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ORIGINAL RESEARCH ARTICLE

Successful Empirical Antifungal Therapy of Intravenous Itraconazole with Pharmacokinetic Evidence in Pediatric Cancer Patients Undergoing Hematopoietic Stem Cell Transplantation

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Abstract

Background and Objectives Empirical antifungal therapy prevents invasive fungal infections in patients with cancer. This study assessed the empirical efficacy of intravenous itraconazole in pediatric patients undergoing hematopoietic stem cell transplantation, and investigated the pharmacokinetics and clinical implications.

Methods Oral itraconazole syrup was started (2.5 mg/kg twice daily) for prophylaxis, and patients with persistent neutropenic fever for more than 2 days were switched to intravenous itraconazole (5 mg/kg twice daily for 2 days for induction and 5 mg/kg daily for maintenance) as empirical treatment. Empirical antifungal efficacy was assessed retrospectively in 159 transplantations, and a full pharmacokinetic study was prospectively conducted in six of these patients. Successful antifungal efficacy was defined as the fulfillment of all components of a five-part composite end point.

Results The overall empirical antifungal success rate fulfilling all criteria was 42.1 %. No death or drug-related serious adverse events occurred during the study. Mean trough plasma concentration of itraconazole after oral prophylaxis and intravenous induction were 577.2 and 1659.7 μg/L, respectively. Mean area under the concentration-time curve of itraconazole and its metabolite at steady state were 42,837 ± 24,746 μg·h/L and 63,094 ± 19,255 μg·h/L.

Conclusions Intravenous itraconazole was effective and safe as an empirical antifungal agent in pediatric patients; this was due to the fast and satisfactory increase in drug concentration by switching from oral to intravenous therapy.

Key Points

Mean trough plasma concentrations of itraconazole after oral prophylaxis and intravenous induction were 577.2 and 1659.7 μg/L, above the sufficient plasma concentration for antifungal activity.

Dose adjusted areas under the concentration-time curve of itraconazole and its metabolite in children were approximately twice that of adults, and the relatively smaller clearance of itraconazole needs to be considered for pediatric use.

An antifungal regimen with intravenous itraconazole preceded by oral itraconazole showed empirical antifungal efficacy and safety in a large number of patients undergoing hematopoietic stem cell transplantation.

H. Kim and D. Shin contributed equally to this work. H. J. Kang and K.-S. Yu contributed equally to the supervision of this work and are the co-corresponding authors.

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1 Introduction

Invasive fungal infections are one of the most serious causes of death in cancer patients with neutropenia or in patients undergoing hematopoietic stem cell transplantations. The incidence of invasive fungal infection is 2–47 % during neutropenia, and the mortality rate ranges from 35 to 90 % based on associated risk factors [1]. The incidence of invasive fungal infection has been increasing with the use of broad-spectrum antibiotics during neutropenia, and persistent neutropenic fever may be the only clinical manifestation of an invasive fungal infection [2]. Thus, empirical antifungal therapy has become the standard of care in order to reduce invasive fungal infections in patients with persistent neutropenic fever [3, 4].

Itraconazole is a broad-spectrum triazole antifungal agent that has a reliable effect on *Aspergillus* and *Candida* species, and has shown a comparable effect and less toxicity compared to amphotericin B in a controlled study [1]. Previously, the capsule formulation of itraconazole showed poor absorption and unpredictable pharmacokinetics, and was difficult for cancer patients to swallow due to chemotherapy-related gastrointestinal toxicity. To overcome pharmacokinetic disadvantages of the capsule formulation, new formulations of an oral and intravenous solution, which were combined with hydroxy-propyl-β-cyclodextrin, were developed [5–7].

Empirical antifungal therapy is usually initiated with intravenous formulations to rapidly increase plasma concentrations [8]. With the increasing risk of invasive fungal infections, suitable empirical antifungal usage to rapidly increase plasma concentration for effective antifungal activity is necessary [9]. The optimal usage of itraconazole according to pharmacokinetic data has been proposed in adults [1, 5, 10–12]. However, pharmacokinetics in children are less known and the pharmacokinetics of repeated-dose intravenous itraconazole has not been reported, so that prediction is difficult in pediatric cancer patients [6, 7, 13].

Based on data from clinical trials, it is important that the itraconazole trough concentration is maintained over 250 or 500 μg/L for enhanced efficacy [14]. However, itraconazole has large inter- and intra-patient variability in its pharmacokinetics and is affected by various pathologic conditions and drug interactions; thus it is difficult to predict steady-state plasma concentrations in individual patients [15, 16].

Our institution has been administering oral itraconazole immediately as antifungal prophylaxis in patients with neutropenic fever, and switching to the intravenous form as empirical antifungal treatment when neutropenic fever persists. This study was conducted to assess the empirical efficacy of intravenous itraconazole in pediatric patients undergoing hematopoietic stem cell transplantation, and to investigate repeated-dose pharmacokinetics of intravenous itraconazole in pediatric patients to determine the clinical implications for antifungal efficacy.

