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Safety, Tolerance, and Pharmacokinetics of Systemic Ribavirin in Children with Human Immunodeficiency Virus Infection

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Eleven pediatric patients, aged 1 to 10 years and with symptomatic human immunodeficiency virus infection, were treated with 6 or 10 mg of oral ribavirin per kg of body weight daily for 60 days. Safety and pharmacokinetic parameters were monitored; five children had comprehensive pharmacokinetic evaluations. The children tolerated the drug well, and treatment was not associated with any clinically significant adverse effects. Peak concentrations in plasma of 2.5 and 3.0 μM were reached at 90 min after single oral doses of 6 and 10 mg/kg, respectively. The mean systemic availability of oral ribavirin was 42.3%. After 60 days of ribavirin administration, mean trough concentrations in plasma of 2.6 and 4.1 μM were obtained. Ribavirin penetrated well into the cerebrospinal fluid, achieving 70% of the concentration in plasma at steady state.

Ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), a broad-spectrum antiviral agent structurally related to guanosine, has activity in vitro against both RNA and DNA viruses (12, 24, 34, 35). Bunyaviruses, including those that cause Rift Valley fever and hemorrhagic fever with renal syndrome, are particularly susceptible to the antiviral action of ribavirin (24). Systemic ribavirin has been used for the treatment of a variety of viral illnesses, including Lassa fever, measles, and hepatitis A (12, 13, 20, 22, 30, 34, 35). Aerosol ribavirin is currently licensed in the United States for the treatment of respiratory syncytial virus infections in children and has been demonstrated to be useful in the treatment of influenza viruses A and B (15, 26, 34, 35).

Ribavirin's broad antiviral spectrum includes activity against human immunodeficiency virus type 1 (HIV). Concentrations of ≥50 μg/ml (205 μM) have been shown to suppress HIV replication in T-lymphocyte cultures, and concentrations as low as 10 μg/ml (41 μM) have been shown to suppress expression of HIV proteins in chronically infected cells (21, 31, 34). Recent evidence suggests that ribavirin acts as an inhibitor of HIV reverse transcriptase (11). Initial studies have suggested that doses above the maximum tolerated dose for HIV-infected adults (2,400 mg/day) are required to achieve levels of ribavirin in plasma approximating the 50% inhibitory concentration for HIV (17, 31). However, evidence of reverse transcriptase inhibition has been observed at steady-state concentrations of >6 μM (29).

Clinical trials of ribavirin in HIV-infected adults have been controversial and disappointing (5, 10, 11, 17, 27, 28, 29, 31, 36). Although doses of 800 to 1,200 mg/day appear to be generally well tolerated in patients with lymphadenopathy and those with AIDS-related complex, the efficacy of ribavirin as a treatment for HIV infection has not been established. Initial studies suggested that ribavirin may have promise as single-agent antiretroviral therapy, but recent data have failed to demonstrate any consistent antiviral effect at clinically tolerated doses. The role of ribavirin in combination antiretroviral therapy is also unclear. Although the drug is antagonistic when tested in vitro with zidovudine, at least one study has suggested that ribavirin enhances the antiretroviral activity of purine analogs such as 2'3'-dideoxyinosine (ddI) (2, 3, 4, 37).

Apart from the potential use as an antiretroviral agent, the broad antiviral spectrum of ribavirin makes it a potentially useful drug in the treatment of serious viral infections that may occur in immunocompromised patients, including children with HIV infection. Respiratory viruses such as respiratory syncytial virus, influenza virus, parainfluenza virus, and measles virus are important causes of morbidity and mortality in immunocompromised hosts and may be amenable to aerosol or systemic ribavirin therapy (7, 16, 19, 32). Progressive and ultimately fatal cases of measles are being reported with increasing frequency among HIV-infected children (16, 19, 32). Theoretically, ribavirin may play a role in the management of disease in these children, for whom alternative treatment is not available.

Ribavirin in HIV-infected children has not been previously studied. Before consideration of studies to assess the clinical value of ribavirin in this population, we conducted a pilot study of the safety, tolerance, and pharmacokinetics of systemically administered ribavirin for a group of symptomatic, HIV-infected pediatric patients.

