Pharmacokinetics of Acyclovir Suspension in Infants and Children

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Eighteen children from 3 weeks to 6.9 years of age were given an oral acyclovir suspension for herpes simplex or varicella-zoster virus infections. Thirteen patients who were 6 months to 6.9 years old received 600 mg/m^2 per dose, and three infants and two children less than 2 years old were given 300 mg/m^2 per dose. The drug was given four times a day, except to one infant who was treated with three doses a day. Among the 13 children who received the 600-mg/m^2 dose, the maximum concentration in plasma (C_{max}) was 0.99 ± 0.38 µg/ml (mean ± standard deviation), the time to maximum concentration (T_{max}) was 3.0 ± 0.86 h, the area under the curve (AUC) was 5.56 ± 2.17 µg · h/ml, and the elimination half-life ($t_{1/2}$) was 2.59 ± 0.78 h. The three infants less than 2 months of age who received the 300-mg/m^2 dose had a C_{max} of 1.88 ± 1.11 µg/ml, a T_{max} of 4.10 ± 0.48 h, an AUC of 6.54 ± 4.32 µg · h/ml, and a $t_{1/2}$ of 3.26 ± 0.33 h. The acyclovir suspension was well tolerated by young children. No adverse effects requiring discontinuation of the drug occurred.

Acyclovir [9-(2-hydroxyethoxymethyl)guanine] is a nucleoside analog which inhibits the replication of herpes simplex virus (HSV) and varicella-zoster virus (VZV). Acyclovir administered parenterally is effective for the treatment of neonatal HSV infections, HSV encephalitis, and genital HSV infections (3, 25, 26). In immunosuppressed patients, intravenous acyclovir is useful for the therapy and suppression of HSV infections and for the therapy of VZV infections (6, 9, 10, 14, 18–20). The oral administration of acyclovir is of benefit for the therapy and suppression of genital HSV infections in the normal adult host (2, 5, 9, 11, 17, 23) and for the treatment and suppression of recurrent mucocutaneous HSV infections in immunocompromised patients (14, 22).

Pharmacokinetic information is available for acyclovir administered intravenously to adults and children and for the capsule formulation given to adults (4, 18). The pharmacology of oral acyclovir tablets has been investigated in children (12, 13). A liquid suspension formulation of the drug was developed for children and other patients who cannot ingest medications in solid form. The purpose of our study was to determine the pharmacokinetics and tolerance of acyclovir suspension in children.

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MATERIALS AND METHODS

Patients. Oral acyclovir suspension was given to children less than 7 years of age who had HSV or VZV infections which were not of a life-threatening nature. Patients were excluded if their serum creatinine concentration was greater than 1.5 mg/dl or if the serum bilirubin or liver transaminase concentration was more than twice the normal value. Patients who had undergone resection of any portion of the gastrointestinal tract, had any malabsorption syndrome, or had received radiation therapy to the abdomen within 3

weeks before possible enrollment were also excluded. The study was approved by the review committees responsible for research involving human subjects at each of the participating institutions. Informed consent was obtained from the parent or guardian of each patient.

Drug dosing. Acyclovir (Zovirax) suspension (40 mg/ml) was provided by the Burroughs Wellcome Co., Research Triangle Park, N.C. The suspension was given orally or by nasogastric tube at 300 or 600 mg/m^2 per dose. The doses were given four times daily at 0800, 1200, 1600, and 2000 h for 5 to 7 days. Thirteen children received 600 mg/m^2 per dose and five patients, including the three infants less than 2 months of age, received doses of 300 mg/m^2. All patients received four doses per day except for one infant who was given 300 mg/m^2 per dose three times per day.

Study design. Blood samples for determination of acyclovir concentrations in plasma were obtained immediately before one of the doses and 2 h after the dose on study day 2, 3, or 4. On the last day of acyclovir administration, blood samples were taken just before and at 1, 2, 3, 4, 6, and 8 h after the final dose. Laboratory screening for toxicity was done on entry, on day 2, 3, or 4, and on the day of the final dose. The laboratory tests performed were complete blood cell counts, including platelet and reticulocyte counts, determination of concentrations of electrolytes in serum, blood urea nitrogen, creatinine, lactate dehydrogenase, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), bilirubin, uric acid, amylase, and alkaline phosphatase, and urinalysis.

