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Pharmacokinetics and Safety of Intravenous Voriconazole in Children after Single- or Multiple-Dose Administration

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We conducted a multicenter study of the safety, tolerability, and plasma pharmacokinetics of the parenteral formulation of voriconazole in immunocompromised pediatric patients (2 to 11 years old). Single doses of 3 or 4 mg/kg of body weight were administered to six and five children, respectively. In the multiple-dose study, 28 patients received loading doses of 6 mg/kg every 12 h on day 1, followed by 3 mg/kg every 12 h on day 2 to day 4 and 4 mg/kg every 12 h on day 4 to day 8. Standard population pharmacokinetic approaches and generalized additive modeling were used to construct the structural pharmacokinetic and covariate models used in this analysis. In contrast to that in adult healthy volunteers, elimination of voriconazole was linear in children following doses of 3 and 4 mg/kg every 12 h. Body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics. Elimination capacity correlated with the CYP2C19 genotype. Exposures were similar at 4 mg/kg every 12 h in children (median area under the concentration-time curve (AUC), 14,227 ng · h/ml) and 3 mg/kg in adults (median AUC, 13,855 ng · h/ml). Visual disturbances occurred in 5 (12.8%) of the 39 patients and were the only drug-related adverse events that occurred more than once. No withdrawals from the study were related to voriconazole. We conclude that pediatric patients have a higher capacity for elimination of voriconazole per kilogram of body weight than do adult healthy volunteers and that dosages of 4 mg/kg may be required in children to achieve exposures consistent with those in adults following dosages of 3 mg/kg.

Developed as intravenous and oral formulations, voriconazole is a novel antifungal triazole with potent in vitro and in vivo activity against a broad spectrum of medically important pathogens, including *Aspergillus*, *Cryptococcus*, and *Candida* species (4, 6, 12). Recent studies have characterized the in vivo pharmacokinetics and pharmacodynamics of voriconazole in a murine model of disseminated candidiasis (1).

The pharmacokinetics of voriconazole have been investigated following single and multiple doses (over a period ranging from 10 to 30 days) in healthy adult volunteers, as well as adult patients. These studies have shown that voriconazole exhibits nonlinear pharmacokinetics in adults (11). This nonlinearity may be due to saturable systemic clearance (CL). Dose-dependent accumulation (up to eightfold) and decreased systemic CL are observed following the administration of multiple doses of voriconazole to adults. At steady state, following multiple oral doses of 200 mg every 12 h, the mean elimination half-life of voriconazole is ~6 to 9 h in adults (11).

Children with cancer who sustain prolonged periods of myelosuppression due to cytotoxic chemotherapy or hematopoietic stem cell transplantation or who have inherited immunodeficiencies are highly susceptible to invasive fungal infections (8, 13, 17, 20). The use of indwelling vascular catheters and broad-spectrum antibiotics further increases the risk in immunocompromised children of development of invasive fungal infections. The broad-spectrum antifungal activity of voriconazole may provide an important therapeutic advance in the treatment and prevention of invasive fungal infections in pediatric oncology patients. However, little is known about the plasma pharmacokinetics and safety of this compound in children. We therefore conducted a multicenter study of the plasma pharmacokinetics and safety of voriconazole in immunocompromised children (age, 2 to 11 years) at risk for invasive fungal infections.

MATERIALS AND METHODS

Objective. The objective of this study was to determine the safety, tolerability, and plasma pharmacokinetics of the parenteral formulation of voriconazole in immunocompromised children (age, 2 to 11 years).

Study design. (i) Single-dose study. The single-dose study was an open, two-center study of immunocompromised children (age, 2 to 11 years) conducted in the United Kingdom.

(ii) Multiple-dose study. The multiple-dose study was an open, multicenter, two-cohort study with each cohort comprising equal numbers of subjects, aged 2 to <6 and 6 to 11 years, requiring treatment for the prevention of invasive fungal

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infections. The multidose study was conducted in the United States, Costa Rica, Panama, and the United Kingdom.

Inclusion and exclusion criteria. Institutional review board approval was required in each participating center. All patients enrolled were required to be aged 2 to 11 years and were expected to develop neutropenia lasting for >10 days following chemotherapy for leukemia, lymphoma, or aplastic anemia or as the preparative regimen for bone marrow transplantation. Children with culture- or biopsy-proven mucosal or deeply invasive fungal infections also were eligible. Informed consent of the parent or legally authorized representative was obtained before enrollment in the study. Informed consent was obtained from patients capable of understanding the study.

Patients were excluded if the serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level was >5 times the upper limit of normal (ULN), if there was a history of hypersensitivity or severe intolerance to azole antifungal agents, if they required treatment with other systemic antifungal agents while receiving voriconazole, or if they had received one or more of the following drugs within 14 days prior to randomization: rifampin, carbamazepine, and barbiturates (potent inducers of hepatic microsomal enzymes).

