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CLINICAL PHARMACOKINETICS OF ALBENDAZOLE IN CHILDREN WITH NEUROCYSTICERCOSIS

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The pharmacokinetics of albendazole sulphoxide, the main metabolite of albendazole, were studied in eight children with brain cysticercosis. Albendazole was given as a single oral dose of 15 mg per kg body weight (Zentel suspension; Smith Kline & Beecham, Philadelphia, PA). Blood samples were taken during 24 h and analyzed by high performance liquid chromatography. Plasma levels showed great interindividual variation. Maximum plasma levels for albendazole sulphoxide ranged from 0.2–1.0 μg/mL. A double peak was found in four children. The half-life for albendazole sulphoxide was from 2.3–8.3 hours and mean residence time values were from 5.1–13.6 hours. These values are shorter than those found in adults. The results suggest that when treating children with neurocysticercosis, albendazole should be administered three times a day rather than twice daily as is currently done in Mexico.

Keywords: brain cysticercosis, pharmacokinetics, albendazole, children.

INTRODUCTION

Neurocysticercosis is the most important parasitic infection of the central nervous system (CNS) and it affects the populations of several countries. The clinical picture of neurocysticercosis is due to the localization of cysticercus or the inflammatory reaction around degenerating cysticercus. Consequently, the clinical course is highly polymorphic and it varies from asymptomatic to severe neurological disease.

In Mexico, as in other countries, the incidence of the disease in children is lower than in the adult population. This is probably due to the long incubation period, which varies from a few months to 30 years and averages 4.8 years [1]. However, this is an important disease in our country. A retrospective study performed in 89 Mexican children diagnosed with neurocysticercosis [2] indicated that the majority of cases of cerebral cysticercosis occurred in children aged 6–15 years with a great variability of clinical symptomatology. Symptoms were totally absent, moderate, or severe and ultimately fatal. In this study, the symptoms of initial cerebral invasion by the parasite were headache, fever, vomiting, and seizures. Cerebral edema was observed more frequently in children than in adults and was a common cause of intracranial hypertension.

Current treatment of neurocysticercosis includes the use of albendazole [3]. Considerable data are available on the clinical pharmacology of albendazole in adults [4,5] but information related to children is limited. The purpose of the present study was to evaluate the pharmacokinetics of albendazole in children with this disease.

MATERIALS AND METHODS

Eight children (five males and three females) with parenchymal neurocysticercosis were selected for the study and they remained hospitalized for three days. The children were between 21 months and 15 years of

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age with an average weight of 26.2 kg (range, 12–52.5 kg). The research protocol was approved by the Research and Ethics Comittee of the National Institute of Pediatrics, S.S. México, and informed written consent was obtained from the parents of each child.

After an overnight fast, an indwelling catheter was placed in an ulnar vein and a blank blood sample was obtained in an heparinized tube. Then a single oral dose of 15 mg albendazole per kg body weight (Zentel suspension, Smith Kline & Beecham, Philadelphia, PA) was administered together with 50 mL of milk with 5 mL of olive oil added to increase absorption. Food was withheld for 3 h after drug administration and then a standard lunch was provided. Consecutive venous blood samples were taken at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours. Total blood volume withdrawn from each child was 20 mL over 24 hours. Plasma was immediately separated by centrifugation, frozen and stored at −4°C until analysis, which was performed within one week of the samples being taken. Analysis of plasma samples for albendazole and albendazole sulphoxide was made using a high performance liquid chromatographic method as previously reported [6]. Briefly, to 1 mL of plasma was added 100 μL of methanolic solution of the internal standard mebendazole (5 μg/ml), then 2 mL of 0.01 M phosphate buffer (pH 7.4) were added, shaken on vortex for 30 seconds and extracted by passing through a Sep-Pak C_{18} cartridge (Watters Assoc.). After plasma had passed through the cartridge it was washed with 20 mL of phosphate buffer (pH 7.4) and 1 mL of methanol-water (20:80 v/v). The compounds were then eluted with 3 mL of methanol and evaporated to dryness under a nitrogen stream at 40°C. Aliquots were injected into the HPLC system (Beckman, USA), using an ODS C_{18} column (250 × 4.6 mm ID) and methanol-0.05 M phosphate buffer (pH 5.7) 70:30 (v/v) as mobile phase and a variable wavelength detector adjusted at 219 nm.

The lower limit of quantitation was 0.05 μg/mL for albendazole and 0.025 μg/mL for albendazole sulphoxide. Interday reproducibilities were 3.92% and 7.7% for albendazole and albendazole sulphoxide, respectively. There was no chromatographic interference from any endogenous compounds or from drugs used in clinical practice such as carbamazepine, dexamethasone, and phenytoin.