MATERIALS AND METHODS

Study subjects. Eleven symptomatic, HIV-infected children between the ages of 1 and 10 years were studied between September 1986 and December 1987. Written in-

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formed consent was obtained from each child's parent or legal guardian. None of the participants had received any other antiretroviral therapy prior to enrollment. Patients were excluded if they had any of the following: granulocyte count of <1,000 cells per mm^3, platelet count of <75,000 cells per mm^3, serum glutamic oxalacetic transaminase of >5 times the upper limit of normal for age, total bilirubin level of >1.0 mg/dl, prothrombin time of >2 times that of control, and serum creatinine of >1.0 mg/dl.

Drug regimen and pharmacokinetic monitoring. Ribavirin (molecular mass, 244 Da) was provided by Viratek, Inc. (Costa Mesa, Calif.). Patients received either 6 or 10 mg/kg of body weight as a single daily dose. For oral dosing, each child's medication was prepared by weighing the proper amount of lyophilized ribavirin and mixing it with 5 ml of water. Each dose was administered under the direct supervision of one of the investigators (S. M.). Following the initial dose and after a minimum of 10 days, daily dosing was begun and continued for 60 days. For pharmacokinetic studies, the drug was administered in the early morning 1 to 2 h prior to a meal.

Blood samples were obtained from children older than 3 years for determination of ribavirin levels at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after the initial oral dose and after the 60th dose. For children between 1 and 3 years of age, blood specimens were obtained at 0, 2, 24, and 48 h after the first and the 60th oral dose. Additional blood samples were obtained from all patients once weekly, just prior to the daily dose.

A single intravenous (i.v.) dose of ribavirin was given over 3 to 5 min to five children either 2 weeks before the 1st oral dose or more than 21 days after the 60th dose. Blood samples for pharmacokinetic analysis were obtained before administration and at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after the i.v. dose.

Urine was collected for 48 h after the first i.v. dose and after the 1st and 60th oral doses. A lumbar puncture was performed prior to instituting treatment and after the 60th oral dose.

Blood specimens for determination of ribavirin concentration were obtained in heparinized tubes and placed immediately at 4°C. The blood samples were centrifuged to separate plasma, and aliquots of plasma and pellets of erythrocytes (RBC) were stored at −70°C. Cerebrospinal fluid (CSF) and urine samples were collected and immediately frozen at −70°C. The ribavirin concentration was determined by a competitive binding radioimmunoassay, described previously, which can detect concentrations as low as 0.01 μM (1). The interassay coefficient of variation of the ribavirin assay was approximately 14%.

Pharmacokinetic analysis was performed by fitting the data (least-squares method) to a two-compartment model with first-order absorption with a lag time for oral dosing and zero-order absorption for i.v. delivery. With the samples available for analysis, a three-compartment model did not improve the fit over that of the two-compartment model (6). The variance model employed was a constant coefficient of variation (proportional-error) model, which corresponds to $1/\text{concentration}^2$.

The area under the curve (AUC) and the area under the moment curve were calculated by integration of the plasma concentration-time data following oral and i.v. doses. The noncompartmental parameters, clearances (CL), and steady-state volumes of distribution (V_{ss}), were calculated by using the values for AUC, area under the moment curve, and dose administered. The renal CL was calculated from the amount excreted in urine over 48 h following an i.v. dose divided by the AUC values with i.v. dosing ($AUC_{i.v.}$) over 48 h. The bioavailability of the oral formulation was determined by comparison of the AUC between oral and i.v. regimens for identical doses. MKMODEL (version 3.36; Biosoft), a nonlinear least-squares-method regression program, was used to aid in the calculation of the parameters described above.

Patient monitoring. Patients were seen weekly during therapy and at 2, 4, 12, and 24 weeks after completion of dosing to monitor for adverse experiences and toxicity. At all visits, medical histories were taken and complete physical examinations were performed. The laboratory parameters that were monitored included a complete blood count, platelet count, reticulocyte count, a chemistry profile (serum electrolytes and liver and kidney function tests), and urinalysis. Prothrombin time and partial thromboplastin time were monitored every 2 weeks. An electrocardiogram was obtained at baseline, on day 60, and at 8 and 24 weeks after discontinuation of the study medication. A chest X ray was done on days 0 and 60.

During the course of the trial, immunologic and retrovirologic parameters were measured monthly. Lymphocyte phenotyping was performed by standard flow cytometry techniques (14). The presence of p24 antigen in serum was determined by a commercially available sandwich solid-phase immunoassay (Abbott Laboratories, Chicago, Ill.). Quantitative immunoglobulins were measured in a commercial laboratory (Roche, Nutley, N.J.) by standard turbidometric techniques (8).