Determination of acyclovir concentrations in plasma. Samples were analyzed for acyclovir concentrations by radioimmunoassay, which has been shown to be sensitive and specific for acyclovir with minimal interference from metabolites (8, 15).

Data analysis. The plasma acyclovir concentration-time data were analyzed by noncompartmental pharmacokinetic methods. The maximum concentration (C_{max}) and associated time point (T_{max}) were determined based on the observed data. The acyclovir elimination half-life ($t_{1/2}$) was determined

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TABLE 1. Demographic information for patients

Sex[a]	Age	Wt (kg)	BSA[b] (m²)	Viral disease	Underlying disease
F	3 wk	3.8	0.25	HSV suppression	Neonatal HSV
F	4 wk	3.4	0.23	HSV suppression	Neonatal HSV
M	7 wk	4.2	0.26	HSV suppression	Neonatal HSV
F	0.5 yr	5.9	0.33	Cutaneous HSV	Eczema
F	0.6 yr	7.8	0.41	Cutaneous HSV	Eczema
M	0.9 yr	8.8	0.44	HSV whitlow	None
F	1.5 yr	10.0	0.46	Recurrent HSV	Neonatal HSV
M	1.8 yr	10.0	0.49	HSV whitlow	None
M	2.0 yr	12.5	0.55	Herpes zoster	Asthma
F	2.3 yr	15.5	0.59	Varicella post-VZIG	Leukemia
M	3.5 yr	12.2	0.56	Varicella	Eczema
F	3.9 yr	15.2	0.65	Varicella postvaccine	Leukemia
F	4.1 yr	17.2	0.70	Varicella	Eczema
F	4.0 yr	14.0	0.63	Retinitis	Neonatal HSV
M	5.7 yr	23.6	0.85	Varicella post-VZIG	Leukemia
F	5.7 yr	19.0	0.80	Varicella post-VZIG	Wilms' tumor
F	6.2 yr	15.1	0.66	Herpes zoster	Leukemia
M	6.9 yr	24.3	0.90	Recurrent oral HSV	Nephrosis

[a] F, Female; M, male.
[b] BSA, Body surface area.

by log-linear least-squares regression of the postabsorption portion of the concentration-time data obtained after the last dose. The area under the plasma concentration-time curve (AUC) resulting from the last dose was estimated by trapezoidal approximation, with extrapolation to infinite time and subtraction of that portion of the AUC resulting from previous doses, by the following equation: $AUC = AUC_{0-8} + C_t/k_{el} - C_0/k_{el}$, where AUC_{0-8} is the 8-h trapezoidal AUC, k_{el} is the terminal elimination rate constant, C_t is the last observed concentration, and C_0 is the concentration at the time of administration of the final dose. The calculated AUC is theoretically equal to the AUC resulting from administration of a single dose. The creatinine clearance (CL_{CR}) values were estimated by the following equation: $CL_{CR} = 0.48 \times$ (height of patient/creatinine concentration in serum) (21, 24).

RESULTS

Patients. Eighteen patients, aged 3 weeks to 6.9 years, participated in the study (Table 1). Eight patients had VZV infections, and 10 patients had HSV infections. Three term infants, aged 3 to 7 weeks, were treated with acyclovir suspension beginning 2 days after the completion of a course of intravenous acyclovir for neonatal HSV infections; acyclovir was not detected in plasma before oral therapy was initiated. One of the five patients with malignancy had
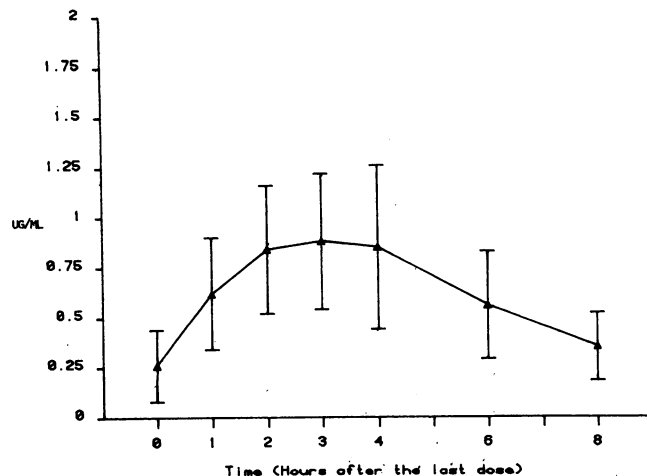

FIG. 1. Acyclovir concentrations in plasma after last dose. The y axis represents acyclovir concentrations (micrograms per milliliter; means ± standard deviations) in plasma, which were plotted against hours after last dose on the x axis for 13 patients 6 months to 6.9 years of age who received 600 mg of acyclovir oral suspension per m² per dose.

herpes zoster, three had received vericella-zoster immune globulin (VZIG) after a chicken pox exposure but subsequently developed varicella, and one developed a varicella-like rash after the administration of an investigational varicella vaccine.

