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Phase I Safety and Pharmacokinetics Study of Micronized Atovaquone in Human Immunodeficiency Virus-Infected Infants and Children

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A phase I dose-escalating safety and pharmacokinetic study evaluated an oral suspension of micronized atovaquone (m-atovaquone) in infants and children stratified into age groups from 1 month to 12 years of age. Dosages of 10, 30, and 45 mg/kg of body weight/day were evaluated as single daily doses over a period of 12 days. Steady-state concentrations in plasma were determined on day 12, and single postdose concentrations were measured on days 1, 3, 5, 7, 9, 13, 15, 18, 21, and 24. Prior studies with adults suggest that the average plasma atovaquone concentration of 15 μg/ml is associated with therapeutic success in more than 95% of patients with *Pneumocystis carinii* pneumonitis. The results showed m-atovaquone to be safe and well tolerated. Dosages of 30 mg/kg/day were adequate to achieve an average steady-state concentration of greater than 15 μg/ml in children ages 1 to 3 months and 2 to 12 years, but a dosage of 45 mg/kg/day was needed to reach this concentration in infants 3 to 24 months of age. The oral suspension of atovaquone is safe and well tolerated in children. A single daily dose of 30 mg/kg provides bioavailability considered adequate for therapy of *P. carinii* pneumonia, but infants between 3 and 24 months of age may require a dosage of 45 mg/kg/day.

Atovaquone is a 1,4-hydroxynaphthoquinone with broad-spectrum antiprotozoan activity, including demonstrated efficacy against *Pneumocystis carinii* (7, 8, 11), *Toxoplasma gondii* (1, 2, 13), *Plasmodium* species (5, 14, 16), and *Babesia microti* (9). Each of these organisms may cause infections in infants and children; so, knowledge of the safety and pharmacokinetics in this age group is essential for optimal use of the drug. Furthermore, the population having the greatest need for atovaquone in the United States is human immunodeficiency virus (HIV)-infected individuals at risk for *P. carinii* pneumonitis and toxoplasmosis.

Much of the clinical research evaluating atovaquone used a Food and Drug Administration-approved tablet formulation with limited bioavailability. Such studies showed that in adults with AIDS and mild to moderately severe *P. carinii* pneumonitis treated with atovaquone tablets, the probability of therapeutic success was strongly associated with concentrations of the drug in plasma ($P < 0.001$). The following average steady-state concentrations of atovaquone in plasma were compared with the observed rates of therapeutic success: <5 μg ml, 0%; 5 to <10 μg/ml, 62%; 10 to <15 μg/ml, 79%; 15 to <20 μg/ml, 95%; and ≥20 μg/ml, 100% (8). These data are especially useful for targeted pharmacokinetic goals in the evaluation of a new formulation for infants and children.

A newly formulated liquid preparation of atovaquone is twice as bioavailable in adults as the tablet preparation (4). In a phase I multiple-dose study of HIV-infected adults given 1,000 mg of atovaquone suspension twice daily the targeted steady-state concentrations in plasma of 15 to 25 μg/ml were achieved in all the patients studied (6). This formulation was approved by the Food and Drug Administration in 1995 for use in adults, with the recommended dosage being 750 mg twice daily. The tablet form has subsequently been taken off the market.

Atovaquone is a structural analog of ubiquinone. The site of action is believed to be the cytochrome bc_1 complex (complex III). The drug may affect metabolic enzymes, such as dihydroorotate dehydrogenase (12), that are linked to the mitochondrial electron transport chain by ubiquinone. Thus, inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. Such a blockage in turn may inhibit nucleic acid and ATP synthesis. The drug is highly lipophilic with low aqueous solubility, and absorption is enhanced with concomitant ingestion of food. Atovaquone's long half-life is probably related to enterohepatic cycling, with eventual fecal elimination of greater that 94% of the drug.