RESULTS

The characteristics of the 11 children enrolled are listed in Table 1. Five patients between the ages of 16 and 61 months received 6 mg of ribavirin per kg per day, and six patients between 12 and 123 months of age received 10 mg/kg/day. One patient missed a single oral dose of ribavirin during the daily-dosing segment of the study, and ribavirin treatment was discontinued for one patient after 38 days of daily dosing because of a possible adverse reaction.

Eleven children received a single oral dose of ribavirin at the start of the study (Table 2). Blood samples were first obtained from children under the age of 3 years for measurement of the ribavirin concentration at 2 h after the dose was given. Five children received 6 mg of oral ribavirin per kg. These included two males and three females, with a mean age of 26.2 months (16 to 61 months). Following a single oral dose, the mean concentration of ribavirin in plasma measured at 1 to 2 h after administration of the drug for the group was 2.5 μM (1.02 to 3.96 μM). Six patients (three male and three female), with a mean age of 52 months (12 to 123 months), received 10 mg/kg. The mean concentration in plasma for this group 1 to 2 h after a single oral dose was 3.05 μM (1.09 to 4.34 μM). There were five children who were older than 3 years and who therefore had the most comprehensive sampling for pharmacokinetic analysis (Table 3). Two patients received 6 mg and three patients received 10 mg of ribavirin per kg. In this group, the time to peak concentration in plasma was 1.8 (standard deviation [SD], 1.3) h. Mean peak concentrations in plasma were 2.5 (range, 1.1 to 4.0) and 3.0 (range, 2.3 to 3.9) μM after doses of 6 and 10 mg of ribavirin per kg, respectively. The mean half-life ($t_{1/2}$) of destruction, $t_{1/2}$ of elimination, and $t_{1/2}$ of absorption were 0.47 (SD, 0.31), 17.7 (SD, 7.2), and 0.36 (SD, 0.31) h, respectively. The AUC for the oral dose was 37.1 (SD, 30.5) μmol · h/liter. The curves for concentrations in plasma for

TABLE 1. Characteristics of study subjects[a]

Patient no.	Ribavirin dose (mg/kg)	Age (yr)	Race or ethnicity	Gender	HIV risk	HIV status	No. of CD4 cells/mm^3	Serum p24 antigen
1	6	1.3	Hispanic	Male	Perinatal	AIDS, LIP	1,400	+
2	6	1.5	White	Male	TX	AIDS, FTT	821	−
3	6	2.2	Hispanic	Male	Perinatal	AIDS, LIP	932	+
4	6	4.3	White	Female	Perinatal	AIDS, FTT	6	−
5	6	6.5	Black	Female	Perinatal	AIDS, LIP	840	−
6	10	1.0	Hispanic	Female	Perinatal	AIDS, LIP	2,431	+
7	10	1.3	Black	Female	Perinatal	AIDS, LIP	992	−
8	10	2.4	Hispanic	Male	Perinatal	AIDS, CNS, FTT	538	+
9	10	5.0	Black	Female	Perinatal	AIDS, LIP	336	+
10	10	6.2	Hispanic	Male	Perinatal	AIDS, LIP	413	−
11	10	10.0	Black	Male	Perinatal	AIDS, LIP	191	−

[a] TX, transfusion; FTT, failure to thrive; LIP, lymphoid interstitial pneumonitis; CNS, HIV encephalopathy.

patients treated with single oral and i.v. doses of 6 or 10 mg of ribavirin per kg are illustrated in Fig. 1 and 2.

Five of the eleven patients received a single i.v. dose of ribavirin. One male and two female children (mean age, 54.6 months) received 6 mg/kg, and two male children (ages, 74 and 123 months) received 10 mg/kg. The mean peak level in plasma for the former was 23.2 μM (18.7 to 28.6 μM), and the latter two achieved levels of 26.7 and 29.1 μM. The mean (standard deviation) $t_{1/2}$ of destruction and $t_{1/2}$ of elimination were 0.49 (0.29) and 18.6 (10.2) h. The mean volume of distribution in the central compartment and V_{ss} were 0.98 (0.17) and 7.7 (5.1) liters/kg. The mean CL and $AUC_{i.v.}$ were 0.39 (0.16) liter/h/kg and 103.0 (70.4) μmol · h/liter, respectively. Sufficient information from four patients (two at each dose level) for both oral and i.v. administration was available to determine the systemic availability of ribavirin (Table 3). The mean bioavailability of oral ribavirin among these patients was 42.3% (33.6%).