Concentrations of acyclovir in plasma. The acyclovir concentrations in plasma on day 2, 3, or 4 and after the last dose are shown in Table 2. For concentrations determined on day 2, 3, or 4, the predose values represent trough concentrations present either 4 or 12 (overnight) h after the preceding dose.

No significant differences were observed between the mean acyclovir concentrations in plasma after the last dose for patients less than 4 years of age and those from 4 to 7 years old who received doses of 600 mg/m². The time profile of mean acyclovir concentrations in plasma after the last dose for all patients who received the 600-mg/m² dose regimen is shown in Fig. 1. Among patients receiving 300 mg/m², the three infants less than 2 months of age had higher mean concentrations 2 to 8 h after the last dose than did the two children who were 1.5 and 1.8 years of age (Table 2).

Pharmacokinetic analysis. Pharmacokinetic parameters determined from individual patient data after the last dose are

TABLE 2. Acyclovir concentrations in plasma

Age group (n)	Dose (mg/m²)	Day 2, 3, or 4[a]		Before last dose	Time (h) after last dose					
		Before	2 h		1	2	3	4	6	8
6 mo–4 yr (7)[b]	600	0.31 ± 0.07	1.03 ± 0.30	0.22 ± 0.20	0.53 ± 0.23	0.84 ± 0.35	0.90 ± 0.40	0.95 ± 0.49	0.60 ± 0.35	0.35 ± 0.17
4–7 yr (6)[c]	600	0.59 ± 0.44	0.97 ± 0.60	0.30 ± 0.14	0.73 ± 0.31	0.84 ± 0.30	0.85 ± 0.29	0.73 ± 0.29	0.51 ± 0.19	0.35 ± 0.20
Mean ± SD (13) 6 mo–7 yr	600	0.45 ± 0.35	1.00 ± 0.47	0.25 ± 0.18	0.62 ± 0.28	0.84 ± 0.32	0.88 ± 0.34	0.85 ± 0.41	0.56 ± 0.27	0.35 ± 0.17
<2 mo (3)	300	1.56 ± 1.51	1.87 ± 1.34	0.69 ± 0.27	0.61 ± 0.16	1.48 ± 0.55	1.82 ± 1.16	1.88 ± 1.11	1.32 ± 0.90	0.84 ± 0.60
6 mo–4 yr (2)	300	1.05 ± 0.10	1.31 ± 0.09	0.49 ± 0.55	0.61 ± 0.19	0.77 ± 0.13	0.73 ± 0.14	0.52 ± 0.13	0.29 ± 0.13	0.21 ± 0.02

[a] Samples were drawn on day 2, 3, or 4 just before and 2 h after dose 1, 2, 3, or 4.
[b] One patient received an extra dose on the last day 3.5 h after the scheduled last dose; 4- to 8-h points were excluded from the mean.
[c] Data for one patient for whom there were substantial deviations from the protocol dosing regimen were excluded from the means.

presented for each age group and dosage regimen in Table 3. The mean values for all patients receiving 600 mg/m² per dose were as follows: C_{max}, 0.99 ± 0.38 μg/ml (mean ± standard deviation); T_{max}, 3.0 ± 0.86 h; AUC, 5.56 ± 2.17 μg · h/ml; and $t_{1/2}$, 2.59 ± 0.78 h. The mean pharmacokinetic values were similar for children between 6 months and 4 years of age and children over 4 years old receiving the 600-mg/m² dose.

Three infants less than 2 months of age and two children between 2 months and 4 years of age were given acyclovir suspension at 300 mg/m² per dose. The three infants who were less than 2 months of age achieved a higher mean C_{max}, 1.88 μg/ml, and had a somewhat longer mean $t_{1/2}$, 3.26 h, than did the older children receiving the same or a higher dose (Table 3).