We previously studied the tablet formulation of atovaquone in 14 infants and children at dosages of 10 and 40 mg/kg of body weight/day administered for 12 days with food. The mean maximal concentration (C_{max}) at the 10-mg/kg/day dosage was 9.4 μg/ml (range, 3.2 to 12.7 μg/ml) and at the 40-mg/kg/day dosage the mean C_{max} was 21.2 μg/ml (range, 13.0 to 34.2 μg/ml). Considerable variation from patient to patient was noted, as indicated by the range of values (15). No adverse effects were encountered. Because atovaquone appears promising as a drug for the treatment and prevention of *P. carinii* pneumonia (PCP) and toxoplasmosis in AIDS patients, a phase I multiple-dose study was undertaken to evaluate the new suspension formulation in HIV-infected children.

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MATERIALS AND METHODS

Study design. The study was a multicenter (four-site), 24-day, phase I, dose-escalating, open-label investigation to evaluate the safety, tolerance, and pharmacokinetics of three doses of the new formulation of micronized atovaquone (m-atovaquone) in HIV-infected and perinatally exposed infants and children (AIDS Clinical Trials Group Protocol no. 227). A 12-day treatment period with daily administration of a dose of m-atovaquone was followed by an observation period of 12 days. Patients were stratified by age and drug dose into seven cohorts. Cohorts 1 and 2 consisted of 2- to 12-year-old children, cohorts 3, 4, and 5 consisted of 3- to 24-month-old children, and cohorts 6 and 7 consisted of 1- to 3-month-old infants. Three different drug levels were evaluated sequentially: 10 mg/kg/day (cohorts 1, 3, and 6), 30 mg/kg/day (cohorts 2, 4, and 7), and 45 mg/kg/day (cohort 5), respectively.

Patient selection. A total of 27 patients from St. Jude Children's Research Hospital, University of California in San Francisco, Chicago Children's Memorial Hospital, and the University of Puerto Rico were enrolled in this study.

Infants and children ages 1 month to 12 years were eligible if they had evidence of HIV infection as documented by a positive HIV culture result, PCR result, or p24 antigen titer with a second confirmatory test with a different specimen for children younger than 15 months of age or at least two positive antibody test results for older children. Infants born to HIV-infected mothers at risk of infection (indeterminate HIV status) were also included in the study. All patients met the criteria for the use of PCP prophylaxis on the basis of the guidelines for prophylaxis against PCP for children published by the U.S. Department of Health and Human Services in March 1991 and amended by the *Pneumocystis carinii* Pneumonia Prophylaxis Evaluation Working Groups in 1995 (3).

Children receiving antiretroviral therapy were included. They were required to be clinically stable, to be free of acute illness and active opportunistic infection, and to have stable and normal or near-normal (less than grade 2) laboratory parameters including those from hematology and chemistry studies on the basis of the Toxicity Tables for Grading Severity of Pediatric Adverse Experiences, Division of AIDS, National Institutes of Health. The following excluded children from the study: concomitant use of nephrotoxic, cardiotoxic, or hepatotoxic drugs; pregnancy; glucose-6-phosphate dehydrogenase deficiency; chronic diarrhea or emesis; and treatment with any other investigational therapy during the study period. Trimethoprim-sulfamethoxazole was allowed up to 3 days prior to the initiation of m-atovaquone and then again 3 days after the last dose was given; inhaled or intravenous pentamidine was allowed up to 1 week prior to study drug initiation.

Patient evaluations. Children were followed every 2 to 3 days in the clinic for a total of 24 days. During each visit a medical history and physical examination were performed. At entry a complete blood count, a glucose-6-phosphate dehydrogenase level, electrocardiograph, and chest radiograph were obtained and coagulation and chemistry studies and urinalysis were performed. Blood and chemistry studies were repeated three times during the study. Following 12 days of daily administration of m-atovaquone, steady-state pharmacokinetic studies were performed.