Steady-state ribavirin concentrations are listed in Table 4. After 60 days of ribavirin administration, the peak ribavirin concentrations in plasma ranged from 4 to 22 μM among those receiving the drug orally. Mean trough concentrations in plasma for the patients receiving doses of 6 and 10 mg/kg were 2.6 (SD, 0.5) and 4.1 (SD, 2.0) μM, respectively. Mean trough CSF concentrations for children treated with 6 and 10 mg of ribavirin per kg for 60 days were 1.5 (SD, 0.6) and 3.0 (SD, 0.9) μM, respectively. The mean CSF penetration (CSF/plasma ratio) of ribavirin was 0.71 (SD, 0.25) when the 6- and 10-mg/kg steady-state dosing values were combined. It should be noted that this ratio will vary during the dosing interval and that the CSF concentration will lag behind the plasma concentration during its rise and fall in the body. However, the trough concentration provides a more stable means of intra- and interstudy comparison, since it avoids the absorptive and distributive phases. Steady-state RBC/plasma concentration ratios were 78.1 (SD, 14.9) and 70.3 (SD, 10.7) for the 6- and 10-mg/kg doses, respectively. Two patients had sufficient urine data following a single i.v. dose. The percentages recovered over 48 h were 41.2 and 38.4% for patients no. 4 (6 mg/kg) and 11 (10 mg/kg), respectively. The renal CL ($A_e/AUC_{i.v.}$ over 48 h, where A_e is the amount excreted in urine at 48°C) for patients no. 4 and 11 were 0.3 and 0.1 liters/h/kg, respectively.

Safety and tolerance. All children tolerated ribavirin treatment well. None experienced gastrointestinal disturbances, and there were no significant drug-associated changes in any of the following: weight, vital signs, physical examination, chest X ray, electrocardiogram, electrolytes in serum, blood urea nitrogen, creatinine, lactate dehydrogenase, calcium, phosphorus, total protein, or albumin.

One patient who received 10 mg/kg had a mild (<3 times the upper limit of normal for age), transient increase in

TABLE 2. Single-dose pharmacokinetic data

Patient no.	Age (yr)	Wt (kg)	Dose (mg/kg)	2-h concn in plasma (μM)	Peak concn in plasma (μM)	
					Oral	i.v.
1	1.3	12	6	3.78		
2	1.5	9.9	6	1.02		
3[a]	2.2	14.7	6	1.31		22.3
4	4.3	12.6	6	0.77	1.08	28.1
5	6.5	20.4	6	3.99	3.99	18.7
11	10.0	24.0	6			15.5
6	1.0	6.7	10	1.96		
7	1.3	10	10	4.34		
8	2.4	9.2	10	3.65		
9	5.0	16.1	10	1.65	3.00	
10	6.2	18.7	10	1.54	2.25	29.1
11	10.0	24.0	10	2.2	3.65	26.7

[a] This patient had initial oral dosing at 2.2 years of age and i.v. dosing at 3.4 years of age.

TABLE 3. Pharmacokinetic parameters for patients receiving oral and i.v. dosing[a]

Dosing route and patient no.	Dose (mg/kg)	$t_{1/2}$[b]			V_1[c] (liter/kg)	V_{ss} (liter/kg)	CL (liter/h/kg)	AUC (μmol · h/liter)
		λ_1 (h)	λ_2 (h)	K_a (h)				
i.v.								
4	6	0.32	8.5		0.71	3.4	0.33	87.6
5	6	0.34	19.0		1.06	12.8	0.60	42.3
3	6	1.0	8.3		0.96	2.5	0.48	51.0
10	10	0.35	29.9		0.97	13.2	0.37	117.1
11	10	0.44	27.5		1.18	6.7	0.18	217.1
Mean		0.49	18.6		0.98	7.7	0.39	103.0
SD		0.29	10.2		0.17	5.1	0.16	70.4
Oral								
4	6	0.22	9.3	0.08				10.7
5	6	0.50	12.5	0.51				37.1
10	10	0.80	27.3	0.32				27.2
11	10	1.26	17.5	0.80				88.9
9	10	0.88	21.7	0.07				21.6
Mean		0.47	17.7	0.36				37.1
SD		0.31	7.2	0.31				30.5

[a] Bioavailability data for patients no. 4, 5, 10, and 11 were 14.2, 90.0, 24.7, and 40.1%, respectively (mean, 42.3%; SD, 33.6%).
[b] λ_1, half-life of destruction; λ_2, half-life of elimination; K_a, half-life of absorption.
[c] V_1, volume of distribution in the central compartment.

serum glutamic oxalacetic transaminase. Another patient at the same dose level entered the study with failure to thrive. She had been receiving parenteral alimentation and developed mild and transient elevations of both serum alkaline phosphatase and serum transaminases (<2 times the upper limit of normal for age). Subsequently, she was diagnosed with disseminated *Mycobacterium avium-M. intracellulare* infection.