By using interpolation and superimposition of mean data, the steady-state acyclovir concentrations in plasma were simulated for the 600-mg/m² dose (Fig. 2). The expected peak acyclovir concentrations after four consecutive doses given at 4-h intervals were approximately 0.9, 1.3, 1.4, and 1.5 μg/ml after successive doses during the day.

Adverse reactions. Three patients experienced adverse clinical reactions which were self-limited and did not require discontinuation of the drug. The adverse effects were mild diarrhea, mild vomiting, or profuse diaphoresis.

Minor variations were observed in the hepatic transaminase levels in seven patients, but five patients had elevated transaminase levels before acyclovir was begun. None of the patients had SGOT or SGPT greater than twice the normal value. Preexisting hematologic abnormalities in patients with malignancy and nephrotic syndrome persisted during the study, as did anemia in the infant with eczema. The older patient with eczema had a decline in hemoglobin from 12.1 to 10.0 g/dl during the study. No significant changes were observed in the CL_{CR} values calculated from the creatinine concentrations in serum obtained on day 1, day 2, 3, or 4, and the last study day. No abnormalities in blood urea nitrogen or creatinine developed during the study. The observed laboratory abnormalities were not considered to be drug related, and none necessitated discontinuing the study drug.

DISCUSSION

Approximately 20% of oral acyclovir given to adults is absorbed. Adults taking acyclovir capsules (200 mg every 4 h) had a C_{max} of 0.5 μg/ml. A 200-mg dose is equivalent to 115 mg/m² for an average adult male. A dose of 400 mg every 4 h produced a C_{max} of 1.2 μg/ml (4). The peak plasma concentration was 1.82 μg/ml when acyclovir was given in tablet form to children at a dose of 600 mg/m² (13). In our study, children who received 600 mg of acyclovir suspension
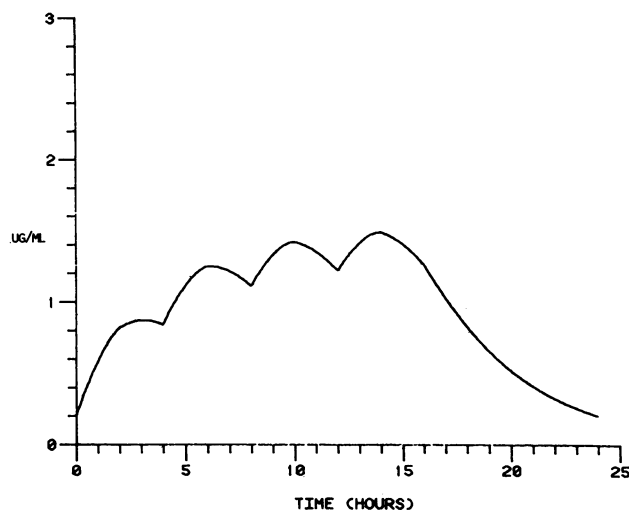

FIG. 2. Simulated steady-state acyclovir concentrations in plasma. The simulated steady-state acyclovir concentrations (micrograms per milliliter) in plasma plotted on the y axis were obtained by interpolation and superimposition of the mean data for 13 patients 6 months to 6.9 years of age who received 600 mg of acyclovir oral suspension per m² per dose. The times indicated on the x axis are based on four doses given every 4 h during the day (i.e., at h 0, 4, 8, and 12).

per m² per dose had mean values for C_{max} of 0.99 μg/ml and $t_{1/2}$ of 2.59 h. On the basis of body surface area, these children received the equivalent of five times the adult oral dose of 200 mg, but the peak concentration in plasma was only twofold higher than the peak concentration in plasma in adults. Thus, with identical dosage regimens, the peak concentration in plasma in children would be about 40% of the expected peak level in adults. This difference can be explained in part by the fact that the C_{max} in the present study was determined after a dose given 12 h after the previous dose. In the adult pharmacokinetic study, the C_{max} was measured at steady state in subjects receiving the drug every 4 h in each 24-h period. The lower peak concentrations in children probably also reflect slower absorption of the drug from the suspension compared with the rate of absorption from capsules given to adults. In contrast to the difference in C_{max}, the dose-normalized AUC in children given acyclovir suspension was approximately 75% of that after capsule administration to adults.