Drug formulation. The atovaquone formulation used in the study included a concentrated bright yellow suspension of m-atovaquone prepared in a 0.5% aqueous solution and then microparticulated to reduce the particle size. The processed suspension was diluted with a solution containing the inactive ingredients benzyl alcohol, poloxamer 188, saccharin, xanthan gum, flavoring, and purified water. The daily dose of m-atovaquone was prepared by the site's pharmacist in amber-colored oral syringes marked with specific instructions and the day and hour that the medication was to be given. Five milliliters of the suspension contained 750 mg of atovaquone. The parents or patients were instructed to save the syringes and to return both used and unused syringes to the investigator at each clinic visit. Patients were given enough premeasured doses of m-atovaquone to last until the next scheduled visit.

Dosing schedule. Children were instructed to receive their daily dose immediately following a full breakfast appropriate to the patient's age and normal eating habits. For infants, parents were instructed to give at least 150 ml of milk or formula prior to m-atovaquone dosing. The food intake prior to the administration of each dose was recorded. The ingestion of two doses (on days 11 and 12) prior to the determination of steady-state levels was required. At day 11 of study drug, children were encouraged to take the study drug within 6 h after a morning meal in order to qualify for determination of steady-state status on day 12. The last dose (day 12) was given at the clinic, and the time of dosing was recorded for the blood samples used for determination of steady-state pharmacokinetics.

Criteria for dose increase or modification. Children ages 2 to 12 years were initially dosed at 10 mg/kg/day. On the basis of the safety and pharmacokinetic data for the 10-mg/kg dose (received by cohorts 1, 3, and 6), progression was made to the next dose (30 mg/kg/day; cohorts 2, 4, and 7). After review of the data for cohort 4, an additional cohort receiving a dosage of 45 mg/kg (cohort 5) was added to the study. Dose escalation did not occur until a thorough review of the safety and pharmacokinetic data had been made by the study team. All but one cohort contained at least three evaluable patients who successfully completed 12 days of dosing. Cohort 6 (infants ages 1 to 3 months receiving a dose of 10 mg/kg) was closed after the first child completed the study and showed low levels similar to those obtained in children in cohort 3 (ages 3 to 24 months receiving the same dose). In any given cohort at least three patients were required to have been followed for 1 week after administration of the last dose of m-atovaquone before escalation to the next dose occurred. No patient was studied more than once.

The participating centers were required to report significant toxicities within 48 h. If two of the four children receiving a particular dose experienced severe toxicity and the toxicity was believed to be due to the drug or if m-atovaquone levels were higher than 60 μg/ml, two additional patients were to be entered into the cohort and to receive the same dose. If one of these two additional patients experienced toxicity enrollment into that cohort was to be stopped.

Pharmacokinetic evaluations. Blood samples for pharmacokinetics studies (1 ml of whole blood) were collected according to the following schedule: days 1, 3, 5, 7, 9, and 12 (steady state). Day 1 was the day that the first dose was administered. After administration of the last dose of m-atovaquone (day 12), blood samples were obtained at the following times: hours 2, 4, 6, 8, 12, 24 (day 13), 72 (day 15), 144 (day 18), 216 (day 21), and 288 (day 24). In the cohorts with infants 1 to 3 months of age, an abbreviated schedule was used; blood was obtained on days 1, 5, 9, and 12 (steady state). After administration of the last dose of m-atovaquone (day 12), blood samples were obtained at the following times: hours 2, 6 (day 12), 24 (day 13), 144 (day 18), and 288 (day 24).