Overall, the hematologic parameters did not change significantly over the 60-day course of ribavirin treatment. Patients receiving 6 mg/kg had median hemoglobin concentrations at the start and completion of dosing of 10.2 and 9.2 g/dl, respectively. Patients receiving 10 mg of ribavirin per kg had median concentrations of hemoglobin of 9.9 g/dl prior to initiation of ribavirin treatment and 9.5 g/dl at the end of 60 days of daily dosing. One patient who received 6 mg of ribavirin (and concomitant amoxicillin) per kg developed eosinophilia (maximum eosinophil count, 1,664 cells per mm^3), which resolved despite continued administration of the drug. No infectious etiology to explain the elevated eosinophil count was found.

One patient developed hematuria after 38 days of oral dosing with ribavirin (10 mg/kg), and the drug treatment was discontinued. Review of the records of his previous hospitalizations revealed that he had microscopic hematuria on two other occasions several months prior to enrollment into the study. A kidney biopsy, performed 3 months after discontinuation of ribavirin treatment, demonstrated mesangial proliferative glomerulonephritis, consistent with HIV nephropathy.

HIV parameters. Immunologic and retrovirologic monitoring revealed no consistent changes in quantitative immunoglobulins, median CD4 lymphocyte count, or serum p24 antigen detection during the course of ribavirin treatment. Although the numbers of patients in each treatment group were small, there appeared to be a trend toward decline of total lymphocyte count after 60 days of ribavirin dosing at 10 mg/kg. Patients who orally received 6 mg of ribavirin per kg for 60 days had a decline in their median lymphocyte counts of 9% (median count on day 0, 4,018 cells per mm^3; median count on day 60, 3,690 cells per mm^3). In contrast, children who received 10 mg/kg for 60 days had a decline of 66% (median count on day 0, 7,191 cells per mm^3; median count on day 60, 2,695 cells per mm^3).

DISCUSSION

Although there was notable interpatient variability, this pilot study suggests that ribavirin pharmacokinetics in symptomatic, HIV-infected children are similar to those reported previously for asymptomatic adults. Following a single oral dose of 6 to 10 mg/kg in children, peak ribavirin concentrations in plasma were 2.5 to 3.0 μM, slightly higher than those reported for adults (1.75 to 1.82 μM) receiving 400 to 600 mg (approximately 6 to 8.5 mg/kg). Time to peak concentration (1 to 2 h) and bioavailability (42%) values were identical to published adult values, despite the fact that some of the children in the present study had evidence of advanced HIV disease, including failure to thrive. The mean distribution $t_{1/2}$ was 30 min, and the mean terminal $t_{1/2}$ was prolonged at 18 h. This latter value is less than the 30 h reported by Lertora et al. for adults receiving a 400-mg (approximately 6-mg/kg) dose of ribavirin. This is a reflection of the smaller weight-normalized volume and higher weight-normalized CL found in the present study compared with the study of Lertora et al.

Studies with adults have previously demonstrated that ribavirin penetrates the blood-brain barrier (9). Data from the present study confirm that ribavirin penetrates into the central nervous systems of pediatric patients well, with a mean CSF/plasma ratio of 0.7. As previously reported for animals and humans, urinary excretion appears to be a major route for ribavirin elimination. Rates of urinary recovery of ribavirin over 48 h in the two children studied were 38 and 41%. Ribavirin accumulated in RBC following repetitive oral dosing in children. At steady state, the RBC/plasma ratios for patients receiving 6 and 10 mg/kg were 70:1 to 80:1. Although insufficient steady-state data for comparison with single-dose data were available, the expected steady-state trough (from single-dose kinetics) was less than the mea-