2 Patients and Methods

2.1 Subjects and Study Registration

Patients undergoing hematopoietic stem cell transplantation at Seoul National University Children's Hospital, Seoul, Republic of Korea from January 2007 to June 2011 were included. Among those, patients who were administered empirical intravenous itraconazole were retrospectively reviewed for efficacy evaluation. For the pharmacokinetic study, patients who underwent transplantation during June 2009 to December 2010 were prospectively enrolled.

This study was approved by the Institutional Review Board of Seoul National University Hospital (0811-043-262). Participants in the pharmacokinetic study provided written informed consent for blood sampling and analysis.

Patients who were enrolled for the pharmacokinetic study were also included in the efficacy evaluation. The first participant was enrolled in January 2010, and this trial was registered from July 2011 at ClinicalTrials.gov (NCT01409018). Registration of the study was delayed because registration was not uniformly required by institutional clinical research regulations when this study was started. However, this prospective study was strictly conducted according to applicable standards of procedure, protocol, and other written instructions and regulatory guidelines.

2.2 Administration of Itraconazole

Prophylaxis with oral itraconazole (Sporanox® oral solution 10 mg/mL, Janssen Korea Ltd, Seoul, Republic of Korea) was started on day −2 of the conditioning course of hematopoietic stem cell transplantation. Oral itraconazole solution was administered at 2.5 mg/kg every 12 h. After 2 days of oral prophylaxis, patients with persistent neutropenic fever (temperature above 38 °C with an absolute neutrophil count below 500/μL) received intravenous itraconazole (Sporanox® INJ 250 mg/25 mL, Janssen Korea Ltd) at 5 mg/kg every 12 h for 2 days for induction and at 5 mg/kg once daily for maintenance. Itraconazole was administered until one of the following occurred: (1) absolute neutrophil count >1000/μL after the nadir absolute count and resolution of fever, (2) development of proven, probable, or possible invasive fungal disease, (3) development of unacceptable drug toxicity, (4) death, (5)

withdrawal from study participation (patient's decision), or (6) discontinuation of treatment (investigator's decision).

2.3 Efficacy Evaluation

Empirical efficacy was evaluated with the five-composite scoring system which was used and validated in other studies of empirical antifungal therapy [17, 18]. Treatment was considered successful if all five of the following criteria were met: (1) successful treatment of baseline fungal infection, (2) absence of breakthrough fungal infection during therapy or within 7 days after completion of study therapy, (3) survival for 7 days after completion of study therapy, (4) resolution of fever (defined as a temperature below 38 °C for at least 48 h) in the setting of neutropenia, and (5) no premature discontinuation of study treatment because of drug-related toxicity or lack of efficacy. Patients who only partially satisfied the efficacy criteria were analyzed separately.

Microbiological data and aspergillus galactomannan tests were also obtained during administration of itraconazole.

2.4 Safety Evaluation

Patients were monitored for adverse events daily during the administration of itraconazole and 7 days thereafter. The safety of itraconazole was assessed by retrospective chart review so that the frequency and intensity of adverse events and the likelihood of their being related to the study drug during the trial were investigated. Drug-related toxicity was graded according to the NCI Common Toxicity Criteria (CTCAE v4.0). CTC grades 3 or 4 were reported as severe grades. Data on concomitant medications during itraconazole administration were collected in all patients.

2.5 Sample Collection and Assay Methods

Trough concentrations during oral administration were measured with blood samples drawn before the fifth oral dose. Blood samples during intravenous administration were collected prior to every intravenous induction dose and the first through to the fifth intravenous maintenance dose. For area under the plasma concentration-time curve (AUC) analysis, serial blood samples were collected 1, 2, 4, 8, 12, and 24 h after the third intravenous maintenance dose. Samples were collected from a different central catheter lumen than the one used for itraconazole infusion. Collected blood samples were centrifuged at $1000 \times g$ for 10 min immediately and the separated plasma was stored at freezing temperatures for transporting to the pharmacology laboratory, where they were stored at −20 °C until analysis.

Plasma concentrations of itraconazole and its active metabolite, hydroxy-itraconazole, were measured by liquid chromatography-tandem mass spectrometry assay with a lower limit of quantitation of 10 ng/ml. High-performance liquid chromatography was performed using Agilent HPLC systems 1200 series (Agilent Technologies, Santa Clara, CA, USA). The analytical column used was a Luna C18 100A (50 × 2.00 mm ID, 5 μm particle, Phenomenex, Torrance, CA, USA). The mobile phase consisted of 10 mM ammonium acetate:100 % acetonitrile acetonitrile (30:50 [vol/vol]) and was run at 0.4 mL/min. Mass spectrometric detection was performed using Applied Biosystems API 3200 mass spectrometry (Applied Biosystems Inc, Foster City, CA, USA). The method was validated for both itraconazole and hydroxy-itraconazole in the linear range 10–1000 ng/mL with an overall precision of >85.3 % and accuracy of 91.0–108.5 %.