Pharmacokinetic parameters were estimated from the concentrations in plasma obtained on the last day of each dosing period. Model-independent methods were used to estimate all parameters. The C_{max} of atovaquone in plasma at steady state ($C_{max,ss}$) and the minimum concentrations of atovaquone in plasma at steady state ($C_{min,ss}$) were observed from the data. The fluctuation index (F1) was calculated as $C_{max,ss}/C_{min,ss}$. The area under the curve of plasma drug concentration versus time (AUC_{0-1}) from the time that the predose sample was obtained to the time that the last sample of the steady-state dosing interval was obtained was calculated for each volunteer by using the linear trapezoidal rule. The average steady-state concentration ($C_{avg,ss}$) was calculated by dividing the AUC_{0-1} by the time difference between the times of collection of the first and last steady-state samples. The area under the curve of concentration versus time at steady state (AUC_{ss}) was estimated as $C_{avg,ss}$ multiplied by the dosing interval (24 h). This approach was taken to accommodate for minor differences in sample collection times and missing samples. Estimates of the elimination rate constant (λ_z) and half-life ($t_{1/2}$) for atovaquone were obtained by log-linear regression of the terminal portion of the concentration versus time curve during the washout phase after the last dose. The apparent total clearance (CL/*F*) and apparent volume of distribution during the elimination phase (V_z/F) were estimated as dose/AUC_{ss} and dose ($\lambda_z \cdot AUC_{ss}$), respectively.

Drug assays. Plasma atovaquone concentrations were determined by a high-pressure liquid chromatographic method (18) in the Drug Assay Laboratory, Division of Medical Biochemistry, Glaxo Wellcome, Inc. The range of the calibration curve for the assay under routine conditions was 0.25 to 50 μg/ml. The accuracy of the assay (determined as percent bias) ranged from −4.8 to −9.4% in the validation runs. The intra- and interassay precisions (determined as the relative standard deviation) were less than 6.8 and 6.4%, respectively (18). The sensitivity of this method is 0.25 μg/ml, and the accuracy is 94.1% (7a).

RESULTS

Tolerance, toxicity, and adverse events. The suspension of m-atovaquone was well tolerated by all the infants and children. No one was discontinued from the study because of refusal to take the medication. Compliance was considered satisfactory on the basis of evaluations of counts of containers and interviews on each visit to the clinic. One child was discontinued from the study because of maternal difficulty in following the rigorous clinical follow-up schedule. One child in cohort 2 (30 mg/kg/day) was discontinued from the study on day 8 of treatment because of a significant elevation in the serum creatinine phosphokinase level (1,830 U/ml; normal range, 0 to 120 U/ml). This increase followed the injection of a dose of a cephalosporin antibiotic for the treatment of an acute infection. The child completed follow-up, and the event resolved with supportive care and the discontinuation of m-atovaquone. One child completed participation in the study; however, blood samples for pharmacokinetics studies were not obtained due to difficulty with venous access. One patient died 13 months after completion of the study. The cause of death was severe immunodeficiency and disseminated *Mycobacterium avium* infection.

There were no serious hematological, coagulation, or other chemistry toxicities during the study period. Among the study population in the various cohorts, there was a trend for a uniform decrease in hemoglobin levels. This effect was evident

in the cohorts consisting of children 3 to 24 months old (cohorts 3 and 4) but was evident only in those receiving the lower doses. Five patients had hemoglobin levels below 9.0 g/ml during the 28-day study period. Three of these patients received m-atovaquone at 10 mg/kg/day and two received the drug at 30 mg/kg/day. All five patients were younger than 10 months of age. The lowest hemoglobin concentrations were 7.9 g/ml in one infant and between 8.0 and 8.9 g/ml in the other four infants and occurred from days 9 to 24 of the study. No patient given 45 mg/kg/day had a decrease in hemoglobin levels. None of the children required a transfusion, and the drop in hemoglobin levels was not a dose-related phenomenon. No patient had a drug-related rash.

In three patients minimal levels of protein (1+ proteinuria) were detected by urinalysis during treatment. None of them was treatment related, and they occurred after the course of atovaquone had been completed for 2 to 10 days.

Pharmacokinetics. Sufficient data were available to complete pharmacokinetic studies for 24 patients. The pharmacokinetic data are summarized in Table 1. In each of the three age groups the administration of doses of 30 mg/kg/day was associated with higher values of C_{max}, C_{min}, $C_{avg,ss}$, AUC_{ss}, and volume of distribution (V) than when dosages of 10 mg/kg/day were given. Intergroup variations occurred with each parameter studied, as reflected in the standard deviations. A single cohort of four patients in the group from 3 to 24 months of age received a dosage of 45 mg/kg/day for 12 days because of the relatively low concentration in plasma obtained with the 10- and 30-mg/kg/day dosages. With the 45-mg/kg/day dosage the concentrations in plasma and AUC_{ss} were proportionately greater than those with the 30- and 10-mg/kg/day doses.

