipt of an allogeneic hematopoietic stem cell transplant [1]. For both adult and pediatric patients, invasive fungal infection can occur after treatments, such as bone marrow transplantation or chemotherapy in patients with blood disorders and is an important complication in patients with cancer [2–6]. Deoxycholate amphotericin B (D-AMB; Fungizone®), with active ingredient amphotericin B (AMPH-B), has a very broad spectrum of antifungal activity. To prevent serious adverse drug reactions, such as hypokalaemia or nephrotoxicity [7], after long-term treatment with D-AMB, AMPH-B was encapsulated in liposomes and developed as a drug for antifungal therapy. Liposomal AMPH-B (L-AMB; AmBisome®) is now commonly used in clinical practice for pediatric patients [8].

In April 2006, L-AMB was simultaneously approved in Japan for both adult and pediatric patients for the treatment of fungemia, respiratory mycosis, fungal meningitis, and disseminated mycosis caused by *Aspergillus*, *Candida*, and *Cryptococcus* as well as for the treatment of febrile neutropenia with suspected fungal infection, which was the first indication in Japan [9]. As the Japanese clinical studies did not involve pediatric patients, the post-marketing clinical study in this report was conducted in Japan for further

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http://dx.doi.org/10.1016/j.dmpk.2015.08.003

evaluation of the safety, efficacy, and pharmacokinetics of L-AMB in the treatment of hospitalized pediatric patients with invasive fungal infection.

The clinical pharmacokinetics of L-AMB have been reported in healthy adult subjects [10], adult patients [11,12] and pediatric patients [13,14]. These studies provided pharmacokinetic (PK) parameters, and one of them reported extremely large increases in the trough concentration (C_{trough}) of AMPH-B in some patients during repeated dosings [12]. However, the cause of this phenomenon and influence of large increases in C_{trough} on safety have not been clarified.

The first objective of the present analysis was to develop a population PK model using data for Japanese pediatric patients obtained in the above-mentioned post-marketing study. The second objective was to compare the PK exposures among Japanese pediatric patients, non-Japanese pediatric patients and Japanese adult patients. The final objective was to investigate whether the extremely large increases in C_{trough} of AMPH-B have relationships with demographic characteristics, clinical laboratory test values, or representative adverse drug reaction (decreased potassium [K]).

2. Methods

2.1. Patients

Thirty-nine Japanese pediatric patients were enrolled in a post-marketing clinical study (Japanese pediatric study), conducted in Japan from September 2006 through June 2009 [15]. The inclusion criteria were as follows: 1) patients with invasive fungal infection or with febrile neutropenia who suffered from suspected invasive fungal infection; 2) patients who required hospitalization; and 3) patients aged from 28 days to 15 years.

The PK parameters of the Japanese pediatric patients were compared with those of non-Japanese pediatric patients [14] and Japanese adult patients [12], based on results in the cited clinical studies. In the non-Japanese pediatric study [14], 47 non-Japanese pediatric patients were enrolled in an open label, sequential dose escalation clinical study conducted in the United States from March 1997 through June 1998. The inclusion criteria were as follows: 1) immunocompromised pediatric patients aged 1–17 years, with (a) persistent or recurrent fever (oral temperature >38 °C) and neutropenia (absolute neutrophil count <500/mm^3) despite >96 h of broad-spectrum antibiotics who would normally be administered empirical deoxycholate amphotericin B, or (b) proven candidemia or mucosal candidiasis: and 2) immunocompromised pediatric patients with confirmed invasive candidiasis. Re-enrollment was permitted. Regarding the PK analysis groups, 23 patients administered 2.5 or 5.0 mg/kg/day were evaluated. These patients had an age range of 1–16 years (2.5 mg/kg/day: mean 6.8 years, SD 4.9; 5.0 mg/kg/day: mean 7.7 years, SD 4.0) and a mean body weight of 22.0 kg (SD 10.6) in the 2.5 mg/kg/day group and 26.3 kg (SD 11.7) in the 5.0 mg/kg/day group. In the Japanese adult study [12], conducted in Japan from October 1998 through January 2001, 32 Japanese adult patients were enrolled. The inclusion criteria were as follows: 1) patients with invasive fungal infection or patients who suffered from suspected invasive fungal infection; 2) patients for whom signed informed consent could be obtained; and 3) patients aged 20–74 years. For the PK analysis group, 31 Japanese adult patients ranged 23–73 years (mean 52.2 years, SD 14.4) and their mean body weight was 52.7 kg (SD 12.2). As the detailed conditions in these two clinical studies were previously reported [12,14], and partial data for PK analysis were used in the present analysis, minimal study information related to comparisons of PK parameters in the present analysis are reported here and below.

2.2. Design of L-AMB dosage

In the Japanese pediatric study, L-AMB was administered at a single dose of 2.5 mg/kg by intravenous infusion for 60–75 min on the first day. On the second day and thereafter, the dosage could be increased to 5.0 mg/kg/day or reduced to 1.0 mg/kg/day, if necessary, and the infusion duration was 60–120 min. Treatment was continued for up to 12 weeks until successful treatment was achieved. Treatment could be suspended for up to 1 week. Details of the dosage and administration method were reported previously [15].

In the non-Japanese pediatric study, L-AMB was administered as a 1-h daily intravenous infusion at dosages of 2.5 and 5.0 mg/kg/day [14]. In the Japanese adult study, L-AMB was administered as a 1-hour daily intravenous infusion at dosages of 1.0, 2.5, and 5.0 mg/kg/day [12].

2.3. Blood sampling

In the Japanese pediatric study, sparse blood samples for serum AMPH-B concentration measurements were obtained for population PK analysis. Two or more samples were obtained between the end of the first dosing and the start of the second dosing, and additional samples were obtained at trough levels after multiple dosings [15]. In the non-Japanese pediatric study, serial blood samples for PK analysis were obtained on day 1 pre-dose and at 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 h after L-AMB administration [14]. In the Japanese adult study, serial blood samples for PK analysis were obtained on day 1 pre-dose and at 1, 4, 8, and 24 h following L-AMB administration [12].

Blood samples for clinical laboratory tests were obtained on day 1 pre-dose, once per week during treatments, and on the next day after the end of treatment.

2.4. Ethics of the present clinical study

The Japanese pediatric study was conducted in accordance with Good Post-marketing Study Practice. The institutional review board or ethical committee of each of the 34 hospitals that participated in the study approved the study protocol. Written informed consent was obtained from each patient's guardian, and consent was obtained from the patients, whenever possible, after the study was explained.

The non-Japanese pediatric study and Japanese adult study were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. In the former, written informed consent was obtained from each patient or legal guardian prior to the initiation of any study-specific procedures. In the latter, written informed consent was obtained from all patients themselves or their legal representative.

2.5. Assay of serum AMPH-B concentrations

After centrifugation, serum samples were frozen at −20 °C and stored until analysis, because their stability for at least 28 weeks has been confirmed. The serum AMPH-B concentrations were determined using high-performance liquid chromatography (HPLC) at Mitsubishi Chemical BCL (Tokyo, Japan). Each serum sample (100 μL) was mixed with 3-nitrophenol (50 μL) as an internal standard and methanol (100 μL) and centrifuged at 12,000 rpm (approximately 8000× *g*) for 10 min. During the extraction procedure, the liposomal bilayer was disrupted so that the total AMPH-B concentration could be measured. The filtrate (70 μL) was injected into the HPLC system via a reversed-phase column (CAPCELL PAK C_{18} SG120; 4.6 mm diameter × 25 cm).