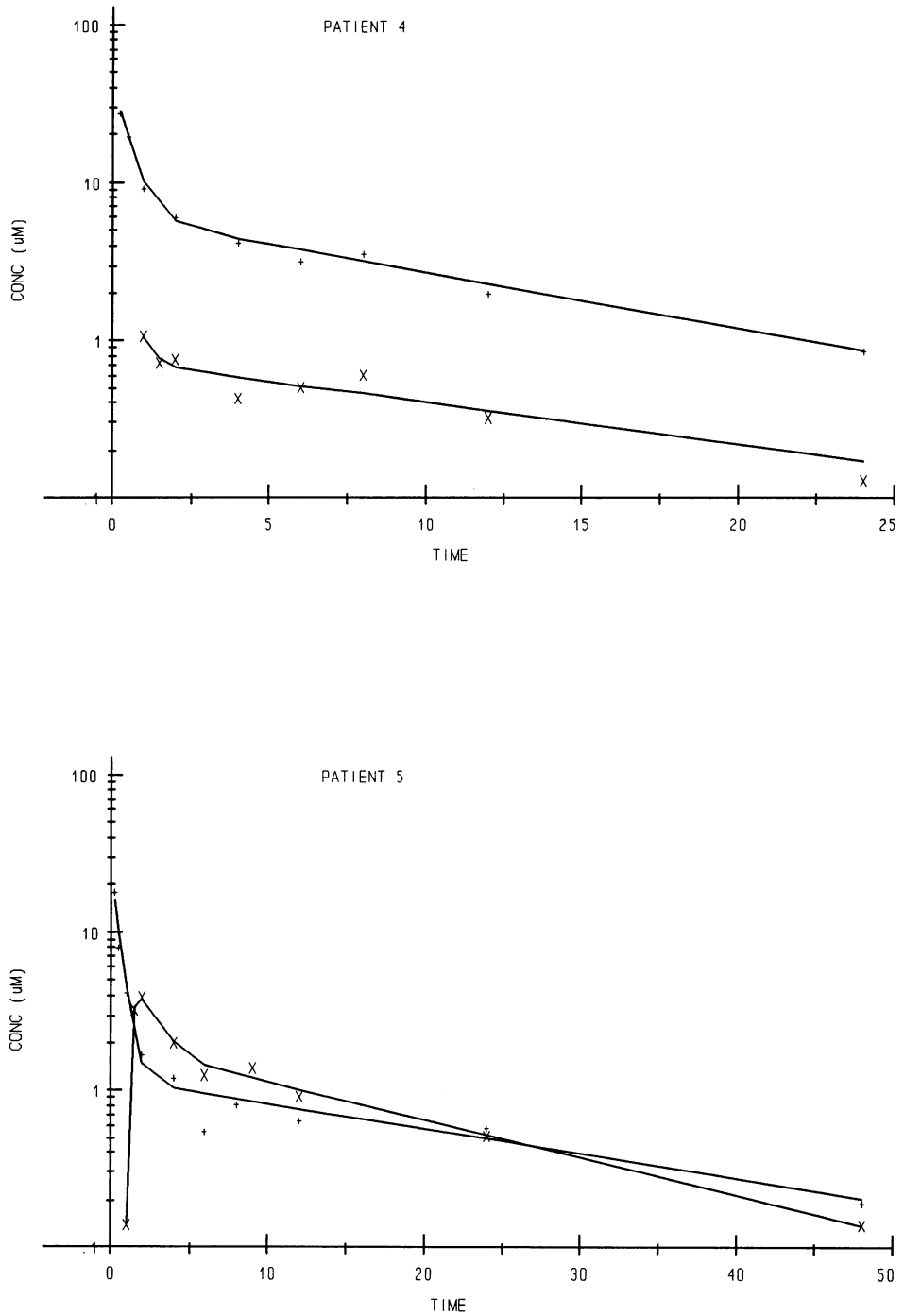

FIG. 1. Time-concentration (conc) curves for patients (no. 4 and 5) treated with single oral and i.v. doses of 6 mg of ribavirin per kg. +, time versus concentration (i.v. dose); ×, time versus concentration (oral dose).

sured steady-state trough (2.6 and 4.0 μM for 6- and 10-mg/kg-dose groups, respectively). This is consistent with studies of adults for whom significant ribavirin accumulation in plasma (RBC/plasma ratio, 63:1) was observed with twice-daily dosing at steady state (18). As described by Laskin et al., the greater-than-expected steady-state troughs are related to the accumulation of ribavirin into RBC.

It should be noted that all of the participants in this study were older than 1 year of age. Since the pharmacokinetic parameters for children during the first few weeks or months of life may be considerably different from those for older children, further studies will be needed to define the kinetics of systemic ribavirin in infants. The sample size of this study was too small to determine whether there were age-related changes in pharmacokinetics within the study population.