Study drug administration. Voriconazole was infused intravenously (i.v.) at a constant rate of 3 mg/kg of body weight/h in all patients. Patients enrolled in the single-dose study received 3 or 4 mg/kg i.v. As the plasma pharmacokinetics of voriconazole are known to have marked interpatient variation and minimal intrapatient variation, dose escalation was conducted within each individual patient in the multiple-dose study. All patients enrolled in the multiple-dose study received two loading doses of 6 mg/kg every 12 h i.v., followed by a maintenance dose of 3 mg/kg every 12 h i.v. for five doses. If the 3-mg/kg dosage was well tolerated, the dosage was increased in that patient to 4 mg/kg every 12 h i.v. thereafter until the morning of day 8. The patients were permitted to continue in the study until day 21 if clinically indicated.

Plasma pharmacokinetic sampling. Four plasma samples drawn at interval windows of 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdose were used in the single-dose study. For patients enrolled in the multiple-dose study, samples were drawn on days 1, 2, 4, and 8 at interval windows of 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdose on each day designated for sample collection. Postinfusion blood samples were collected via peripheral lines, and all other blood samples were collected via double-lumen venous catheter. All samples were separated by a time interval of >1 h.

Safety assessments and criteria. Physical examinations and routine clinical laboratory tests were conducted at baseline and twice weekly, including the last day of administration of the study drug. As voriconazole is known to be associated with transient visual changes, the patients were assessed for visual symptoms and signs at baseline and during therapy. If the subjects were able and willing to cooperate, the following tests were performed by an ophthalmologist. (i) For all children who were old enough, near visual acuity in each eye was obtained using Snellen letters. This testing was performed at a distance of 14 in (with glasses, if they had them) with adequate illumination, which was kept consistent throughout the study. For children who were too young to perform the tests, fixation was assessed as to whether it was central, steady, and maintained in each eye. (ii) Dilated fundoscopic examination with indirect ophthalmoscopy was performed, paying particular attention to the optic nerves, retinal vessels, macula, retina, and choroid vessels.

Ophthalmological examinations were performed at screening, after the morning dose on the last day of dosing, and at follow-up (if voriconazole dosing had stopped prior to the end of day 21).

An adverse event (AE) was defined as any event that was not present at the onset of use of voriconazole but which developed during its use. An attributable AE was any event which, in the opinion of the investigator, was possibly or probably related to voriconazole. A serious AE was defined as one which resulted in death, was life threatening, required (or prolonged) hospitalization, caused persistent or significant disability or incapacity, resulted in congenital anomalies or birth defects, or as other conditions which, in the judgment of the investigators, represented a significant hazard. Follow-up for serious AEs was conducted for 30 days after discontinuation of the study drug.

Analytical assay. Voriconazole and its major metabolite, voriconazole *N*-oxide (UK-121,265), were quantified in plasma samples using a previously validated liquid chromatography-tandem mass spectrometry assay (15). The lower limits of quantification for voriconazole and UK-121,265 were 10 and 20 ng/ml, respectively.

Quality control samples were included with all analytical runs. The quality control samples at each of three different concentrations of voriconazole and the metabolite UK-121,265 were run in duplicate and interspersed throughout each batch. In addition, calibration standards were prepared fresh for each analytical batch. For voriconazole, the calibration standards 10, 50, 100, 500, 1,000, 2,000, and 3,000 ng/ml were prepared, and for the metabolite UK-121,265, the standards were 20, 50, 100, 500, 1,000, 3,000, and 5,000 ng/ml, i.e., a total of seven calibration standards per analytical run for each of the analytes.

The previously validated analytical procedure for the analysis of voriconazole and UK-121,265 utilized automated solid-phase extraction, with liquid chromatography for separation of the analytes prior to tandem mass spectrometric detection. The overall imprecisions for voriconazole were 4.5, 9.5, and 7.1% at voriconazole concentrations of 25, 400, and 2,500 ng/ml, respectively. The inaccuracy (bias) of the assay at all concentrations ranged from 5.2 to 3.0%. The overall imprecisions for UK-121,265 were 9.0, 6.1, and 6.6% at UK-121,265 concentrations of 50, 400, and 4,000 ng/ml, respectively. The inaccuracy (bias) of the assay at all concentrations ranged from 9.2 to 2.6%.

