Pharmacokinetic and Tolerability Assessment of a Pediatric Oral Formulation of Pentoxifylline in Kawasaki Disease

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ABSTRACT

Background: In infants and children, treatment of Kawasaki disease (KD) with high-dose intravenous immunoglobulin (IVIG) and acetylsalicylic acid ([ASA] aspirin) diminishes inflammatory response and reduces the risk for coronary artery abnormalities. However, patients with high serum concentrations of tumor necrosis factor (TNF)-alpha, which is associated with vascular damage, may develop coronary artery lesions even with treatment. The hemorheologic agent pentoxifylline blocks the production of TNF-alpha and may be an appropriate adjunctive therapy to IVIG and ASA.

Objective: The objective of this study was to assess the pharmacokinetic characteristics and tolerability of a new oral syrup formulation of pentoxifylline as an adjunct to IVIG and ASA in the treatment of KD in children.

Methods: Hospitalized boys and girls aged 6 months to 5 years and who were diagnosed with KD within the first 10 days of illness were eligible. Patients were assigned to 1 of 4 pentoxifylline treatment groups, by dose level (dose levels 1, 2, 3, and 4: 10, 15, 20, and 25 mg/kg daily, respectively, divided into 3 doses). Six plasma samples collected at the time the first dose was administered, and 4 samples collected after administration of the last dose on study day 6, were

A preliminary analysis of the first 2 dose levels was presented at the American College of Clinical Pharmacy Spring Research Forum in Salt Lake City, Utah, April 22–25, 2001. The preliminary results from all dose levels were presented at the 7th International Kawasaki Disease Symposium, Hakone, Japan, December 4–7, 2001.

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assessed by high-performance liquid chromatography using noncompartmental and 1-compartment pharmacokinetic analyses for pentoxifylline and its active metabolite (M-1). TNF-alpha levels on days 1 and 6 were assessed using electro-immunoassay.

Results: Fourteen boys and 10 girls were enrolled. The mean age, body weight, and illness day at study entry were 34.5 months, 13.8 kg, and 6, respectively. Pentoxifylline exhibited nonlinear kinetic characteristics, with median area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$) values of 622, 3428, 8416, and 10,347 ng/mL · h for dose levels 1 to 4, respectively, on study day 1. Pentoxifylline noncompartmental oral clearance and volume of distribution were significantly lower, and dose-normalized $AUC_{0-\infty}$ was significantly higher, for dose level 3 than dose level 1. M-1 parameters were not significantly different between dose levels. No accumulation of pentoxifylline or M-1 was noted. Fifteen of 24 patients (63%) reported mild to moderate adverse events that may or may not have been treatment related. Frequency and severity did not differ significantly between dose levels.

Conclusions: In the children in this study, pentoxifylline was well tolerated at the doses studied. No notable differences in clinical outcomes were observed between dose levels, and dose levels 3 and 4 (20 and 25 mg/kg daily, respectively) resulted in similar exposure to both pentoxifylline and M-1. Future efficacy and tolerability studies should use a daily dose of 20 mg/kg of pentoxifylline in acute KD. (*Curr Ther Res Clin Exp.* 2003;64:96–115) Copyright © 2003 Excerpta Medica, Inc.

Key words: pentoxifylline, pharmacokinetics, pediatrics, Kawasaki disease, TNF-alpha.

INTRODUCTION

Kawasaki disease (KD) is an acute, multisystem vasculitis of unknown cause that mainly affects infants and young children. It has replaced acute rheumatic fever as the most common cause of acquired heart disease in childhood in the United States.¹ Clinical symptoms of KD include fever, rash, mucosal inflammation, lymphadenopathy, and extremity changes, including erythema, swelling, and desquamation. If untreated, the vasculitis causes damage to coronary arteries in 20% to 25% of patients, which can lead to coronary artery aneurysm, myocardial infarction, coronary artery stenosis and obstruction, valvular disease, and sudden death.² Treatment with high-dose intravenous immunoglobulin (IVIG) and acetylsalicylic acid ([ASA] aspirin) diminishes the inflammatory response and reduces the prevalence of coronary artery abnormalities.^{3–5} Approximately 15% of patients do not respond to the first dose of IVIG and require additional therapy. A subset of these patients (10%) develop coronary artery lesions.⁶ Overall, 2% to 6% of patients who receive appropriate treatment still develop coronary artery abnormalities.⁷

Tumor necrosis factor (TNF)-alpha is an inducible cytokine that is markedly elevated during the acute phase of KD and may be involved in the pathogenesis of vascular damage.⁸⁻¹⁰ Patients with higher concentrations of TNF-alpha are more likely to develop coronary artery lesions, even when treated with IVIG. Therefore, modulation of TNF-alpha and its effects may benefit patients with acute KD.^{9,10} The hemorheologic agent pentoxifylline blocks the production of TNF-alpha in monocytes and macrophages, thereby lowering serum TNF-alpha concentrations.¹¹