The maximum tolerated dose of ribavirin in adults has been estimated to be approximately 2,400 mg/day (approximately 34 mg/kg), with dose-limiting toxicities such as neu-

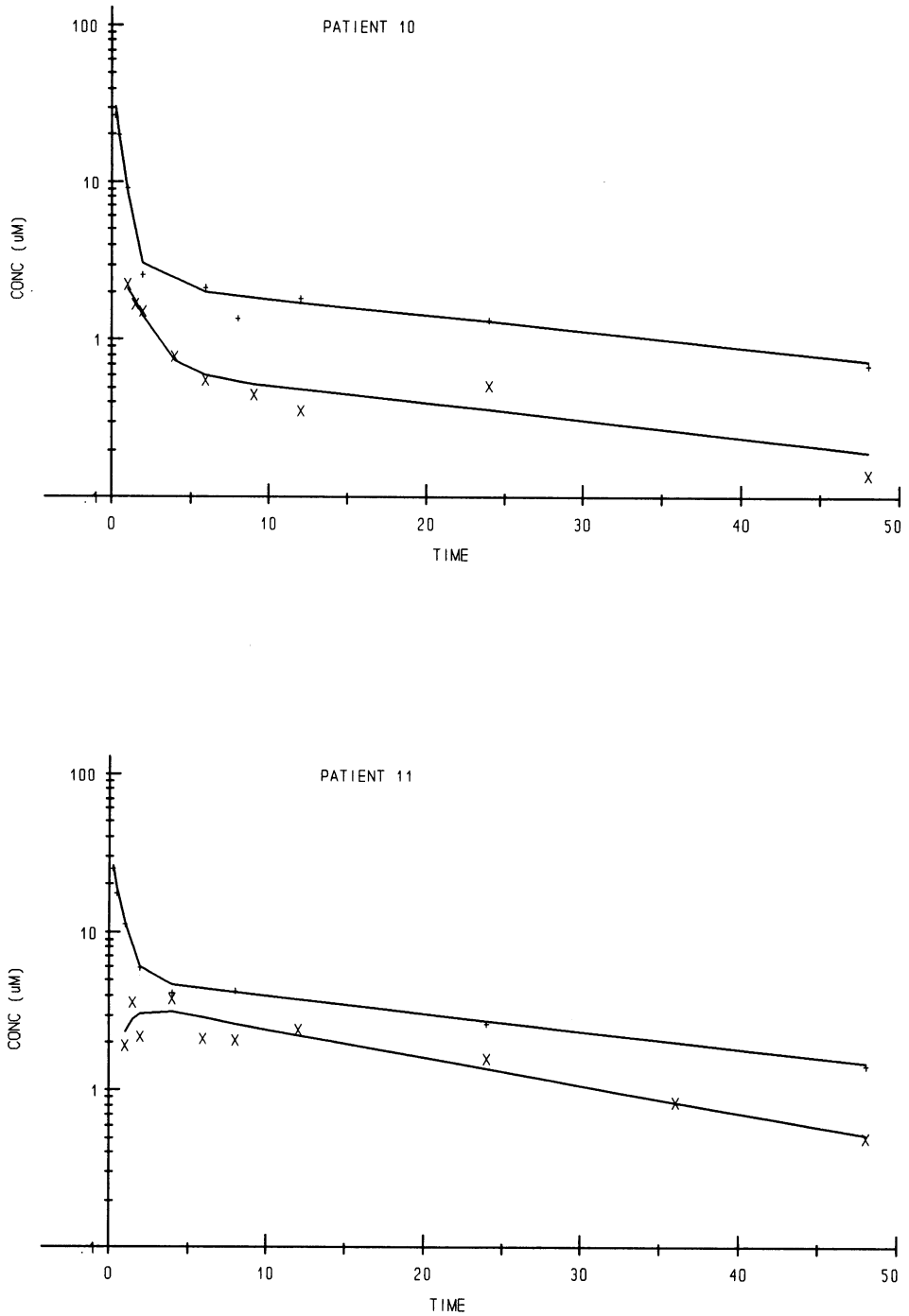

FIG. 2. Time-concentration (conc) curves for patients (no. 10 and 11) treated with single oral and i.v. doses of 10 mg of ribavirin per kg. +, time versus concentration (i.v. dose); ×, time versus concentration (oral dose).

rologic and hematologic abnormalities (17, 31). Ribavirin doses ranging from 600 to 1,200 mg/day (approximately 9 to 17 mg/kg/day) are generally well tolerated in adult HIV-infected patients with HIV-associated symptoms that are mild to moderate (10, 17, 18, 29, 31).