Pharmacokinetic analysis and modeling. Formal population pharmacokinetic analysis of plasma concentration data was performed using the nonlinear mixed-effects modeling approach. All patients from both the single- and multiple-dose studies were included in the population pharmacokinetic analysis if one or more levels were available and if CYP2C19 information (see Discussion) was available for that individual. The software package NONMEM, version V, level 1.0 or 1.1 (University of California—San Francisco), was used to derive the population means (and variances) for specific pharmacokinetic parameters (3). Appropriate structural pharmacokinetic models were fitted to concentration-versus-time data using standard population pharmacokinetic methodology. The majority of the analysis was carried out using the first-order conditional estimation method with the interaction option.

Generalized additive models (GAM) and tree models were used to aid covariate selection. Each GAM was derived using an automated stepwise addition-deletion method. To protect against data overfitting, a pruning procedure based on cross-validation was performed (16). The GAM and tree models used in this analysis were implemented in the software Xpose version 3.0 (10) developed to be run in an S-Plus environment (version 2000 for Windows; Insightful, Oxford, United Kingdom).

Molecular genotyping. Allelic polymorphisms of CYP2C19 were determined in all subjects at baseline upon enrollment in the study. Molecular genotyping was performed by multiplex fluorescent minisequencing as previously described (14).

RESULTS

Study populations. Eleven patients were enrolled in the single-dose study (Table 1). Six were allocated to receive voriconazole (3 mg/kg i.v.), and five were allocated to receive 4 mg/kg i.v. Due to errors in dosing calculations, two patients in the 3-mg/kg group and one in the 4-mg/kg group received more than their intended doses (16.3, 13.4, and 14.5 mg/kg, respectively). The three patients who received the higher than intended single doses were included in the pharmacokinetic analysis. The addition of data from these three patients did not affect the linearity of the pharmacokinetic model. No AEs were associated with these higher dosages. Twenty-eight patients from eight centers were enrolled in the multiple-dose study (Table 1). Data from a total of 35 patients (aged 2 to 11 years) were incorporated into the combined data set of the population pharmacokinetic model. A total of 355 plasma voriconazole concentration samples (average, 10.1 per individual) and a range of both single and multiple i.v. dosage regimens were examined.

Pharmacokinetics. (i) Mean concentrations in plasma. The geometric mean concentrations in plasma (C_{mean}) at the end of the voriconazole infusion in the single-dose study were 2,201 (range, 1,771 to 2,488) and 2,523 (range, 1,651 to 3,565) ng/ml for 3- and 4-mg/kg i.v. doses, respectively. The geometric mean maximum and minimum concentrations of voriconazole in plasma (C_{max} and C_{min}) in the multiple-dose study pre- and postdose (3 and 4 mg/kg) are summarized in Table 2.

Figure 1 illustrates the observed mean concentration-time curves of voriconazole after multiple-dose administration in

TABLE 1. Demographic characteristics of patients enrolled in study

Parameter	Value		
	Single-dose study (n = 11)	Multiple-dose study (n = 24)[a]	Total (n = 35)
Mean age (yr)	5.9	6.4	6.2
Age distribution (yr)	2–<6 6–<12	2–<6 6–<12	
Mean wt (kg) (range)	21.5 (15–36)	24.3 (12–54)	23.4 (12–54)
No. of patients with CYP2C19 genotype			
EM	4	18	22
PM	2	0	2
HEM	5	6	11
No. of patients with ethnic origin			
Caucasian	10	16	26
Black	1	0	1
Asian	0	1	1
Other	0	7	7
No. of patients with underlying condition			
Leukemia	5	11	16
Bone marrow transplant	0	8	8
Lymphoma	1	1	2
Other	5	4	9

[a] Twenty-eight subjects entered the study; four were not included in the population pharmakokinetic modeling, as their CYP genotypes were not determined.

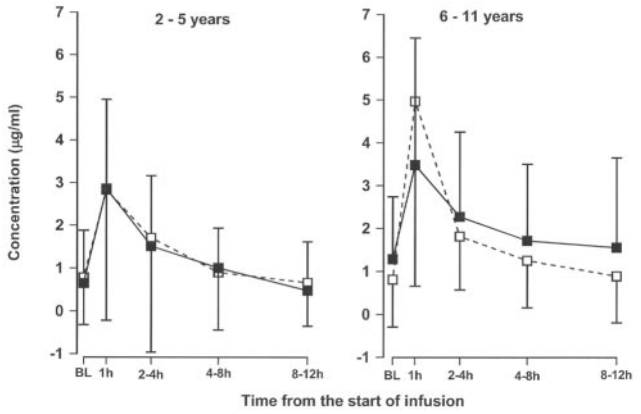

FIG. 1. Concentration-time curve of voriconazole after multiple-dose administration in subjects aged from 2 to 5 years and from 6 to 11 years. Voriconazole was given i.v. in doses of 3 (solid lines) and 4 (dashed lines) mg/kg every 12 h. The samples were collected on day 4 of each dosing regimen. The points represent means, and the error bars represent standard deviations. BL, baseline.

subjects aged from 2 to 5 and from 6 to 11 years. Voriconazole was given i.v. in doses of 3 and 4 mg/kg every 12 h. There was no significant difference in mean C_{max} or area under the concentration-time curve (AUC) between the two age groups at either dosage.