DISCUSSION

The m-atovaquone suspension at dosages as high as 45 mg/kg/day administered over a period of 12 days was well-tolerated by HIV-infected infants and children of the ages of 1 month to 12 years.

At the dosage of 30 mg/kg/day, the mean $C_{avg,ss}$ for the 1- to 3-month-old age group was 27.8 ± 5.8 μg/ml, for the 3- to 24-month-old age group the concentration was 9.9 ± 3.2 μg/ml, and for those patients from 2 to 12 years of age the mean m-atovaquone concentration was 37.1 ± 10.9 μg/ml. The reason that values were lower for those in the 3- to 24-month-old age group than for those in both older and younger age groups is not clear, although intergroup variation was broad. When the 3- to 24-month-old age group was given 45 mg/kg/day, a proportionate increase in $C_{avg,ss}$ to 15.4 ± 6.6 μg/ml occurred. On the basis of the results of clinical trials of atovaquone for therapeutic efficacy in the management of PCP, the $C_{avg,ss}$s resulting from treatment with 45 mg/kg/day in this study make the dosage adequate for therapeutic use in children. In the study of 133 adults with AIDS and mild and moderate PCP treated with atovaquone tablets (none was treated with the suspension), the outcome was successful for 96.7% of those with steady-state concentrations in plasma of 15 μg/ml or greater. Whether or not this concentration is needed for prophylactic use is not known. The ranges of values of C_{max} presented in Table 1 suggest that patients with the lowest peak concentrations after receiving the 30-mg/kg dose exceed the 15-μg/mL level in those between the ages of 2 and 12 years and those ages 1 to 3 months. For those ages 3 to 24 months, 45 mg/kg was required to achieve approximately this level. Because such levels are at the low ends of the ranges, monitoring of concentrations in blood in practice is not necessary if these dosages are used.

TABLE 1. Values of pharmacokinetic parameters

Age group and no. of patients	Dosage (mg/kg/day)	C_{max} (μg/ml)	C_{min} (μg/ml)	C_{max}/C_{min}	AUC_{ss} (μg · h/ml)	$C_{avg,ss}$ (μg/ml)	CL/F (ml/min)	V_z/F (liters)	λ_z (h^{-1})	$t_{1/2}$ (h)
1 to 3 mo										
$n = 1$	10	6.86	4.51	1.52	141.54	5.90	4.83	7.1	0.0407	17.04
$n = 4$	30	32.4 ± 7.0 (26.0–40.9)[a]	24.9 ± 6.7	1.3 ± 0.2	667.6 ± 139.5	27.8 ± 5.8 (21.6–33.9)	3.9 ± 0.8	25.5 ± 8.1	0.010 ± 0.003	75.17 ± 20.8
3 to 24 mo										
$n = 4$	10	7.4 ± 7.0 (2.3–17.6)	4.5 ± 4.1	1.8 ± 0.6	137.9 ± 122.0	5.7 ± 5.1 (1.4–12.8)	14.8 ± 10.8	35.8 ± 16.1	0.023 ± 0.010	34.44 ± 14.5
$n = 4$	30	12.0 ± 4.9 (6.5–17.4)	7.0 ± 2.1	1.7 ± 0.4	236.3 ± 77.1	9.8 ± 3.2 (6.1–12.7)	18.2 ± 6.2	59.2 ± 34.9	0.021 ± 0.009	36.1 ± 11.1
$n = 4$	45	23.3 ± 13.5 (11.9–42.0)	9.9 ± 7.5	1.9 ± 0.6	370 ± 158.7	15.4 ± 6.6 (9.5–23.7)	22.4 ± 9.8	112.5 ± 86.	0.014 ± 0.005	54.6 ± 18.3
2 to 12 yr										
$n = 4$	10	21.7 ± 6.8 (12.3–28.6)	14.2 ± 5.9	1.6 ± 0.3	402.3 ± 152.9	16.8 ± 6.4	8.4 ± 3.2	44.1 ± 18.3	0.012 ± 0.003	59.8 ± 12.8
$n = 3$	30	40.5 ± 12.2 (32.95–54.57)	34.0 ± 11.7	1.2 ± 0.1	590.5 ± 262.6	37.1 ± 10.9 (29.8–49.7)	11.4 ± 4.7	56.6 ± 27.4	0.013 ± 0.004	56.6 ± 17.2