Pentoxifylline is a synthetic dimethylxanthine derivative prescribed for complications of peripheral vascular diseases. The pharmacokinetic characteristics of pentoxifylline in adults have been well characterized.¹²⁻¹⁴ Although pentoxifylline is almost completely absorbed, it undergoes significant first-pass metabolism resulting in a bioavailability of 20% to 33%. Pentoxifylline is extensively metabolized and forms an active 1-(5'-hydroxyhexyl)-3,7-dimethylxanthine metabolite (M-1) through aldo-keto-reductase. Pentoxifylline and M-1 have similar potency, have short half-lives of 0.4 to 2.0 hours, and exhibit nonlinearity with respect to serum area under the plasma concentration-time curve (AUC) and half-life. Currently, no evidence suggests significant protein binding of pentoxifylline or M-1. Pentoxifylline is not known to induce its own metabolism after multiple oral doses of the drug. Other recognized metabolites have lower plasma concentrations and less or no activity.

Pentoxifylline, given as the crushed adult tablet, has been assessed as adjunctive therapy to IVIG and ASA in Japanese children with acute KD. In 1 study,¹⁵ assessment of patients treated with adjunct pentoxifylline therapy showed a trend toward fewer coronary artery lesions, but no information on pharmacokinetic characteristics was reported.

The potential for altered pharmacokinetic characteristics in patients with KD complicates the choice of an appropriate pentoxifylline dose. Both altered protein binding and decreased bioavailability have been associated with the low ASA levels documented in patients during the acute phase of KD.^{16,17} In addition, preliminary studies¹⁵ of pentoxifylline in KD suggested a dose-related effect on the prevention of coronary artery abnormalities. To make a rational dose selection when assessing the potential benefits of pentoxifylline, an accurate description of pentoxifylline pharmacokinetics in KD is needed.

The objective of this study was to assess the pharmacokinetic characteristics and tolerability of a new oral syrup formulation of pentoxifylline as adjunct therapy to IVIG and ASA in the treatment of KD in children.

PATIENTS AND METHODS

Study Design

This was a prospective, unblinded, multicenter, Phase I to II, dose-escalating study. Participants were enrolled from January 1998 to July 2001 at 5 pediatric pharmacology research unit (PPRU) study sites, as follows: University of Califor-

nia at San Diego/Children's Hospital and Health Center ([UCSD/CHHC] San Diego, California), University of Tennessee Health Sciences Center ([UTHSC] Memphis, Tennessee), Rainbow Babies and Children's Hospital ([RBCH] Cleveland, Ohio), Children's Hospital Research Foundation of Columbus ([CHRFC] Columbus, Ohio), and Children's Hospital of Michigan–Wayne State University ([CHM-WSU] Detroit, Michigan). The institutional review boards at each of the study sites approved the protocol, and written informed consent was obtained from the parent(s), or legal guardians as appropriate, for every participant before study enrollment.

Participants were enrolled consecutively, 6 patients per dose level (levels 1, 2, 3, and 4: 10, 15, 20, and 25 mg/kg daily, respectively, divided into 3 doses). All participants received a single dose of IVIG (2 g/kg) and daily doses of ASA (80 to 100 mg/kg), per the current standard of care in the United States.¹⁸ Participants also received pentoxifylline oral solution 3 times daily with meals or feedings (infants) for 6 ± 2 days. The first dose of pentoxifylline was administered by study personnel 6 to 24 hours after the start of the IVIG infusion. Clinical data collected included demographic data (age, sex, ethnicity, body weight), vital signs (measured daily until discharge), and laboratory tests performed before IVIG administration (complete blood cell count with differential, platelet count, erythrocyte sedimentation rate, chemistry panel including gamma-glutamyltransferase [GGT] and alanine aminotransferase [ALT], quantitative C-reactive protein, albumin, TNF-alpha, and urinalysis). Echocardiography was performed before IVIG administration and again at study day 6 ± 2 (hereafter referred to as *study day 6*) or according to the standard of care at each study site. *Coronary artery dilatation* was defined as a Z score of >2 according to the criteria of de Zorzi et al.¹⁹

The pentoxifylline solution contained 20 mg/mL of pentoxifylline in alcohol-free syrup.

Patient Population

Hospitalized boys and girls aged 6 months to 5 years and who were diagnosed with KD within the first 10 days of illness were eligible. Patients were required to have fever plus 4 of the 5 standard diagnostic criteria¹⁸ and to have IV access for obtaining blood samples for the pharmacokinetic studies. Patients were excluded if they had a known allergy or hypersensitivity to methylxanthines.