2.6 Pharmacokinetic Analysis

Noncompartmental methods were used to calculate steady-state pharmacokinetic parameters of itraconazole and hydroxy-itraconazole from plasma concentration data using WinNonlin®, version 6.0 (Pharsight Corporation, Mountain View, CA, USA). The maximum plasma concentration (C_{max}) and the time to C_{max} (t_{max}) were the observed values. AUC at steady state (AUC_{ss}) was calculated using the log-linear method. Clearance (CL) was calculated by dividing the dose by AUC_{ss}, and volume of distribution at steady state (V_{ss}) was calculated by multiplying the clearance by the mean residence time.

2.7 Definition and Statistical Considerations

Proven, probable, or possible invasive fungal infection and breakthrough fungal infection were defined according to the Mycology Study Group of the European Organization for Research and Treatment of Cancer (EORTC/MSG) criteria (2008) [19]. The characteristics of patients, pharmacokinetic parameters, and safety data of itraconazole were summarized using descriptive statistics. Analyses of the five components of the efficacy criteria were subdivided into each criterion according to the retrospective data of all patients. Differences in response rates between allogeneic and autologous transplantation groups were analyzed using the chi-squared test or Fisher's exact test. SPSS version 19.0 was used for all statistical analyses, and statistical significance was set at $p < 0.05$. Data from patients prospectively enrolled in the pharmacokinetic study were summarized in the pharmacokinetic profiles. All data are presented as mean ± standard deviation unless otherwise stated.

3 Results

3.1 Clinical Characteristics

A total of 143 patients were included in the efficacy evaluation (Table 1). There were 83 males and 60 females, and the median age at the time of transplantation was 7.8 years (range 0.9–23 years). Fifty-seven patients (39.9 %) underwent allogeneic hematopoietic stem cell transplantations, and 86 patients (60.1 %) received autologous transplantation. Among 86 patients who underwent autologous transplantation, 16 received a second transplantation so that a total of 159 transplantations occurred in 143 patients. There was a predominance of brain tumor and acute lymphoblastic leukemia. All patients received concomitant antibacterial agents during itraconazole administration. The median number of doses of oral itraconazole before intravenous administration was 9 (range 4–32), and the median days of intravenous itraconazole treatment was 10 days (range 1–26 days). Median time to absolute neutrophil count over 1000/μL was 11 days (range 7–52 days), and the median duration of fever was 7 days (range 2–32 days).

For the pharmacokinetic study, six patients were enrolled during the study period (Table 2). The median age was 12 years (range 9.4–14.8 years). Mean body weight and body surface area were 29 kg and 1.05 m^2, respectively. All six patients received autologous stem cell transplantations for medulloblastoma or lymphoma. The median number of oral itraconazole doses before empirical intravenous administration was 15 (range 9–23). One of the patients (Patient 4) discontinued the study after four doses of intravenous itraconazole for induction because of improvement in his medical condition. The trough plasma

Table 1 Characteristics of the total patient population evaluated for efficacy ($N = 143$)

Characteristic	Value
Age (years)	7.8 (0.9–23)
Sex, *n* (%)	
Male	83 (58)
Female	60 (42)
Type of transplantation and stem cell source, *n* (%) (total 159 transplantations)	
Allogeneic	57 (35.8)
Peripheral blood stem cell	32 (20)
Cord blood transplantation	20 (12.6)
Bone marrow transplantation	5 (3.2)
Autologous	102 (64.2)
Diagnosis, *n* (%)	
Brain tumor	37 (25.9)
Acute lymphoblastic leukemia	28 (19.6)
Neuroblastoma	23 (16.1)
Acute myeloid leukemia	17 (11.9)
Aplastic anemia	9 (6.3)
Osteosarcoma	7 (4.9)
Lymphoma	6 (4.2)
Acute biphenotypic leukemia	4 (2.8)
Ewing sarcoma	4 (2.8)
Other hematologic diseases[a]	3 (2.1)
Other solid tumors[b]	5 (3.5)
Number of oral itraconazole doses before IV form	9 (4–32)
Days of IV itraconazole	10 (1–26)
Days from d0 to ANC over 1000/μL	11 (7–52)
Duration of fever (days)	7 (2–32)

Values are expressed as median (range) unless specified otherwise

ANC absolute neutrophil count, *IV* intravenous

[a] This category included hemophagocytic lymphohistiocytosis, juvenile myelomonocytic leukemia, and myelodysplastic syndrome

[b] This category included Wilms tumor, rhabdoid tumor, and retinoblastoma

Table 2 Characteristics of six patients enrolled for pharmacokinetic analysis

Patient	Sex	Diagnosis	Age (years)	Weight (kg)	Height (cm)	Body surface area (m^2)	Doses of PO ITZ before IV start	Duration of IV ITZ (days)
Pt 1[a]	M	Medulloblastoma	10.8	28.1	141.1	1.05	15	10
Pt 2	M	Medulloblastoma	11.8	30.4	144.8	1.11	15	7
Pt 3	M	NK-T cell lymphoma	9.5	25	118.2	0.91	23	8
Pt 4[b]	M	Medulloblastoma	14.4	40	151.9	1.30	21	4
Pt 5	F	Medulloblastoma	12.1	27	132.7	1.00	13	10
Pt 6	F	Medulloblastoma	10.2	23.9	135.5	0.95	9	15

ITZ itraconazole, *IV* intravenous, *PO* per oral, *Pt* patient

[a] Trough sample of fourth maintenance dose was not collected

[b] Discontinued after first maintenance dose

concentration after oral prophylaxis and intravenous induction were evaluated including this patient, and steady-state pharmacokinetic analysis was performed using data of the remaining five patients.