Pharmacokinetic analysis

Since albendazole appeared at undetectable concentrations in blood, all results refer to levels of albendazole sulphoxide. The parameters of the appropriate pharmacokinetic model were estimated using the PCNONLIN regression program [7]. The area under the plasma concentration-time curve (AUC) was determined using the trapezoidal rule. The area from the last point to infinity was determined by dividing the last plasma concentration by the terminal slope. Mean residence time was determined by the method of Yamaoka *et al.* [8] using the relationship AUMC/AUC. The apparent clearance (Cl_t/F) was calculated according to the equation: Cl_t/F = dose/AUC. Statistical comparisons between adults and children were made using a paired *t*-test. The level of significance was set at $p < 0.05$.

RESULTS

As has been previously reported in adults [9–13] the parent drug albendazole could not be detected at any sampling time in children. Only the main metabolite albendazole sulphoxide could be determined. Albendazole is metabolized rapidly in humans and cannot be detected after an oral dose. Plasma concentration-time profiles of albendazole sulphoxide in the eight children after the administration of the single oral dose of 15 mg ABZ per kg body weight are presented in Figure 1. The pharmacokinetic parameters are summarized in Table 1. Concentrations of albendazole sulphoxide showed a great intersubject variability. Maximum plasma concentrations (C_{max}) obtained were from 0.2–1.0 μg/mL and the time corresponding to the maximal plasma concentration (t_{max}) was from 2–4 h. The total area under the plasma concentration-time curve ranged from 1.7 to 9.3 μg · h/mL, and AUC corrected by the dose ranged from 4.8×10^{-6} h/mL to 19.8

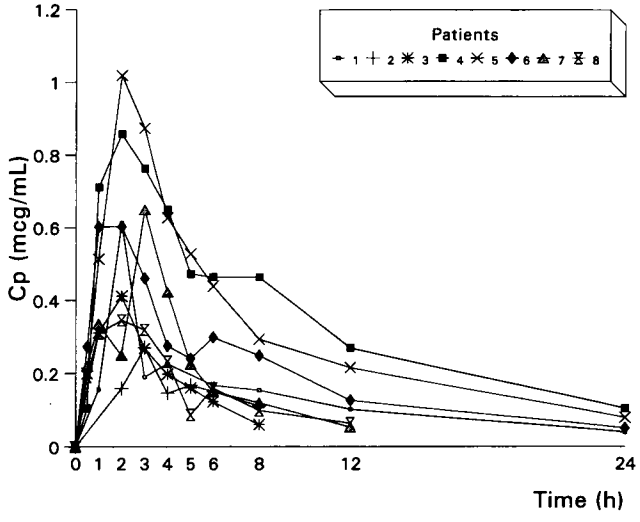

Fig. 1. Plasma concentration-time profiles of albendazole sulphoxide in eight children after single oral dose of albendazole of 15 mg per kg body weight.

Table 1. Pharmacokinetic parameters of albendazole sulphoxide in children.

Patient	Age (y)/ sex	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (μg · h/mL)	AUC/D (h/mL x10^{-6})	Cl_t/F (mL/h x 10^3)	MRT (h)
1	9/M	0.2	4	8.3	3.0	7.3	136.7	13.6
2	8/F	0.3	3	4.9	1.9	4.8	207.6	8.7
3	1.9/M	0.4	2	2.3	1.7	9.6	104.7	4.3
4	8/M	0.9	2	7.5	9.3	19.8	50.5	11.3
5	15/M	1.0	2	6.6	8.0	10.2	97.9	9.8
6	7/M	0.6	2	7.1	5.2	14.0	71.3	9.9
7	1.9/F	0.6	3	2.6	2.8	14.4	69.6	5.1
8	6/F	0.3	2	4.8	2.4	7.0	142.2	7.0
$\bar{X}$ =	7.1	0.5	2.5	5.5	4.3	10.9	110.1	8.7
SD =	4.2	0.3	0.8	2.2	2.9	4.9	50.9	3.1

AUC—area under curve; AUC/D—AUC corrected by the dose; Cl_t/F—apparent clearance; C_{max}—maximal plasma concentration; MRT—mean residence time; t_{max}—time corresponding to C_{max}; $t_{1/2}$—elimination half life.

x 10^{-6} h/mL. The Cl_t/F values ranged from 50.5 x 10^3 mL/h to 207.6 x 10^3 mL/h and mean residence time ranged from 4.3–13.6 hours. Values for the elimination constant (k_{el}) ranged from 0.1–0.3 h^{-1} and the corresponding elimination half-life ($t_{1/2}$) was from 2.3–8.3 hours.