Tolerability Assessment

As each dose level was completed, participants were assessed for significant dose-limiting toxicity before proceeding to the next-higher dose level. Study nurses collected data on adverse events (AEs) at least once daily during hospitalization using a standardized collection form. Parents were given a digital thermometer for measuring axillary temperature and instructed on its use before their child's discharge from the hospital. Study personnel contacted parents daily until the first follow-up visit at study day 6 and asked them to record

on their home logs fever, nausea, vomiting, abdominal complaints, and any other AEs.

Sample Collection

Plasma samples of 1.5 mL were collected before dosing and at 0.25, 0.5, 1, 2, 3, and 5 hours after the first dose of pentoxifylline on study day 1. On study day 6, additional samples were collected at 0.5, 1, 2, and 3 hours after dosing. TNF-alpha levels were measured before pentoxifylline administration on study days 1 and 6. Patients who did not complete the pharmacokinetic assessment on study day 1 due to problems with IV access were replaced.

Analytical Procedures

Pentoxifylline and M-1 were measured in the Louisiana State University Medical Center's PPRU laboratory (Shreveport, Louisiana). Plasma samples containing pentoxifylline and M-1 were prepared for analysis by adding an acetonitrile-containing internal standard (phenacetin). Samples were mixed to precipitate proteins, centrifuged at 1200 rcf for 10 minutes, and the supernatant was dried under nitrogen. After reconstitution with mobile phase, a 20 μ L aliquot was injected onto the high-performance liquid chromatography system for analysis. Separation was achieved using a 100- and 200-mm eta-octadecylsilane column in tandem and a mobile phase consisting of 24% acetonitrile in 1% acetic acid and 0.3% triethylamine. The detection wavelength was 272 nm using a diode array detector. Calibration curves using peak area ratios of drug to internal standard for pentoxifylline and M-1 were linear from 63 to 6000 ng/mL, with a correlation of 0.997 for pentoxifylline and 0.997 for M-1. The lower limit of quantization was 63 ng/mL, with mean back-calculated values for M-1 and pentoxifylline of 68.7 (2.8) ng/mL and 70.0 (3.9) ng/mL, respectively; with biases of -9.1% and -11.2%, respectively; and coefficient of variations (CV%)s of 4.1 and 5.5, respectively. The high point on the standard curve was 6000 ng/mL for M-1 and pentoxifylline, with a mean back-calculated value of 6015.4 (162.4) ng/mL and 5961.8 (208.7) ng/mL, respectively; with biases of -0.26% and 0.64%, respectively; and CV% of 2.7 and 3.5, respectively.

TNF-alpha samples were frozen at -70°C, batched, and assessed using a commercially available enzyme-linked immunosorbent assay kit (Quantikine® HS TNF-alpha Immunoassay, R&D Systems, Inc., Minneapolis, Minnesota). The lower and upper limits of quantization were 0.5 and 32.0 pg/mL, respectively.

Pharmacokinetic and Pharmacodynamic Analyses

The maximum plasma concentration ($C_{\max}$) and the corresponding time ($T_{\max}$) were determined using observation of the plasma concentration-time profile for each patient. The $AUC_{0-\text{last}}$ for pentoxifylline and M-1 were estimated using the trapezoidal rule up to the last measurable concentration. The extrapolated area after the last concentration was estimated as $C_{\text{last}}/\lambda_z$, where C_{last} was the last measurable concentration and λ_z was the terminal slope of the curve.

AUC from time 0 to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-last} + C_{last}/\lambda_z$. Non-compartmental oral clearance rate (Cl/F_{NC}) was calculated as the ratio of dose to $AUC_{0-\infty}$. Apparent volume of distribution (Vd_{NC}/F) was calculated as Cl/F_{NC} over λ_z . Half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Plasma pentoxifylline concentrations collected in the subacute phase (study day 6) were compared with those collected during the acute phase (study day 1). $AUC_{0-\infty}$, Cl/F_{1-C} (oral clearance from 1-compartment model), and Vd_{1-C}/F (volume of distribution from 1-compartment model) also were determined using a 1-compartment model with first-order absorption. This second modeling approach was used because the data were sparse, limiting our ability to estimate parameters for some patients. Obtaining similar parameters with each approach indicates that the limitations of each methodology did not affect the results. WinNonlin, version 2.0 (Pharsight, Mountain View, California) was used for the pharmacokinetic analyses.