3.2 Empirical Antifungal Efficacy of Intravenous Itraconazole

Table 3 reports response rates according to each of the five criteria. There were two and one patients who developed breakthrough fungal infections in the allogeneic and autologous transplantation groups, respectively. One patient with acute lymphoblastic leukemia who underwent umbilical cord transplantation and one patient with acute myeloid leukemia who underwent unrelated bone marrow transplantation developed pulmonary aspergillosis after 7 and 15 days of intravenous itraconazole, respectively. One patient with brain tumor developed systemic invasive aspergillosis after 3 days of intravenous itraconazole in the autologous transplantation group. These patients were treated with amphotericin B liposome complex, caspofungin, and/or voriconazole. The patient with acute myeloid leukemia recovered from pulmonary infection, and others died due to additional lung complications and invasive pulmonary infection, respectively.

All patients survived for 7 days after itraconazole. Fever was resolved before the absolute neutrophil count recovered to at least 1000/μL in 79 transplantations (49.7 %). There was no premature discontinuation due to toxicity or lack of efficacy in 118 patients (74.2 %). Among 41 transplantations in which itraconazole was discontinued prematurely, itraconazole was changed to liposomal amphotericin B or voriconazole due to persistent fever in 38 patients, and was changed to intravenous micafungin in three patients because they could not take oral itraconazole syrup due to nausea or vomiting. Premature discontinuation occurred more frequently in the allogeneic transplantation group, which was mainly due to persistent fever. There was one patient whose serum galactomannan test for aspergillus infection was positive (index: 1.33) at the beginning of the conditioning chemotherapy, but subsequent galactomannan tests were negative at the end of itraconazole treatment. Sixty-seven patients fulfilled all criteria so that the overall success rate was 42.1 %. There was no significant difference in the overall efficacy rate between allogeneic and autologous transplantation groups except for the rates of premature discontinuation.

Table 3 Outcomes of empirical antifungal therapy

Response indicator	No. of HSCTs (%)			
	Total (%) ($n = 159$)	Allo (%) ($n = 57$)	Auto (%) ($n = 102$)	p value
No breakthrough fungal infections within 7 days of end of therapy	156 (98.1)	55 (96.5)	101 (99)	0.34
Survival for 7 days after therapy	159 (100)	57 (100)	102 (100)	1.00
Resolution of neutropenic fever	79 (49.7)	32 (56.1)	47 (46)	0.33
No. of premature discontinuations due to toxicity or lack of efficacy	118 (74.2)	35 (61.4)	83 (81.4)	0.01
Complete or partial response of patients with baseline fungal infections by end of treatment, no./total no. (%)	1/1 (100)	0/0 (100)	1/1 (100)	1.00
Overall response	67 (42.1)	22 (38.6)	45 (44.1)	0.82

No. number, *HSCT* hematopoietic stem cell transplantation, *Allo* allogeneic, *Auto* autologous

3.3 Safety

Itraconazole was generally well tolerated. Three patients developed grade III–IV nausea possibly related to itraconazole. Symptoms were relieved after changing itraconazole to micafungin. All other patients tolerated oral and intravenous itraconazole well so that no apparent toxicity was recorded.

3.4 Pharmacokinetics of Itraconazole and its Metabolite

Figure 1 shows trough concentrations of itraconazole and hydroxy-itraconazole after 2 days of intravenous induction administration and subsequent daily maintenance administration. After oral itraconazole prophylaxis at 2.5 mg/kg twice a day for more than 4 days, mean trough plasma concentrations of itraconazole and hydroxy-itraconazole were 577.2 ± 456.5 and 1387.8 ± 784.4 μg/L, respectively. Upon reaching steady state, the mean trough plasma concentrations of itraconazole and the metabolite were 1659.7 ± 789.4 and 2995.6 ± 883.6 μg/L, respectively. Since one patient discontinued intravenous maintenance, his data could not be included for steady-state pharmacokinetic analysis. Mean trough concentrations of both itraconazole and its metabolite during the maintenance period were retained up to day 7 in five patients.

Figure 2 shows the concentration profiles for plasma itraconazole and hydroxy-itraconazole after the third intravenous maintenance dose. Table 4 reports corresponding pharmacokinetic parameters. The mean area under the curve at steady state ($AUC_{24,ss}$) and the half-life ($t_{½}$) of itraconazole were 42,837 ± 24,746 μg·h/L and 39.5 ± 33.5 h, respectively. The maximum plasma concentration (C_{max}) of hydroxy-itraconazole in plasma was 3778 ± 722 μg/L, and occurred after a median of 4 h post dosing. Mean $AUC_{24,ss}$ was 63,094 ± 19,255 μg·h/L and hydroxy-itraconazole was eliminated from plasma with a mean $t_{½}$ of 51.0 ± 17.9 h.