Figure 2 illustrates individual concentration-time curves around the geometric mean concentrations of voriconazole in immunocompromised children aged from 2 to 5 years (A and B) and from 6 to 11 years (C and D). The data illustrate substantial interindividual variation of concentration-time curves of voriconazole across both dosage groups and age cohorts.

(ii) Population pharmacokinetic modeling. Initially, the (nonlinear) pharmacokinetic model developed in 236 healthy adult volunteers was used to describe the pediatric data. However, the model proved to be unsatisfactory. Additional modeling confirmed that a linear structural pharmacokinetic model could appropriately describe the pediatric data. The basic model consisted of a two-compartment disposition model (with pharmacokinetic parameters expressed per kilogram of body weight) with CL dependent on the individuals' CYP2C19 genotype statuses. Further exploration of additional covariate relationships indicated that increased levels of ALT and alkaline phosphatase (ALKP) were associated with lower voriconazole CL. As these covariates, at initiation of therapy, were not predictive of voriconazole CL, initiating dosing based on these covariates would not be supported by the present analysis. Age did not significantly influence voriconazole pharmacokinetics in this group of patients following the introduction of body weight into the model.

For a typical model patient, CL was 0.40 (relative standard error [RSE], 14%) liter/h/kg. ALT and ALKP were both log-linearly related to CL. The 5th and 95th percentiles of the ALT distribution (corresponding to 7 and 114 IU/liter) illustrate the influence of ALT on CL. In comparison to individuals with ALT concentrations of 25 IU/liter (the median), these ALT values would be associated with a 35% increase and a 42% decrease in predicted CL, respectively. For ALKP, the 5th and 95th percentile values (corresponding to 70 and 308 IU/liter) would be associated with a 23% increase and a 29% decrease in predicted CL, respectively (median ALKP, 136 IU/liter). CL was 46% (RSE, 32%) lower in heterozygous extensive metabolizers (HEMs)-poor metabolizers (PMs) than in extensive metabolizers (EMs) (see Discussion). The unexplained between-subject variability in CL after incorporation of these covariates

TABLE 2. Maximum and minimum observed plasma voriconazole concentrations after multiple dosing

Day (dose [mg/kg])	Parameter	Value[a]		
		age group (yr)		All subjects
		2–<6	6–<12	
4 (3)	C_{min}	166.9 (58.6, 475.5) (n = 12)	507.4 (251.6, 1,023) (n = 14)	303.7 (165.0, 559.1) (n = 26)
	C_{max}	1,642 (610.3, 4,415) (n = 10)	3,843 (2,438, 6,059) (n = 12)	2,611 (1,582, 4,309) (n = 22)
8 (4)	C_{min}	263.3 (94.0, 737.7) (n = 11)	696.7 (303.7, 1,598) (n = 12)	437.5 (231.4, 827.1) (n = 23)
	C_{max}	2,192 (1,257, 3,821) (n = 10)	2,560 (1,381, 4,746) (n = 10)	2,369 (1,626, 3,450) (n = 20)

[a] Values are geometric means (nanograms per milliliter) with 95% confidence intervals (CI) in parentheses.

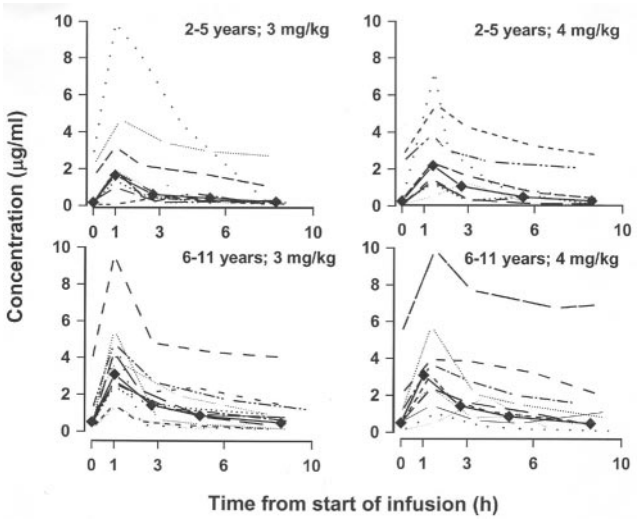

FIG. 2. Individual concentration-time curves of voriconazole in immunocompromised children aged from 2 to 5 and from 6 to 11 years. Each line represents an individual subject. The solid lines with diamonds demonstrate geometric mean concentrations.

was 66.5% (RSE, 10%). Given the degree of interindividual variability within the 3- and 4-mg/kg dosage range, dosage adjustment based upon the model's parameters is not feasible between individual patients. However, intraindividual variability is minimal. These findings suggest that for the general pediatric population, a dosage of 4 mg/kg would be preferable to 3 mg/kg in order to optimize drug exposure toward that of an adult. These findings have prompted the initiation of a second study of voriconazole plasma pharmacokinetics in pediatric patients receiving higher dosages. This study is ongoing.