The mean C_{max} after a 300-mg/m² dose and the AUC were proportionately less than the values for 600 mg/m². Only three infants less than 2 months of age received oral acyclovir suspension. However, the administration of the

TABLE 3. Noncompartmental analysis of acyclovir concentrations in plasma after last dose of oral acyclovir suspension

Age group (n)	Dose (mg/m²)	C_{max} (μg/ml)	T_{max} (h)	AUC (μg · h/ml)	$t_{1/2}$ (h)	CL_{CR} (ml/min per 1.73 m²)
6 mo–4 yr (7)[a]	600	1.07 ± 0.44	3.21 ± 0.99	5.68 ± 2.40	2.61 ± 0.75	88 ± 27
4–7 yr (6)[b]	600	0.89 ± 0.30	2.64 ± 0.47	5.38 ± 2.12	2.57 ± 0.95	99 ± 19
Mean ± SD (13) 6 mo–7 yr	600	0.99 ± 0.38	3.00 ± 0.86	5.56 ± 2.17	2.59 ± 0.78	93 ± 24
<2 mo (3)[c]	300	1.88 ± 1.11	4.10 ± 0.48	6.54 ± 4.32	3.26 ± 0.33	50 ± 14
6 mo–4 yr (2)	300	0.77 ± 0.13	2.00 ± 0.00	2.87 ± 0.85	2.75 ± 0.17	92 ± 8.5

[a] One patient received an extra dose 3.5 h after the last scheduled dose; the AUC was excluded from the mean calculation.

[b] One patient was not included in the mean calculations because of substantial deviations from the protocol dose schedule. The elimination rate was indeterminable for one patient who had identical concentrations at 3.0 h and at the last sampling time (8.0 h). Therefore, T_{max}, AUC, and $t_{1/2}$ were not included.

[c] The data for one patient were insufficient for determination of the k_{el}; therefore, AUC and $t_{1/2}$ are not reported; in this instance, the T_{max} was set equal to the mean at consecutive time points (3.083 and 4.167) at which C_{max} occurred.

300-mg/m^2 dose produced a higher C_{max} and a longer $t_{1/2}$. The estimated CL_{CR} in these patients was 50 ml/min per 1.73 m^2, which reflects immature renal function in this age group and probably accounts for the higher concentrations of acyclovir in plasma.

As was expected, the concentrations of acyclovir in plasma after its oral administration to children were significantly lower than those observed with intravenous therapy. Children given doses of 250 mg of acyclovir per m^2 intravenously had a mean C_{max} of 10.3 ± 4.0 μg/ml. Doubling the dose to 500 mg/m^2 produced a mean C_{max} of 20.7 ± 5.0 μg/ml, and the overall mean $t_{1/2}$ for children was 2.52 ± 1.04 h (1). Neonates receiving 10 mg/kg per dose had a mean peak acyclovir level of 13.9 ± 4.2 μg/ml, with a $t_{1/2}$ of 3.78 ±1.21 h (7). No serious toxicity was observed in our study, which was predictable since the higher acyclovir concentrations in plasma after intravenous administration were tolerated well.

The antiviral activity of acyclovir has been determined by in vitro assays, but extrapolation to in vivo inhibitory effect must be made with caution. A number of factors may alter the in vitro effects of the drug upon viral replication, and the correlation of specific drug concentrations in plasma with the clinical outcome has not been proved. Acyclovir concentrations of 0.01 to 0.7 μg/ml inhibit HSV type 1 cytopathic effects by 50%, and concentrations of 0.01 to 3.2 μg/ml inhibit HSV type 2. The in vitro inhibition of VZV occurs at 0.3 to 10.8 μg/ml (18). Thus, the drug concentrations required to inhibit many VZV isolates may be greater than the C_{max} of 0.99 μg/ml which was obtained in children given the oral suspension of acyclovir.

The present study provides the pharmacologic basis for investigating the efficacy of oral acyclovir suspension for the treatment of herpesvirus infections in pediatric patients. Placebo-controlled clinical trials will be necessary to determine whether the peak concentrations in plasma of approximately 1.0 μg/ml obtained in our patients receiving the 600-mg/m^2 dose are adequate for the treatment of infections caused by VZV and some strains of HSV. Although many patients with non-life-threatening herpesvirus infections may benefit from oral suspension therapy, these pharmacokinetic data suggest that oral acyclovir therapy is not appropriate for the initial treatment of neonatal HSV infections or other severe herpesvirus infections in children.

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