4 Discussion

The aim of this study was to investigate empirical antifungal efficacy and pharmacokinetics of intravenous itraconazole for evaluating clinical implications of the pharmacokinetics on antifungal efficacy in pediatric patients.

Our empirical antifungal regimen had a sufficient effect to prevent breakthrough fungal infections and resolve baseline fungal infection. The overall response rate was 42.1 %. According to previous randomized trials comparing empirical antifungal efficacy in adult cancer patients with neutropenic fever, voriconazole and liposomal amphotericin B showed overall response rates of 26 and 30.6 %, respectively [17]; caspofungin and liposomal amphotericin B showed response rates of 33.9 and 33.7 %, respectively, in another study [18]. Although our assessment for efficacy was a not prospective study, intravenous itraconazole showed an equivalent efficacy with other antifungal agents.

Cancer patients have lower antifungal steady-state concentrations than do healthy volunteers [16, 20]. Decreased absorption in case of oral administration due to chemotherapy-related gastrointestinal complications and

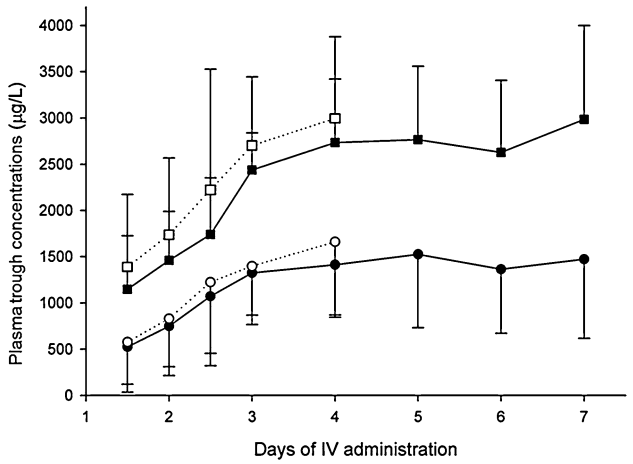

Fig. 1 Trough plasma concentrations of itraconazole and hydroxy-itraconazole. Mean (±SD) plasma trough concentrations of itraconazole (*circles*) and hydroxy-itraconazole (*squares*) as a function of time during induction and maintenance periods. *Closed circles* and *squares* are the means of five patients who completed the study; *open circles* and *squares* are means of the total six patients. *IV* intravenous

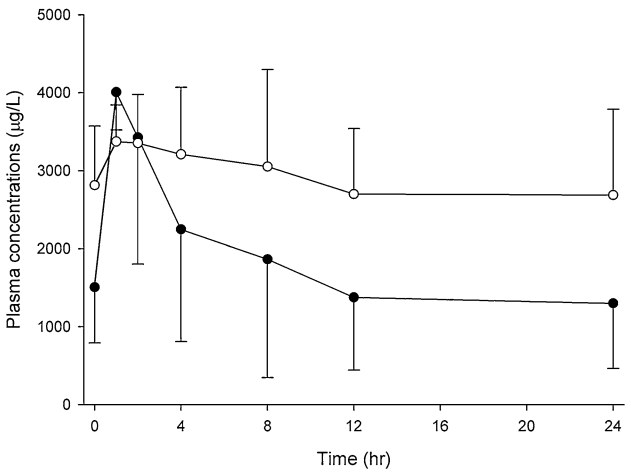

Fig. 2 Pharmacokinetic curve of intravenous itraconazole. Mean (±SD) plasma itraconazole (*closed circles*) and hydroxy-itraconazole (*open circles*) concentrations in five patients after the third intravenous maintenance dose

Table 4 Steady-state pharmacokinetic parameters after intravenous administration of itraconazole

Parameter	Itraconazole	Hydroxy-itraconazole
$AUC_{24,ss}$ (μg·h/L)	42,837 ± 24,746	63,094 ± 19,255
C_{max} (μg/L)	4429 ± 1072	3778 ± 722
CL_{ss} (L/h)	3.807 ± 1.639	2.311 ± 0.772
V_{ss} (L)	201.8 ± 200.0	164.1 ± 67.9
$t_{½}$ (h)	39.5 ± 33.5	51.0 ± 17.9
t_{max}[a] (h)	(Not applicable)	4 (1.0–7.6)
Metabolic ratio	(Not applicable)	1.7 ± 0.4

All values except t_{max} are presented as mean ± standard deviation (SD)

$AUC_{24,ss}$ area under the plasma concentration-time curve at steady state, *C_{max}* maximum plasma concentration, *CL_{ss}* clearance at steady state, *V_{ss}* volume of distribution at steady state, *$t_{½}$* half-life, *t_{max}* time to maximum plasma concentration

[a] t_{max} is presented as median (range)

possible drug interactions are the major causes of lower drug concentrations in cancer patients, especially in transplantation recipients. Thus, special considerations for transplantation recipients are needed to achieve effective pharmacokinetics. Most previous analyses were conducted with adult patients [21, 22]. Hennig et al. [13] reported a population pharmacokinetic study with pediatric bone marrow recipients; however, they used various dosages and two different formulations (capsule or oral) of itraconazole so that variables might not have been controlled completely. The present analysis was conducted in a homogeneous group of patients undergoing hematopoietic stem cell transplantation with an identical dosage, and this antifungal regimen showed generally consistent pharmacokinetics.