The disposition parameter estimates were as follows: for volume of distribution of the central compartment, 0.80 (RSE, 20%) liter/kg; for volume of distribution of the peripheral compartment, 1.7 (RSE, 7.5%) liters/kg; and for intercompartmental-CL rate, 0.64 (RSE, 15%) liter/h/kg. After the introduction of body weight, the level of interindividual variability remaining for each of these parameters was not significant; therefore, no further covariate relationships were investigated. Based on the individual patient parameter estimates, the median (5th and 95th percentiles) terminal half-life values were 7.5 (3.5 and 21.4) h.

Using the linear population pharmacokinetic model, a series of simulations (model interpolations) was performed. The AUC measured over the dosing interval (AUC$_\tau$) and C_{mean} in children receiving 4 mg of voriconazole/kg i.v. were similar to values obtained in adults receiving 3 mg/kg i.v. (Table 3). Further simulations (model extrapolations) revealed that in order for children to achieve concentrations in blood equivalent to those following 4-mg/kg doses in adults, dosages on the order of 10 to 11 mg/kg (Table 4) might be required. This statement should be treated with caution, as it will be valid only if the linear pharmacokinetic characteristics of voriconazole are maintained throughout this full dosage range, which is as yet unstudied. In order to make more conclusive statements about pediatric dosages equivalent to 4 mg/kg in adults, we conclude that further clinical and pharmacokinetic data are required.

TABLE 3. Simulated pharmacokinetic data for pediatric and adult populations

Parameter	Value[a]			
	Pediatric		Adult	
	3[b]	4	3	4
AUC$_\tau$ (ng · h/ml)	10,670	14,227	13,855	38,605
C_{mean} (ng/ml)	889	1,186	1,155	3,217

[a] Data are reported as medians following 6 mg/kg 12 every h on day 1 and maintenance dose 3. The values are derived from population pharmacokinetic analyses of 236 healthy volunteers.
[b] Dosage (milligrams per kilogram).

Safety. Five patients discontinued voriconazole or had dosage reductions during the study. All of these events were caused by either underlying disease or concomitant illness or were due to reactions to other treatment interventions (Table 5).

Few patients had clinically significant elevations in serum bilirubin, hepatic transaminases, ALKP, and serum creatinine (Table 6). Dosage reduction or discontinuation of voriconazole was required in three cases but was not attributable to the study drug.

AEs are classified here as visual and nonvisual. Half of all visual AEs were considered by the investigators to be possibly or probably treatment related (Table 7). The visual AEs consisted of blurred vision, itchy eyes, eye pain, photophobia, and strabismus. All of these visual AEs were mild or moderate in nature and resolved without intervention while the patients were still receiving voriconazole. Nonvisual AEs possibly or probably attributed to voriconazole by an investigator consisted of one case each of abdominal pain, hypertension, phlebitis, facial flushing, diarrhea, gingival hyperplasia, arthralgia, dry cough, and pruritus. These AEs were self-limiting.

Visual AEs due to all causalities were reported by two subjects during treatment among subjects receiving the single 6-mg/kg or multiple 3-mg/kg doses and six subjects during treatment with 4 mg of voriconazole/kg. Treatment-related visual AEs possibly or probably related to voriconazole were reported by one subject (itchy eyes) in the 3-mg/kg group and three subjects (eye pain, itchy eyes, photophobia, blurred vi-

TABLE 4. Extrapolated plasma pharmacokinetic parameters for pediatric population

Dosage (mg/kg)	AUC (ng · h/ml)	C_{mean}
Pediatrics		
5	17,783	1,482
6	21,340	1,778
7	24,897	2,075
8	28,453	2,371
9	32,010	2,668
10	35,567	2,964
11	39,123	3,260
12	42,680	3,557
Adult		
4	38,605	3,217

TABLE 5. Patients with voriconazole dose reduced or discontinued due to AE or laboratory abnormalities