Statistical Analysis

Dose proportionality of pentoxifylline and M-1 noncompartmental pharmacokinetic parameters was assessed by testing Vd_{NC}/F , Cl/F_{NC} , T_{max} , $t_{1/2}$, and dose-normalized C_{max} and $AUC_{0-\infty}$ using the Kruskal-Wallis 1-way analysis of variance on ranks. $AUC_{0-\infty}$ and C_{max} were normalized to the daily dose level of 10 mg/kg by dividing the values in dose levels 2, 3, and 4 by 1.5, 2.0, and 2.5, respectively. When a statistically significant difference was detected, the Kruskal-Wallis multiple-comparison Z-value test with Bonferroni criteria was used for pairwise comparisons of medians. The differences in concentrations of pentoxifylline, M-1, and TNF-alpha between study day 1 and study day 6 were assessed with the Wilcoxon signed rank test for paired data. The Spearman rank correlation coefficient was used to examine the relationships between (1) age and oral clearance and (2) active drug exposure and percentage change in TNF-alpha from study days 1 to 6. The statistical tests were performed using the Number Cruncher Statistical System (NCSS) 2001/PASS 2000 software (NCSS Statistical Software, Kaysville, Utah). Statistical significance was set at $P < 0.05$.

RESULTS

Patients' Demographic Characteristics

Twenty-four children were enrolled at 5 PPRU study sites, as follows: UCSD/CHHC, $n = 12$; UTHSC, $n = 5$; RBCH, $n = 5$; CHRFC, $n = 1$; and CHM-WSU, $n = 1$.

The participants in each dose-level group ($n = 6$ patients per group) had similar demographic characteristics. The mean (SD) age, body weight, and illness day at study entry were 34.5 (18.2) months, 13.8 (3.7) kg, and 6 (1), respectively. Fourteen of 24 patients were boys. Eight of the patients (33%) were white, 7 (29%) were black, 3 (13%) were Hispanic, 1 (4%) was Asian, and 5 (21%) were >1 race.

Pharmacokinetic Characteristics

All 24 patients (100%) completed the pharmacokinetic assessment on study day 1, and 10 participants (42%) underwent the additional pharmacokinetic assessment on study day 6. Of the 14 participants who did not complete the sampling on study day 6, 2 (14%) were lost to follow-up, and 12 (86%) either had no IV access or their parents declined the second assessment. One participant in the group receiving 15 mg/kg inadvertently was given 15 mg/kg per dose rather than 15 mg/kg per day, for a total dose of 45 mg/kg daily, and was excluded from the pharmacokinetic analyses.

Single-dose noncompartmentalized and 1-compartment pharmacokinetic parameters for pentoxifylline and M-1 from study day 1 are listed in Table I. For the pentoxifylline 1-compartment model, the terminal slope of the concentration–time curve could not be determined due to an insufficient number of measurable concentrations in 2 patients and the flatness of the curve in 2 additional patients. For M-1, the terminal slope could not be determined due to the flatness of the curve in 2 patients for the 1-compartment analysis and an insufficient number of measurable concentrations in 1 patient for both the noncompartmental and 1-compartment analyses. The median $AUC_{0-\infty}$ values were 622, 3428, 8416, and 10,347 ng/mL · h for dose levels 1 to 4, respectively, on study day 1. The median pentoxifylline and M-1 plasma concentration–time profiles are shown in Figure 1. The pentoxifylline exposure for dose levels 3 and 4 was greater than for dose levels 1 and 2, and the M-1 exposure was greatest for dose level 3.

For pentoxifylline, T_{max} and $t_{1/2}$ were similar across dose levels. The dose-normalized pentoxifylline C_{max} showed a numerically higher-than-proportional C_{max} in the higher dose levels, but these differences did not reach statistical significance. Significant differences were observed between dose levels for Cl/F_{NC} , Vd_{NC}/F , and dose-normalized pentoxifylline $AUC_{0-\infty}$ ($P = 0.03$, 0.02 , and 0.03 , respectively). Dose level 3 had significantly higher median $AUC_{0-\infty}$ values and significantly lower Cl/F_{NC} and Vd_{NC}/F values than dose level 1 (Figures 2 to 4). In Figure 3, the 1 patient in dose level 2 with a high oral clearance rate of 23.5 L/h had 5 of 7 samples drawn on study day 1, with only the 0.5- and 1.0-hour postdose samples containing measurable pentoxifylline. Consequently, the estimated $AUC_{0-\infty}$ was 16-fold less than the median AUC for that dose level. For M-1, none of the parameters tested were different between groups. Age was explored as a possible determinant of oral clearance rate for pentoxifylline and M-1, with little or no relationship found.

In the assessment of accumulation with multiple doses, the average ratios of pentoxifylline and M-1 concentrations on study day 6 to study day 1 were 1.18 (95% CI, 0.59–1.77) and 1.06 (95% CI, 0.57–1.55), respectively.