The rapid attainment of therapeutic itraconazole concentrations in high-risk patients is a major advantage of intravenous itraconazole [14]. The intravenous formulation achieves effective concentrations much faster with fewer side effects than oral administration [23, 24]. The therapeutic range for itraconazole was suggested from several studies reporting that trough plasma concentrations at a steady state of over 250 μg/L are needed to secure effective antifungal prophylaxis [11, 14, 16]. Some investigators concluded that itraconazole plasma concentrations should exceed 500 μg/L [14, 25]. When itraconazole is administered as loading dose with 200 mg twice daily for 2 days in adults, this therapeutic concentration was achieved in most patients within 48 h [26]. In our study, the plasma concentration of itraconazole already approached 500 μg/L after prophylaxis with oral itraconazole syrup formulation, and plasma itraconazole concentrations rapidly rose during intravenous induction and was maintained above sufficient plasma concentrations for antifungal activity so that there was no vulnerable window of fungal infection due to insufficient antifungal plasma concentrations.

In addition, our regimen was feasible considering patients' clinical course during transplantation. In most studies, intravenous loading to oral maintenance was preferred for full therapeutic concentrations [27]. However, these loading regimens were associated with a high incidence (>35 %) of nausea and diarrhea [28]. Moreover, the use of oral maintenance doses of itraconazole is often not feasible in patients with chemotherapy-induced nausea and vomiting or mucositis. In this study, an oral to intravenous switch strategy was tolerable with regard to patients' clinical course during hematopoietic stem cell transplantation. In the early stage of the conditioning regimen, gastrointestinal complications are not marked so that the administration of an oral formulation is usually possible. However, mucositis, nausea, or vomiting become more severe with continuation of the transplantation regimen, and usually recover along with hematologic recovery. This pre-engraftment period is also highly vulnerable to invasive fungal infection so that an intravenous formulation to maintain effective antifungal plasma concentrations is critical for transplantation recipients.

There is limited data on itraconazole pharmacokinetics among children. Only one pediatric itraconazole intravenous pharmacokinetic study is reported, where pediatric pharmacokinetic characteristics were investigated after a single intravenous administration [29]. However, the steady-state pharmacokinetics could not be simulated from single-administration data due to the complex pharmacokinetic behavior such as the increase in half-life with increasing duration of therapy observed in oral formulation studies.

In our study, the trough concentrations of itraconazole and hydroxy-itraconazole were increased during four doses of intravenous administration. The steady-state plasma concentrations of itraconazole and hydroxy-itraconazole during intravenous dosing were reached after intravenous induction, with the mean steady-state trough concentration of itraconazole being well above the minimum concentration of 500–1000 μg/L known to be associated with positive clinical outcomes [30]. Considering the pediatric $t_{½}$ (39.5 ± 33.5 h) found in this study, it would take more than 5 days to reach steady state with intravenous administration if there was no induction phase. Since the serum concentration of itraconazole is related to both prophylactic efficacy and treatment outcome, our regimen was favorable for the attainment and maintenance of appropriate drug concentrations [30, 31].

AUC_{24}, clearance, and volume of distribution of a single administration of 2.5 mg/kg itraconazole in pediatric patients are reported as 4922 μg·h/L, 702.8 ml/h/kg, and

185 L/kg, respectively [29]. While dose-adjusted plasma itraconazole AUC_{∞} (3291.3 μg·h/L/mg) of a single intravenous administration calculated from previous data showed first-degree elimination, dose-adjusted plasma itraconazole AUC_{24},ss (8567.4 μg·h/L/mg) after multiple intravenous doses of this study showed increased exposure during multiple administrations. The pharmacokinetics of itraconazole in this study were non-linear, and similar non-linear pharmacokinetics of multiple administration of itraconazole were also reported in an adult study; the AUC was four to five times greater and the terminal half-life was slightly longer after 2–3 weeks' treatment in adult patients, suggesting Michaelis–Menten metabolism [16].

Compared with the trough concentration of itraconazole following multiple doses of oral itraconazole (2.5 mg/kg every 12 h) in adults with hematological malignancies (715 ± 380 μg/L), the trough concentration after multiple oral prophylaxis in this study was relatively low [32]. There were similar results in the study of De Repentigny et al. [6], which showed that the exposure of repeated-dose administration of an oral itraconazole solution in children was smaller than that in adults; the authors suggested that a higher dosage was required for equivalent therapeutic effects in children.

To explain this lower trough concentration after oral itraconazole administration in our study, the lower bioavailability in pediatric patient caused by mucositis, vomiting, or administration through a feeding tube could be considered [6, 33]. All patients in the current study had oral mucositis during hospitalization, and one of them vomited irregularly during the first 3 days of oral prophylaxis. However, intravenous administration for empirical treatment produced relatively higher drug concentrations than oral dosing as in previous adult studies [34]. Dose-adjusted AUCs of itraconazole and hydroxy-itraconazole after multiple intravenous doses were about twice that of adults [34]. The differences between pediatric and adult use need to be considered based on data reported here, as pediatric patients showed higher exposure and relatively slower clearance of itraconazole with multiple intravenous administrations compared to adults.