The study reported here demonstrates that once-daily oral administration of ribavirin at doses of 6 to 10 mg/kg for 60 days appears to be safe and well tolerated in symptomatic, HIV-infected children. No clinically significant toxicities during the course of treatment were noted. Median hemoglobin values declined by less than 1 g/dl over 60 days of ribavirin therapy, and most of this could be accounted for by the volume of blood obtained for clinical monitoring and pharmacokinetic analysis. Recent reports of the use of ribavirin either as a single agent or in combination with isoprinosine have suggested that the drug may cause dose-related lymphotoxicity (25, 27, 31). It is of interest that children orally receiving 10 mg of ribavirin per kg per day for

TABLE 4. Steady-state ribavirin concentrations (60 days)

Patient no.	Dose (mg/kg)	Peak concn in plasma (μM)	Trough concn in plasma (μM)	Trough concn in CSF (μM)	CSF/plasma ratio (trough concn)
1	6	NA[a]	2.33	1.02	0.44
2	6	NA	2.75	2.09	0.76
3	6	22.3	2.99	0.96	0.32
4	6	9.52	1.82	1.34	0.74
5	6	4.31	3.10	2.19	0.71
Mean		12.0	2.6	1.5	0.59
SD		9.3	0.5	0.6	0.28
6	10	8.88	2.45	2.47	1.01
7	10	8.0	3.49	3.38	0.97
8	10	3.88	2.3	2.66	1.16
9	10	4.85	3.46	1.94	0.56
10	10	7.13	5.35	2.84	0.55
11	10	10.3	7.43	4.38	0.59
Mean		7.2	4.1	3.0	0.81
SD		2.4	2.0	0.9	0.27

[a] NA, not applicable.

60 days had a larger decline in total lymphocyte count than patients receiving 6 mg/kg (66 versus 9%). Although the significance of this finding is unclear because of the small number of patients in each group and differences in the lymphocyte count at baseline, the potential for lymphotoxicity of ribavirin is an important consideration for future investigations. Recent studies have suggested that ribavirin accumulates in peripheral blood lymphocytes in addition to RBC (23). Since lymphocytes are a primary target for HIV infection, this property may be a therapeutic advantage, concentrating the drug at the site of infection and replication.

Combination antiretroviral therapy is now becoming an important strategy in the treatment of HIV-infected patients. This approach has theoretical advantages, including the reduction of drug toxicity by using lower exposures to individual agents, the enhancement of antiretroviral activity by using agents that are synergistic or additive when used in combination, and the prevention of the development of drug resistance. Initial studies of ribavirin demonstrated that it was antagonistic when used in combination with zidovudine or 2'3'-dideoxycytidine. Recent information, however, has demonstrated that ribavirin enhances the activity of purine analogs such as ddI (4). Concentrations of ribavirin of 2.5 to 10 μM appear to demonstrate the maximum enhancing effect on the anti-HIV activity of ddI (2, 4). This suggests that ribavirin may still play a role in combination chemotherapy for HIV infection.

Although the role of ribavirin as an antiretroviral agent is uncertain, the drug may have potential in the treatment of serious childhood viral illnesses in HIV-infected pediatric patients. Recent epidemiologic data indicate that the incidence of measles is increasing dramatically, especially in urban settings. Despite vaccination and/or immunoglobulin, the potential for fatal cases of measles exists in children with HIV infection (16, 19). Three symptomatic children with moderate to advanced HIV disease who were monitored at Children's Hospital of New Jersey have died of measles during the past year. In addition, HIV-infected children with measles virus identified in central nervous system tissue have been reported, suggesting that chronic measles virus infection may occur in these children (33). Ribavirin's activity against measles virus makes it potentially useful in the treatment of children with acute measles; theoretically, ribavirin may also be useful in the prophylaxis of children who have been exposed to measles virus. Oral dosing of ribavirin has been reported to be of benefit in the treatment of measles in studies performed outside the United States; doses of 10 mg/kg were associated with reduction of duration and severity of clinical manifestations without evidence of hematologic or other toxicities (12).

The data presented here suggest that the pharmacokinetics and safety profile of systemically administered ribavirin in symptomatic, HIV-infected pediatric patients are similar to those reported for adults. Determination of the value of ribavirin for the treatment of HIV and/or other viral illnesses that occur in HIV-infected children awaits further study.

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