Tolerability Assessment

All patients were included in the tolerability analysis. Parents or legal guardians of 15 of 24 patients (63%) reported mild to moderate AEs that may or may not have been related to the study medication. None of the AEs required discontinuation from the study. No dose-limiting, unusual, or idiosyncratic reactions to pentoxifylline were observed, and the frequency and severity of AEs did not

Table 1. Single-dose noncompartmentalized and 1-compartment pharmacokinetic parameters for pentoxifylline (PTX) and 1-(5'-hydroxyhexyl)-3,7-dimethylxanthine (M-1) from study day 1.

Noncompartmental Analysis									
	Dose Level	C _{max} ng/mL	T _{max} h	Cl/F _{NC} L/kg · h	Vd _{NC} /F L/kg	t _{1/2} h	AUC _{0-∞} ng/mL · h	PTX + M-1 AUC, μM × h	M-1/PTX AUC Ratio
1	PTX (n = 6)								
	Median	315	0.4	6.1	6.2	0.7	622	6.4	1.7
	Range	83–2582	0.3–2.0	1.8–13.6	1.5–16.9	0.5–1.2	252–1819	1.9–10.5	0.6–2.1
	M-1 (n = 6)								
2	Median	632	0.3	–	–	0.8	914	–	–
	Range	192–1190	0.3–0.5	–	–	0.6–1.4	279–1629	–	–
	PTX (n = 5)								
	Median	797	0.5	1.5	4.9	1.0	3428	21.2	1.7
3	Range	342–2924	0.3–0.5	0.9–23.5	1.5–7.3	0.2–2.3	213–5426	4.3–62.6	0.7–4.6
	M-1 (n = 5)								
	Median	833	1.0	–	–	1.3	2477	–	–
	Range	435–2715	0.5–3.0	–	–	0.4–2.6	785–12,055	–	–
4	PTX (n = 6)								
	Median	3016	0.8	0.9	1.0	0.9	8416	58.8	1.0
	Range	1025–5230	0.3–1.0	0.5–3.8	0.6–3.4	0.2–2.3	1771–13,653	20.0–96.4	0.4–2.2
	M-1 (n = 6)								
5	Median	2607	1.0	–	–	1.3	8000	–	–
	Range	803–3391	0.5–2.0	–	–	0.5–3.1	1696–13,235	–	–
	PTX (n = 6)								
	Median	3235	0.5	0.9	2.3	1.3	10,347	49.4	0.4
6	Range	2007–8270	0.3–1.0	0.5–4.0	1.0–6.7	0.6–3.5	2080–15,922	10.1–83.5	0.04–0.8
	M-1 (n = 5)								
	Median	1424	1.0	–	–	1.3	6037	–	–
	Range	341–2169	0.5–2.0	–	–	0.7–3.4	727–8193	–	–

(continued)

Table I. (Continued)

1-Compartment Model Analysis			
	Cl/F _{1-C} , L/kg · h	Vd _{1-C} /F, L/kg	AUC _{0-∞} , ng/mL · h
1	PTX (n = 5)		
	Median	4.3	749
	Range	4.0–14.2	241–839
	M-1 (n = 6)		
	Median	–	701
	Range	–	209–1637
2	PTX (n = 4)		
	Median	1.4	3701
	Range	1.0–5.6	893–5268
	M-1 (n = 4)		
	Median	–	4684
	Range	–	1258–10,969
3	PTX (n = 6)		
	Median	0.9	7721
	Range	0.5–5.0	1333–13,623
	M-1 (n = 6)		
	Median	–	5488
	Range	–	976–14,238
4	PTX (n = 4)		
	Median	1.8	5263
	Range	0.6–5.5	1510–13,836
	M-1 (n = 4)		
	Median	–	2879
	Range	–	372–8488

C_{max} = maximum plasma concentration; T_{max} = time to C_{max}; Cl/F_{NC} = noncompartmental oral clearance; Vd_{NC}/F = volume of distribution based on terminal slope (λ_z); t_{1/2} = half-life; AUC_{0-∞} = area under the plasma concentration-time curve from time 0 to infinity; Cl/F_{1-C} = oral clearance from 1-compartment model; Vd_{1-C}/F = volume of distribution from 1-compartment model.

Figure 1. Values are medians with interquartile ranges. (A) Pentoxifylline plasma concentration versus time profiles, and (B) pentoxifylline active metabolite (M-1) plasma concentration versus time profiles.