Change in voriconazole	Underlying disease[a]	Day of dose reduction or discontinuation	Reason	Outcome
Discontinued	AML	13	Subdural hematoma	Died 4 days later
Discontinued	ALL	6	Fever and viral enteritis	Resolved in 3 days
Discontinued	ALL	3	Fever	Resolved in 33 days
Dose reduced then discontinued	Relapsed ALL BMT	Dose reduced on day 8, discontinued on day 11	Elevated serum creatinine (1.2 × ULN)	Died 6 days later due to bacterial sepsis and meningitis[b]
Discontinued	Fanconi's anemia; autoimmune hepatitis	7	Elevated AST and ALT (10 × ULN)	AST and ALT normalized in 34 days
Dose reduced	ALL; BMT	14	Abnormal renal function and elevated serum creatinine	Resolved in 27 days

[a] ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BMT, blood and marrow transplantation.
[b] *Stomatococcus mucilaginosus*.

sion, and strabismus) during multidose treatment with 4 mg of voriconazole/kg (Table 7).

These visual AEs will be discussed in greater detail below. One 7-year-old patient experienced mild conjunctivitis (indicated by the investigator as eye itching) on day 1 during the 6- plus 3-mg/kg period; this event resolved on day 3. Three patients experienced five treatment-related visual AEs during the 4-mg/kg treatment period: one 4-year-old patient had mild strabismus (investigator entry, "squinting of eyes") 10 min after dosing on day 4, which lasted for 1 h 50 min; a 3-year-old child experienced moderate photophobia, conjunctivitis (investigator entry, "eye itching"), and eye pain 1 h 45 min postdosing) on day 7, and all three events lasted for 2 min each; and a 7-year-old patient experienced mild blurred vision starting 2 h 30 min after dosing and lasting 22 h 15 min.

Sixteen patients had visual-acuity examinations at baseline and/or at the end of therapy and/or at the 1-month follow-up visit. Visual acuity did not change in any of these patients. Dilated fundoscopy was performed for 23 patients at baseline and/or at the end of therapy and/or at the follow-up visit. With the exception of one patient, no fundoscopic changes were seen. This patient, who was noted to have normal findings at baseline on day 1, had macular and retinal hemorrhages on day 8. The child was receiving chemotherapy for acute lymphoblastic leukemia and at the time of the visual examinations was thrombocytopenic (70,000/μl) and neutropenic. These changes are considered compatible with acute lymphoblastic leukemia and thrombocytopenia but not with voriconazole.

TABLE 6. Clinically significant elevations in serum bilirubin, hepatic transaminases, ALKP, and serum creatinine

Biochemical parameter	Criterion for elevation (ULN)	No. of patients receiving loading dose followed by 3 mg/kg (*n*/*N*)[a]	No. of patients receiving 4 mg/kg (*n*/*N*)
Bilirubin	>1.5	1/27	5/27
ALT	>3	2/27	3/27
AST	>3	1/27	1/27
ALKP	>3	0/25	0/26
Creatinine	>1.3	0/26	0/27

[a] *n*, number of patients with abnormal values; *N*, number of patients studied and for whom serial laboratory values were recorded.

DISCUSSION

This multicenter study is to our knowledge the first systematic investigation of the safety, tolerability, and plasma pharmacokinetics of the parenteral formulation of voriconazole following multiple dosing in immunocompromised pediatric patients. The elimination of voriconazole in children was linear over the dosage range of 3 and 4 mg/kg every 12 h. These findings contrast with those of adults, where the elimination of voriconazole follows Michaelis-Menten-type plasma pharmacokinetics over the approved dosage range of 3 and 4 mg/kg. Voriconazole was well tolerated but was associated with transient visual disturbances in several patients.

The pediatric patients enrolled in this study were immunocompromised children who were at risk for development of invasive fungal infections. The dosages administered in this trial were those that have been found to be effective in clinical trials in adults. This trial was designed to investigate the difference in plasma pharmacokinetics between dosages of 3 and 4 mg/kg every 12 h within each patient. This dosage range was selected to explore the same dosage that is used in adults. Safety was an overarching concern in designing this pediatric

TABLE 7. Visual AEs in pediatric patients receiving voriconazole

Dosage	AE	Total no. of events	No. of events attributed to voriconazole
6 mg/kg loading dose + 3 mg/kg every 12 h	Eye pain	1	0
	Itchy eyes	1	1
	Total no. of patients with visual AEs	2	1
4 mg/kg every 12 h	Retinal hemorrhage	2	0
	Eye pain	2	1
	Itchy eyes[a]	2	1
	Photophobia	1	1
	Blurred vision	1	1
	Strabismus	1	1
	Total no. of patients with visual AEs	6	3
7 days postvoriconazole treatment	Eye hemorrhage	2	0

[a] Described in one case as conjunctivitis.

study, particularly given previous data in adults demonstrating nonlinear kinetics and potentially marked increases in plasma drug concentrations between the dosages of 3 and 4 mg/kg.