Concomitant use of gastric acid-lowering agents, such as antacids or H_2-antagonists, can reduce drug absorption, and anticonvulsants, including phenobarbital and phenytoin, and the antimycobacterial agents rifampin and isoniazid can decrease plasma concentrations of itraconazole by increasing metabolism [16, 32]. In the current study, five of six participants received an H_2-receptor antagonist such as ranitidine or omeprazole during itraconazole treatment. Although further controlled studies are needed to elucidate the precise pharmacokinetic differences between children and adults, our patients' clinical condition and/or concomitant medication could be the etiology of reduced exposure of oral itraconazole administration compared to adults.

Our study has several limitations in that the number of patients enrolled for a prospective pharmacokinetic study was small, and pharmacokinetic analysis was limited to the pediatric cancer patients, so that these results might not apply to the children without malignancy directly. Also, for the safety evaluation, we might not have obtained thorough data about specific toxicities and grades of those toxicities due to retrospective data collection.

5 Conclusion

This was the first pharmacokinetic study of repeated-dose intravenous itraconazole in pediatrics patients, and there were considerable pharmacokinetic differences between children and adults. With this usage, sufficient trough concentrations were achieved during oral prophylaxis, and concentrations were rising rapidly with successive intravenous inductions, so that this regimen showed satisfactory empirical antifungal efficacy. Although the number of patients enrolled for the pharmacokinetic study was small, this antifungal regimen not only showed generally consistent pharmacokinetics in a homogeneous group of patients, but also showed empirical antifungal efficacy and safety in a large number of patients who were administered the same antifungal regimen.

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Conflicts of interest Hyery Kim, Donghoon Shin, Hyoung Jin Kang, Kyung-Sang Yu, Ji Won Lee, Sung Jin Kim, Min Sun Kim, Eun Sun Song, Mi Kyoung Jang, June Dong Park, In-Jin Jang, Kyung Duk Park, Hee Young Shin, and Hyo Seop Ahn have no potential conflicts of interest.

References

1. Boogaerts M, Winston DJ, Bow EJ, Garber G, Reboli AC, Schwarer AP, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized, controlled trial. Ann Intern Med. 2001;135(6):412–22.
2. Richardson MD, Kokki MH. Diagnosis and prevention of fungal infection in the immunocompromized patient. Blood Rev. 1998;12(4):241–54.
3. Gotzsche PC, Johansen HK. Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in