Figure 2. Dose-normalized pentoxifylline area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$) grouped by dose level. * $P < 0.05$ versus 10 mg/kg daily.

increase with increasing exposure. The most common AEs reported were gastrointestinal (28 episodes in 11 patients), whereas 14 nongastrointestinal events were reported in 8 patients. These AEs included mild cough, inability to walk without help, I/VI systolic flow murmur, anemia, clear rhinorrhea, diaper rash, irritability, and temporary hearing loss. Vomiting was the most common AE (11 episodes in 7 patients), followed by abdominal pain (6 episodes in 3 patients). The reported episodes of vomiting were in part due to patients' spitting out the medication immediately after dosing. The patient who received a total dose of 45 mg/kg daily reported the following AEs: persistent fever (102.3°F) at 48 hours after IVIG administration, mild cough, and occasional vomiting after pentoxifylline administration. A maximum tolerated dose was not identified in this study.

Dose-Response Relationships

For 19 patients (79%) (6, 5, 5, and 3 patients in dose levels 1 to 4, respectively), the findings on echocardiography remained unchanged over the course of the study. Pretreatment and posttreatment echocardiograms were normal for 18 of the study patients (75%) (6, 5, 5, and 2 in dose levels 1 to 4, respectively), and 1 patient (4%) in the dose level 4 group had coronary artery dilatation before and after treatment that resolved 1 month after the end of the study. Four patients (17%) exhibited improvement in their coronary arteries during the study. One patient (4%) in the dose level 3 group and 3 patients (13%) in the

Figure 3. Pentoxifylline noncompartmental oral clearance rate by dose level. * $P < 0.05$ versus 10 mg/kg daily.

dose level 4 group had coronary artery dilatation on admission that normalized over the course of the study. No patients had coronary artery measurements that worsened over the course of the study. Finally, 1 patient (4%) in the dose level 2 group had coronary artery dilatation on the initial echocardiogram, but no follow-up echocardiogram was available.

Body temperatures following pentoxifylline administration were highly variable. Five of 24 patients (21%) received an additional dose(s) of IVIG due to persistent or recrudescent fever at 48 hours after the end of IVIG infusion (1, 3, and 1 patient(s) from dose levels 1, 2, and 3, respectively). The patient in dose level 2 who received 45 mg/kg daily of pentoxifylline was one of the patients requiring additional IVIG. This patient was also the only Asian patient in this study. No patient in the group receiving the highest dose of pentoxifylline required a second IVIG dose.

TNF- α levels were assessable in 22 of 24 patients before pentoxifylline administration on study day 1. Follow-up levels were obtained in 12 of 24 patients on study day 6. The TNF- α levels did not differ in the 12 paired sera from study days 1 to 6. For the 12 patients with TNF- α levels measured on study day 6, the relationship between percentage change in TNF- α from study days 1 to 6 and the amount of active drug (pentoxifylline + M-1 $AUC_{0-\infty}$) was examined. An association was observed between active drug exposure and percentage decreases in TNF- α ($r = -0.53$; Figure 5).

DISCUSSION

The current standard treatment for acute KD in the United States, high-dose IVIG plus high-dose ASA, reduces cardiac sequelae, but 2% to 6% of patients still

Figure 4. Volume of distribution ($V_{d_{NC}}/F$) by dose level. * $P < 0.05$ versus 10 mg/kg daily.

develop coronary artery abnormalities. Moreover, children without coronary artery abnormalities during the acute phase of KD still may have abnormal test results for ventricular contractility and endothelial cell reactivity decades after the acute illness.^{20–22} The contribution of KD to cardiovascular disease in adults remains unclear. Additional therapies may be desirable to further reduce the elevated inflammatory cytokines that appear to mediate vascular damage in KD. As a TNF- α inhibitor, pentoxifylline is a logical candidate for treatment of this disease.

This study described the pharmacokinetic characteristics of pentoxifylline with escalating doses in children with acute KD. The doses selected for this trial were based on the normal dose of pentoxifylline in adults, 400 mg 3 times daily, or ~17 mg/kg daily for a 70-kg adult. It is difficult to compare adult and pediatric pentoxifylline pharmacokinetic parameters because the pharmacokinetic characteristics may be dose dependent. Nonetheless, the values observed for the pentoxifylline pharmacokinetic parameters in the children in this study were similar to reported values in adults for the standard 400-mg dose.^{12–14} Likewise, the range of several M-1 pharmacokinetic-parameter values in this study approximated the reported values in adults (Table II).