As previous studies in adults demonstrated marked interindividual variation in plasma pharmacokinetic parameters but only minimal intraindividual variation, dosage escalation was conducted within patients in this study. Intrapatient dosage escalation also allowed the patients to serve as their own controls for variables such as CYP2C19 genotype and body weight, thus permitting a more reliable analysis in differences of plasma pharmacokinetics between the dosages of 3 and 4 mg/kg every 12 h.

Voriconazole is cleared principally by metabolism through three key hepatic microsomal enzymes, CYP2C19, CYP2C9, and CYP3A4. Most voriconazole metabolism is mediated through CYP2C19. Allelic polymorphisms of CYP2C19 are important determinants of the CL of voriconazole. Critical single-nucleotide polymorphisms in the gene encoding the protein CYP2C19 result in two phenotypes: PMs and EMs (7). EMs may be further classified into homozygous (EM) and HEM populations. Approximately 3 to 5% of the Caucasian and African human populations consists of PMs. By comparison, 15 to 20% of the Asian population is comprised of PMs. Although the CYP2C19 genotype was the most important determinant of voriconazole CL in this pediatric pharmacokinetic study, genotypic classification did not account for the differences in drug exposure observed between children and adults.

As shown in Table 3, dosages of voriconazole (3 and 4 mg/kg every 12 h) in adults demonstrate nonlinear saturation plasma pharmacokinetics, resulting in an ~3-fold increase in AUCτ following a 33% increase in dosage. By comparison, children receiving the same dosages of voriconazole (3 and 4 mg/kg every 12 h) demonstrated linear plasma pharmacokinetics. As children have a higher elimination capacity than adults on a body weight basis, differences in body weight between pediatric and adult patients was the most important factor accounting for this difference in CL of voriconazole.

The most common AEs ascribed to voriconazole were transient visual disturbances. Several studies of voriconazole found that the most distinctive visual reaction to the drug is an altered or enhanced perception of light (2, 5, 9, 18, 19). Other effects are reported as blurred vision, color vision change, and photophobia. Occurring most frequently at the time of first infusion, this visual effect disappeared in subsequent infusions. Recognizing the importance of documenting the safety profile of voriconazole in pediatric patients, we undertook an intensive effort in this study to characterize its visual effects. The visual reactions observed in this study were similar to those previously reported and had no structural or functional sequelae.

No patient had the study drug discontinued due to an AE attributable to the study drug. Although hepatotoxicity is a known class-related adverse reaction to antifungal triazoles, the frequency of hepatotoxicity possibly or probably attributable to voriconazole was relatively small. This is consistent with the observation that in three large randomized trials of voriconazole therapy there was no increase in the frequency of elevation of serum hepatic transaminases, bilirubin, or ALKP (1, 9, 19).

Based upon the plasma pharmacokinetic findings of this study, we would recommend that children receiving a maintenance dose of voriconazole do so at a dosage of 4 mg/kg every 12 h in order to approximate the adult maintenance dose of 3 mg/kg every 12 h. Invasive fungal infections in pediatric patients have been successfully treated with this maintenance dose. Nonetheless, the pediatric dosage that is equivalent in drug exposure to the adult dosage of 4 mg/kg every 12 h remains to be determined. If one assumes linearity over the possible dosage range, then a dosage of 11 mg/kg would be required. However, the exact dosage at which voriconazole saturation of the hepatic microsomal enzymes occurs is not known and may be substantially less than 11 mg/kg. Thus, further studies of the safety and plasma pharmacokinetics in pediatric patients at dosages of >4 mg/kg are warranted before a formal dosage above this level can be recommended. Whether these higher dosages will safely result in improved therapeutic response remains to be determined through carefully monitored clinical trials.