patients with cancer complicated by neutropenia. BMJ. 1997;314(7089):1238–44.
4. Link H, Bohme A, Cornely OA, Hoffken K, Kellner O, Kern WV, et al. Antimicrobial therapy of unexplained fever in neutropenic patients–guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). Ann Hematol. 2003;82(Suppl 2):S105–17. doi:10.1007/s00277-003-0764-4.
5. Michallet M, Persat F, Kranzhofer N, Levron JC, Prat C, Belhabri A, et al. Pharmacokinetics of itraconazole oral solution in allogeneic bone marrow transplant patients receiving total body irradiation. Bone Marrow Transplant. 1998;21(12):1239–43. doi:10.1038/sj.bmt.1701270.
6. de Repentigny L, Ratelle J, Leclerc JM, Cornu G, Sokal EM, Jacqmin P, et al. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. Antimicrob Agents Chemother. 1998;42(2):404–8.
7. Groll AH, Wood L, Roden M, Mickiene D, Chiou CC, Townley E, et al. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. Antimicrob Agents Chemother. 2002;46(8):2554–63.
8. Mendes AV, Sapolnik R, Mendonca N. New guidelines for the clinical management of febrile neutropenia and sepsis in pediatric oncology patients. J Pediatr (Rio J). 2007;83(2 Suppl):S54–63. doi:10.2223/JPED.1624.
9. Martino R, Viscoli C. Empirical antifungal therapy in patients with neutropenia and persistent or recurrent fever of unknown origin. Br J Haematol. 2006;132(2):138–54. doi:10.1111/j.1365-2141.2005.05838.x.
10. Schmitt C, Perel Y, Harousseau JL, Lemerle S, Chwetzoff E, le Moing JP, et al. Pharmacokinetics of itraconazole oral solution in neutropenic children during long-term prophylaxis. Antimicrob Agents Chemother. 2001;45(5):1561–4. doi:10.1128/AAC.45.5.1561-1564.2001.
11. Kanbayashi Y, Nomura K, Fujimoto Y, Shimura K, Shimizu D, Okamoto K, et al. Population pharmacokinetics of itraconazole solution used as prophylaxis for febrile neutropenia. Int J Antimicrob Agents. 2008;31(5):452–7. doi:10.1016/j.ijantimicag.2007.12.017.
12. Caillot D. Intravenous itraconazole followed by oral itraconazole for the treatment of amphotericin-B-refractory invasive pulmonary aspergillosis. Acta Haematol. 2003;109(3):111–8 **69281**.
13. Hennig S, Wainwright CE, Bell SC, Miller H, Friberg LE, Charles BG. Population pharmacokinetics of itraconazole and its active metabolite hydroxy-itraconazole in paediatric cystic fibrosis and bone marrow transplant patients. Clin Pharmacokinet. 2006;45(11):1099–114.
14. Buchkowsky SS, Partovi N, Ensom MH. Clinical pharmacokinetic monitoring of itraconazole is warranted in only a subset of patients. Ther Drug Monit. 2005;27(3):322–33. doi:10.1097/01.ftd.0000150135.22645.ea.
15. Willems L, van der Geest R, de Beule K. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. J Clin Pharm Ther. 2001;26(3):159–69.
16. Poirier JM, Cheymol G. Optimisation of itraconazole therapy using target drug concentrations. Clin Pharmacokinet. 1998;35(6):461–73.
17. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med. 2002;346(4):225–34. doi:10.1056/NEJM200201243460403.
18. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med. 2004;351(14):1391–402. doi:10.1056/NEJMoa040446.
19. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813–21. doi:10.1086/588660.
20. Persat F, Marzullo C, Guyotat D, Rochet MJ, Piens MA. Plasma itraconazole concentrations in neutropenic patients after repeated high-dose treatment. Eur J Cancer. 1992;28A(4–5):838–41.
21. Prentice AG, Warnock DW, Johnson SA, Phillips MJ, Oliver DA. Multiple dose pharmacokinetics of an oral solution of itraconazole in autologous bone marrow transplant recipients. J Antimicrob Chemother. 1994;34(2):247–52.
22. Prentice AG, Warnock DW, Johnson SA, Taylor PC, Oliver DA. Multiple dose pharmacokinetics of an oral solution of itraconazole in patients receiving chemotherapy for acute myeloid leukaemia. J Antimicrob Chemother. 1995;36(4):657–63.
23. De Beule K, Van Gestel J. Pharmacology of itraconazole. Drugs. 2001;61(Suppl 1):27–37.
24. Boogaerts MA, Maertens J, Van Der Geest R, Bosly A, Michaux JM, Van Hoof A, et al. Pharmacokinetics and safety of a 7-day administration of intravenous itraconazole followed by a 14-day administration of itraconazole oral solution in patients with hematologic malignancy. Antimicrob Agents Chemother. 2001;45(3):981–5. doi:10.1128/AAC.45.3.981-985.2001.
25. Glasmacher A, Hahn C, Leutner C, Molitor E, Wardelmann E, Losem C, et al. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. Mycoses. 1999;42(7–8):443–51.
26. Caillot D, Bassaris H, McGeer A, Arthur C, Prentice HG, Seifert W, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. Clin Infect Dis. 2001;33(8):e83–90. doi:10.1086/323020.
27. Grigull L, Kuehlke O, Beilken A, Sander A, Linderkamp C, Schmid H, et al. Intravenous and oral sequential itraconazole antifungal prophylaxis in paediatric stem cell transplantation recipients: a pilot study for evaluation of safety and efficacy. Pediatr Transplant. 2007;11(3):261–6. doi:10.1111/j.1399-3046.2006.00643.x.
28. Glasmacher A, Hahn C, Molitor E, Marklein G, Sauerbruch T, Schmidt-Wolf IG. Itraconazole trough concentrations in antifungal prophylaxis with six different dosing regimens using hydroxypropyl-beta-cyclodextrin oral solution or coated-pellet capsules. Mycoses. 1999;42(11–12):591–600.
29. Abdel-Rahman SM, Jacobs RF, Massarella J, Kauffman RE, Bradley JS, Kimko HC, et al. Single-dose pharmacokinetics of intravenous itraconazole and hydroxypropyl-beta-cyclodextrin in infants, children, and adolescents. Antimicrob Agents Chemother. 2007;51(8):2668–73. doi:10.1128/AAC.00297-07.
30. Goodwin ML, Drew RH. Antifungal serum concentration monitoring: an update. J Antimicrob Chemother. 2008;61(1):17–25. doi:10.1093/jac/dkm389.
31. Smith J, Andes D. Therapeutic drug monitoring of antifungals: pharmacokinetic and pharmacodynamic considerations. Ther Drug Monit. 2008;30(2):167–72. doi:10.1097/FTD.0b013e318167d0e0.
32. Groll AH. Itraconazole–perspectives for the management of invasive aspergillosis. Mycoses. 2002;45(Suppl 3):48–55.

33. Simon A, Besuden M, Vezmar S, Hasan C, Lampe D, Kreutzberg S, et al. Itraconazole prophylaxis in pediatric cancer patients receiving conventional chemotherapy or autologous stem cell transplants. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2007;15(2):213–20. doi:10.1007/s00520-006-0125-7.

34. Heykants J, Van Peer A, Van de Velde V, Van Rooy P, Meuldermans W, Lavrijsen K, et al. The clinical pharmacokinetics of itraconazole: an overview. Mycoses. 1989;32(Suppl 1):67–87.