In addition to the similar pharmacokinetic-parameter estimates between children and adults, the participants in this study demonstrated nonlinear kinetic characteristics of pentoxifylline, which have been described in the adult population over an oral dosing range of ~4 to 17 mg/kg daily.¹² Our patients with KD exhibited higher-than-proportional increases in $AUC_{0-\infty}$ and decreases in Cl/F_{NC} and $V_{d_{NC}}/F$ between the 10 and 20 mg/kg daily dose levels, whereas $t_{1/2}$ did not

Table II. Pharmacokinetic parameters for pentoxifylline (PTX) and 1-(5'-hydroxyhexyl)-3,7-dimethylxanthine (M-1) in pediatric patients (current study) compared with adults.¹²⁻¹⁴

Study	Dose	T _{max} , h	C _{max} , ng/mL	t _{1/2} , h	AUC _{0-∞} , ng/mL · h	Clearance, L/kg · h	Volume, L/kg
PTX							
Smith et al, ¹² mean	400 mg PO	0.29	1607	0.84	1229	–	–
Rames et al, ¹³ mean	100 mg IV	–	–	0.83	–	3.62	4.15
Current study, range	10–25 mg/kg PO daily	0.3–2.0	83–8270	0.2–3.5	213–15,922	0.5–23.5	0.6–16.9
M-1							
Smith et al, ¹² mean	400 mg PO	0.83	2000	0.96	5101	–	–
Beermann et al, ¹⁴ mean	400 mg PO	1.80	1937	0.90	5031	–	–
Current study, range	10–25 mg/kg PO daily	0.3–3.0	192–3391	0.4–3.4	279–13,235	–	–

T_{max} = time to C_{max}; C_{max} = maximum plasma concentration; t_{1/2} = half-life; AUC_{0-∞} = area under the plasma concentration–time curve from time 0 to infinity.

Figure 5. The percentage of change in tumor necrosis factor (TNF)-alpha levels from study days 1 to 6 versus active medication (pentoxifylline [PTX] + its active metabolite [M-1]) area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$). A correlation was found ($r = -0.53$) but it did not reach statistical significance.

change. Nonlinearity of both Cl/F_{NC} and Vd_{NC}/F but not $t_{1/2}$ in our population could indicate absorption differences with differing doses. In other words, bioavailability of this investigational oral solution may increase as dose increases, causing the higher-than-proportional decreases in Cl/F_{NC} and Vd_{NC}/F . Studies of pentoxifylline in other pediatric populations with healthy gastrointestinal tracts would help clarify whether this finding is related to the drug itself or the patient population in this study. In contrast, adults had a higher-than-proportional increase in $t_{1/2}$, as well as AUC and C_{max} . Oral clearance rate and volume of distribution were not reported.¹² The nonlinear increases in pentoxifylline $t_{1/2}$ in adults suggest decreased clearance rate with increased doses.

Higher-than-proportional increases in AUC, C_{max} , and $t_{1/2}$ also were described for M-1 in adults, but were not demonstrated in this study. The M-1 dose-normalized $AUC_{0-\infty}$ in our population approached a significant difference between dose levels 1 and 3, but the high degree of variability in parameters may have prevented the detection of significant nonlinearity of M-1. No evidence of pentoxifylline or M-1 accumulation with multiple doses was noted in this study; these findings are similar to findings in an adult study.¹² However, 6 of the 10 patients (60%) for whom pentoxifylline and M-1 concentrations were determined on study day 6 were from dose level 1, the lowest-dose group. Although no evidence of pentoxifylline or M-1 accumulation was noted, these findings are based mainly on a daily dose of 10 mg/kg and may not apply to the higher-dose groups.

Pharmacokinetic parameters of pentoxifylline and M-1 were similar from the noncompartmental and the 1-compartment analyses for dose levels 1, 2, and 3 (Table I). For dose level 4, the 1-compartment median $AUC_{0-\infty}$ for pentoxifylline and M-1 were approximately half and the oral clearance rates were 2- to 3-fold higher than the corresponding parameters estimated by the noncompartmental analysis. These discrepancies were the result of a selection issue related to the 2 patients excluded from the 1-compartment analysis due to the inability to determine the terminal slope of the curve. If these 2 patients are excluded from the noncompartmental analysis, the resultant median parameters from both types of analyses are similar.

The ratios of M-1 to pentoxifylline seen in this study were highly variable. Dose levels 1 and 2 showed a slightly higher M-1 concentration versus parent drug concentrations (1.7 fold). Dose level 3 had equal concentrations of both compounds, and dose level 4 had lower M-1 concentrations (~50%) compared with the parent drug. In contrast, adults exhibit M-1 concentrations ~3-fold higher than pentoxifylline concentrations.¹³ The lower ratios of M-1 to parent drug seen in this study might indicate lower activity of aldo-ketoreductase, the enzyme responsible for M-1 metabolite formation, in children than in adults. Previous evidence of this lower activity in children has been documented by Rady-Pentek et al,²³ who found significantly decreased 15-ketoreductase activity in liver cytosol in children aged ≤ 10 years ($n = 15$) compared with activity in adolescents and adults aged ≥ 13 years ($n = 22$). This decrease in metabolite ratios in our study population also may indicate saturation of aldo-ketoreductase at a pentoxifylline daily dose of 20 mg/kg, with pentoxifylline being shunted to its various other metabolic pathways with higher doses.