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REFERENCES

1. **Ally, R., D. Schurmann, W. Kreisel, G. Carosi, K. Aguirrebengoa, B. Dupont, M. Hodges, P. Troke, A. J. Romero, and the Esophageal Candidiasis Study Group.** 2001. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin. Infect. Dis. **33:**1447–1454.
2. **Andes, D., K. Marchillo, T. Stamstad, and R. Conklin.** 2003. In vivo pharmacokinetics and pharmacodynamics of a new triazole, voriconazole, in a murine candidiasis model. Antimicrob. Agents Chemother. **47:**3165–3169.
3. **Beal, S. L., L. B. Sheiner, et al. (ed.).** 1992. NONMEM users guides. University of California at San Francisco, San Francisco, Calif.
4. **Chiou, C. C., A. H. Groll, and T. J. Walsh.** 2000. New drugs and novel targets for treatment of invasive fungal infections in patients with cancer. Oncologist **5:**120–135.
5. **Denning, D. W., P. Ribaud, N. Milpied, D. Caillot, R. Herbrecht, E. Thiel, A. Haas, M. Ruhnke, and H. Lode.** 2002. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin. Infect. Dis. **34:**563–571.
6. **Ghannoum, M. A., and M. A. Hossain.** 2000. New investigational antifungal agents for treating invasive fungal infections. Expert Opin. Investig. Drugs **9:**1797–1813.
7. **Goldstein, J. A., and S. M. F. de Morais.** 1994. Biochemistry and molecular biology of the human CYP2C subfamily. Pharmacogenetics **4:**285–299.
8. **Groll, A. H., M. Kurz, W. Schneider, V. Witt, H. Schmidt, M. Schneider, and D. Schwabe.** 1999. Five-year survey of invasive aspergillosis in a pediatric cancer centre. Epidemiology, management and long-term survival. Mycoses **42:**431–442.
9. **Herbrecht, R., D. W. Denning, T. F. Patterson, J. E. Bennett, R. E. Greene, J. W. Oestmann, W. V. Kern, K. A. Marr, P. Ribaud, O. Lortholary, R. Sylvester, R. H. Rubin, J. R. Wingard, P. Stark, C. Durand, D. Caillot, E. Thiel, P. H. Chandrasekar, M. R. Hodges, H. T. Schlamm, P. F. Troke, B. de Pauw, et al.** 2002. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N. Engl. J. Med. **347:**408–415.
10. **Jonsson, E. N., and M. O. Karlsson.** 1999. Xpose—an SPLUS based population pharmacokinetic-pharmacodynamic model building aid for NONMEM. Comput. Methods Programs Biomed. **58:**51–64.
11. **Lazarus, H. M., J. L. Blumer, S. Yanovich, H. Schlamm, and A. Romero.** 2002. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. J. Clin. Pharmacol. **42:**395–402.
12. **Sheehan, D. J., C. A. Hitchcock, and C. M. Sibley.** 1999. Current and emerging azole antifungal agents. Clin. Microbiol. Rev. **12:**40–79.
13. **Shetty, D., N. Giri, C. E. Gonzalez, P. A. Pizzo, and T. J. Walsh.** 1997. Invasive aspergillosis in human immunodeficiency virus-infected children. Pediatr. Infect. Dis. J. **16:**216–221.
14. **Sitbon, G. and A.-C. Syvänen.** 2001. Multiplex fluorescent minisequencing

applied to the typing of genes encoding drug-metabolizing enzymes, p. 191–200. *In* W. Kalow, U. A. Meyer, and R. F. Tyndale (ed.), Pharmacogenomics. Drugs and the pharmaceutical sciences. Marcel Dekker, New York, N.Y.

15. **Stopher, D. A., and R. Gage.** 1997. Determination of a new antifungal agent, voriconazole, by multidimensional high-performance liquid chromatography with direct plasma injection onto a size-exclusion column. J. Chromatogr. **691:**441–448.
16. **Venables, W. N., and B. D. Ripley.** 1999. Modern applied statistics with S-PLUS, 3rd ed. Springer Verlag, New York, N.Y.
17. **Walsh, T. J., C. Gonzalez, C. A. Lyman, S. Chanock, and P. A. Pizzo.** 1995. Invasive fungal infections in children: recent advances in diagnosis and treatment. Adv. Pediatr. Infect. Dis. **11:**187–290.
18. **Walsh, T. J., I. Lutsar, T. Driscoll, B. DuPont, M. Roden, P. Gharamani, M. Hodges, A. H. Groll, and J. R. Perfect.** 2002. Voriconazole in the treatment of aspergillosis, scedosporiosis, and other invasive fungal infections in children. Pediatr. Infect. Dis. J. **21:**240–248.
19. **Walsh, T. J., P. Pappas, D. J. Winston, H. M. Lazarus, F. Petersen, J. Raffalli, S. Yanovich, P. Stiff, R. Greenberg, G. Donowitz, J. Lee, M. Schuster, A. Reboli, J. Wingard, C. Arndt, J. Reinhardt, S. Hadley, R. Finberg, M. Laverdiere, J. Perfect, G. Garber, G. Fioritoni, and E. Anaissie.** 2002. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy in persistently febrile neutropenic patients: a prospective, randomized, multicenter, international trial. N. Engl. J. Med. **346:**225–234.
20. **Winkelstein, J. A., M. C. Marino, R. B. Johnston, Jr., J. Boyle, J. Curnutte, J. I. Gallin, H. L. Malech, S. M. Holland, H. Ochs, P. Quie, R. H. Buckley, C. B. Foster, S. J. Chanock, and H. Dickler.** 2000. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) **79:**155–169.