DISCUSSION

Children have unique age-related characteristics that influence their drug disposition. Moreover, wide interpatient idiosyncracies can lead to diverse capacities that eliminate and respond to drugs. In recent years, neurocysticercosis has been found more frequently in children with different neurological disorders. In Mexico, common treatments for the disease include symptomatic medication such as analgesics, steroids, and antiepileptics; praziquantel and albendazole also offer a reasonable treatment for some types of neurocysticercosis [14,15]. At the time this article was written, the dosage regimen for albendazole is the same as in adults because there has been no information about the drug disposition in pediatric patients. Data on the disposition of albendazole in adults have shown that absorption is limited by its poor solubility in water [9], yet bioavailability is increased when it is administered with a fatty meal [13]. Extensive metabolism of albendazole sulphoxide and great intraindividual variability in plasma levels also have been found. The half-life values of the metabolite range from 6.3–15.4 hours [16]. It has been shown that albendazole undergoes high first-pass extraction and rapid and apparently complete metabolism to albendazole sulphoxide. It is probable that the cysticidal activity is due to the sulphoxide metabolite [9].

Our study showed albendazole is rapidly metabolized to its main metabolite albendazole sulphoxide in children as in adults. We also found a great interindividual variability in plasma levels. There was a 52.4% variation in maximum plasma levels of albendazole sulphoxide, which could be related to differences in absorption or to pharmacogenetic polymorphism for sulphoxidation of albendazole [9,10].

Four children exhibited a double peak although they ingested a suspension. Enterohepatic recirculation is an unlikely explanation considering that biliary concentrations of albendazole sulphoxide are very low [9]. Although it is difficult to postulate an explanation, a plausible reason could be that in suspension albendazole also has limited solubility in the gastrointestinal tract. This could cause precipitation and the need to be solubilized by bile for its absorption. Gastric emptying and peristalsis also should be taken into account.

Great interindividual variability was found in the AUC values even after correcting the AUC by the dose. When comparing our results obtained in children aged 6–15 years with those obtained in children aged 21 months we found that the mean half-life obtained and the mean residence times were shorter in children younger than 2 years of age. Clearance often increases with age and consequently half-life is shorter [18].

When comparing our results with those previously obtained in adults with the same disease and the same dose [16], we found that maximum plasma levels were reached faster in children, perhaps because of the pharmaceutical dosage form used. However, plasma levels were higher in adults than in children. Figure 2 shows the results obtained by comparing plasma levels of adults and children.

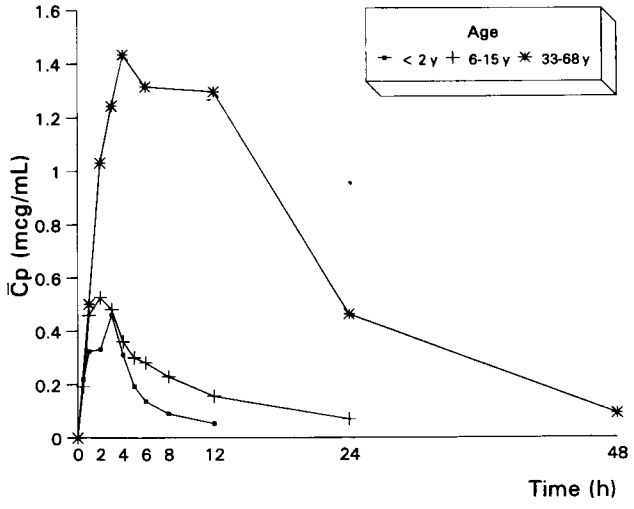

Fig. 2. Comparison of mean plasma levels of albendazole sulphoxide in patients of different ages after single oral dose of 15 mg albendazole per kg body weight.

Length of therapy and dose of albendazole for children have been established based on results obtained in adults, and this recommended dose in Mexico is 7.5 mg per kg body weight twice a day. Despite dose adjustments by body weight, plasma levels in children were lower than in adults in our study. This proves that young children require a larger dose by kilogram of body weight than adults.

Our results indicate that dose adjustment for albendazole should be made on the basis of surface area instead body weight. Body surface area has been found to be a better correlate of dosing requirements than body weight in children. The half-life indicates that albendazole should be administered three times a day instead of twice a day as currently used in our country. However, no clear information regarding the relation between plasma concentrations and therapeutic effect has been obtained and this requires further study.

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