[a] Values are median ± 1 standard deviation (ranges).

The two major clinical trials that have evaluated atovaquone for PCP therapy and that led to FDA approval for this purpose used the tablet formulation of atovaquone (7, 8). The tablet was replaced with the suspension because of the superior bioavailability of the latter (6). In immunocompromised infants and children with AIDS or cancer, a dosage of atovaquone tablets of 40 mg/kg/day or greater was estimated to achieve approximately the therapeutic concentration achieved in the studies with adults (15). In this study, as well as others, the concentrations in plasma reached with a dose in suspension is two to three times greater than that reached with the same dose in tablet formulation.

With the suspension, as with the older tablet formulation, the concentration in plasma is greater when the drug is administered with food. It must be emphasized that food increases the bioavailability of atovaquone 1.4-fold over that achieved in a fasting state (6) and that in the study reported here the drug was administered postprandially. The lack of linearity of the AUC values with dose has not been explained in this study, but it may be secondary to both enterohepatic circulation with a threshold needed for saturation and saturation of absorption at higher doses.

The only adverse effects so far reported with an increasing concentration of atovaquone in plasma is rash. With $C_{avg,ss}$ values greater than 20 μg/ml in adults, the incidence of rash was found to be significantly greater ($P < 0.05$) than that with $C_{avg,ss}$ values of 10 μg/ml and less (10). However, in the infants and children reported here, no rash was encountered, despite mean atovaquone $C_{avg,ss}$s of 27.8 and 37.1 μg/ml in two of the groups.

Because almost all AIDS patients who might be given atovaquone will also receive other medications, the impact of such drugs on the steady-state concentrations of atovaquone in plasma is of interest. In a study of adults with PCP treated with atovaquone tablets a comparison was made (17). By using stepwise multiple linear regression techniques, zidovudine, plasma protein binders, clofazimine, antacids, erythromycin, clotrimazole, nonsteroidal anti-inflammatory drugs, ketoconazole, hydroxyzine, megestrol, antiemetics, systemic steroids, and H_2 antagonists were not associated with a significant change ($P > 0.15$) in atovaquone concentrations. However fluconazole and prednisone were associated with significant increases in the atovaquone concentration (2.5 and 2.3 μg/ml, respectively). Rifampin and metoclopramide were associated with significant decreases in the plasma atovaquone concentration (7.8 and 7.2 μg/ml, respectively). Acetaminophen, acyclovir, opiates, antidiarrheal medication, cephalosporins, benzodiazepines, and laxatives were also associated with significant decreases of 3.4 μg/ml or less. Although this study lacked the precision of a prospective study, it provides the best information on drug interactions with atovaquone available. Because atovaquone is highly bound to plasma proteins, the potential for the displacement of other drugs that are highly bound to these proteins exists. However, atovaquone binding has not been affected by phenytoin, and the binding of phenytoin has not been affected by atovaquone in vitro.

In conclusion, m-atovaquone suspension at dosages of 10 to 45 mg/kg/day was found to be safe and well tolerated in infants and children when it was given over a period of 12 days. Dosages of 30 mg/kg/day were adequate to achieve a $C_{avg,ss}$ of greater than 15 μg/ml in children ages 1 to 3 months and 2 to 12 years, but a dosage of 45 mg/kg/day was needed to reach this concentration in children ages 3 to 24 months.

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