Several markers of effect were collected to gain insight into possible dose-response relationships, although the study was not powered to detect significant differences in these biomarkers. In this study, 5 of 24 patients (21%) required IVIG retreatment for persistent or recrudescing fever 48 hours after administration of IVIG. This result is comparable to a previously reported retreatment rate of 15%.⁶ None of the patients who required retreatment with IVIG had abnormalities of their coronary arteries in the acute or subacute phase of KD, unlike previously reported groups of patients.⁶ This finding could be due to the small number of patients in this study. Importantly, all patients in this study had improved or unchanged coronary artery assessments after treatment with pentoxifylline, suggesting that pentoxifylline either improves or does not affect coronary artery abnormalities.

Fever was an insensitive marker of pentoxifylline effect in this study. Because these patients received IVIG before and ASA concurrently with pentoxifylline, any effect that pentoxifylline might have had on body temperature could have been masked in this study, especially because the participants may have been afebrile by the time pentoxifylline was administered. TNF-alpha levels were also insensitive markers of pentoxifylline effect in this study. Because of the small number of

TNF-alpha samples collected on study day 6 and the large variation in measured levels, an overall decrease in TNF-alpha from study day 1 to study day 6 was difficult to detect. However, when the percentage of decrease in TNF-alpha in each patient was compared with that patient's active drug exposure, a possible relationship emerged. The trend toward decreasing TNF-alpha with increasing active drug exposure suggests a dose-response relationship between active drug (pentoxifylline plus M-1) and decreased circulating TNF-alpha.

In the previous study of pentoxifylline in KD by Furukawa et al,¹⁵ trends toward accelerated resolution of fever and normalization of C-reactive protein were noted in children receiving 20 mg/kg daily of pentoxifylline. The relationship seen in this study between decreases in TNF-alpha levels in patients with greater pentoxifylline and M-1 exposure further supports the hypothesis that pentoxifylline may have anti-inflammatory effects in acute KD. In the study from Japan,¹⁵ no patients in the group who received 20 mg/kg daily of pentoxifylline developed cardiac abnormalities. In the present study, improvement in coronary artery dimension was noted in 4 patients receiving 20 or 25 mg/kg daily. No patients receiving pentoxifylline in either study developed worsening coronary artery abnormalities.

Evidence of pentoxifylline effect in KD has been difficult to detect, in part because of the unknown cause of KD and the lack of sensitive, reliable biomarkers or surrogate end points for disease progression and/or resolution. Although pentoxifylline efficacy has not been proved in this and another small study¹⁵ to date, no harmful effects of pentoxifylline have been noted. Without notable differences in clinical outcomes, dose selection is based on the pharmacokinetic data observed. In this study, dose levels 1 and 2 demonstrated highly variable pharmacokinetic characteristics and low overall exposure. Dose levels 3 and 4 resulted in similar exposure to both pentoxifylline and the active metabolite, M-1. Increasing the daily dose to 25 mg/kg did not increase systemic exposure to either pentoxifylline or its active metabolite over what was seen with the 20-mg/kg daily dose. Therefore, a pentoxifylline daily dose of 20 mg/kg divided into 3 doses is a rational choice for future studies in KD.

Due to its tolerability and theoretic benefits, pentoxifylline is a reasonable candidate for Phase II or III clinical trials in KD. IVIG is not available in many countries because of its high cost. In addition, IVIG is currently in short supply worldwide. Pentoxifylline could be tested in combination with high-dose ASA in countries where IVIG is unavailable in the hopes of identifying a safe, inexpensive, and readily available agent that is effective in preventing coronary artery lesions. In countries where IVIG is available, the use of pentoxifylline may reduce the number of patients in whom coronary artery abnormalities develop. Another therapeutic niche for pentoxifylline would be as adjunctive therapy in the subset of patients with KD who enter the health care system with coronary artery abnormalities already detectable. Increased susceptibility to coronary artery lesions has been associated with increased TNF-alpha levels, so this subgroup of patients may benefit from treatment with pentoxifylline,

a TNF- α inhibitor.⁹ In our current study, we chose to delay administration of pentoxifylline until after IVIG was given and tolerated to fully assess the tolerability of pentoxifylline, but the ideal pentoxifylline administration time is not known. Given its tolerability and ease of administration, early pentoxifylline administration may be advantageous. Oral pentoxifylline could be administered while IVIG is being prepared.

CONCLUSIONS

In the children in this study, pentoxifylline was well tolerated at the doses studied. No notable differences in clinical outcomes were observed between dose levels, and dose levels 3 and 4 resulted in similar exposure to both pentoxifylline and M-1. Future efficacy and tolerability studies should use a daily dose of 20 mg/kg of pentoxifylline in acute KD.

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