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Brief Report

Pharmacokinetic Comparison of Two Albendazole Dosage Regimens in Patients with Neurocysticercosis

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Summary: To evaluate two different dosage regimens for albendazole (7.5 mg/kg twice a day or 5.0 mg/kg three times a day), a study was performed in 10 patients with a diagnosis of parenchymal brain cysticercosis. Each patient received both regimens sequentially according to a randomized, crossover design. Blood and urine samples were taken once the drug steady state had been reached. Plasma levels of albendazole sulfoxide at steady state were determined using a HPLC method. In spite of a great intersubject variability observed with both regimens in the area under the curve (AUC) and in the minimum steady-state plasma concentration ($C_{p\ min\ ss}$), no statistically significant differences were found in these parameters. We suggest that a regimen of 7.5 mg/kg every 12 h can favorably replace the currently used regimen of 5 mg/kg every 8 h. **Key Words:** Neurocysticercosis—Dosage regimen—Albendazole.

Neurocysticercosis (NCC) is a common neurological disorder that affects communities living in conditions of poor hygiene. Several years ago, there was no specific pharmacologic treatment for NCC (1); surgery and steroids were the only medical alternatives. Albendazole, a benzimidazole, is an antiparasitic drug with intense cysticidal properties that has recently proved its efficacy in patients with parenchymal brain cysticercosis (2); however, dosage intervals have been established on empirical grounds; schemes of therapy have been designed after toxicologic studies (3–5). In a previous study, we observed that after the administration of a single oral dose of 15 mg/kg of albendazole, plasma levels of albendazole

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sulfoxide at steady state were quite variable, and the average half-life of albendazole sulfoxide in patients with NCC was 11 h (6). Based on these findings, we suggested the drug could be administered twice a day. The present study was designed to determine, by measurement of drug plasma levels, the best schedule for therapeutic administration of albendazole.

METHODS

Ten patients with a diagnosis of parenchymal NCC confirmed by imaging studies, either computed tomography (CT) or magnetic resonance imaging (MRI), and by immunological tests, were included and randomly separated into two groups of five subjects each; five were male and five were female, with an age range from 18 to 58 years (mean of 33 years). The patients remained hospitalized during the study. Hepatic, renal, and biochemical profiles in the blood were within normal limits. Steroids were withdrawn at least 8 days before the beginning of the trial. Albendazole (Zentel, 200 mg tablets) at 15 mg/kg/day was given to patients in group I in three doses (5 mg every 8 h, t.i.d.) for the first 7 days of treatment; from days 8 to 13, the same 15 mg/kg/day was continued but divided into two doses (7.5 mg every 12 h, b.i.d.).

Blood samples at steady state were taken on day 5 at 0800, 1600, and 2400 h (just before the next dose of albendazole) and on days 6 and 7 at 0800, 1000, 1200, 1400, and 1600 h. On day 7, urine was collected during an 8 h interval. On day 8, the dosage regimen was changed to 7.5 mg/kg every 12 h and blood samples were taken after reaching a new steady state. On day 11, blood samples were taken at 0800 and 2000 h, also before the next dose of albendazole, and on days 12 and 13 it was taken at 0800, 1000, 1200, 1400, 1600, and 2000 h. On day 13, a urine sample was collected during a 12 h interval.

The same doses of albendazole (15 mg/kg/day) were given to patients from group II, but in contrast with group I, the regimen of administration was every 12 h (0800 and 2000 h) from days 1 to 7 and every 8 h (0800, 1600, and 2400 h) from days 8 to 13. Blood and urine samples were taken with the same schedule as that followed for patients from group I. The dosage schedule and sampling times are shown in Table 1.

Albendazole sulfoxide in plasma and urine was measured in all samples by high-pressure liquid chromatography (HPLC) as previously described (7); every sample was analyzed at least twice.

Data Analysis

The area under the curve at steady state (AUC_{ss}) was calculated by the trapezoidal rule; the total clearance (Cl_t) divided by the extent of bioavailability (aparent clearance, $Cl_{t/F}$) was calculated as $Cl_{t/F}$ = dose/AUC; the renal clearance of sulfoxide was determined using the formula $Cl_r = U/AUC$, were Cl_r = renal clearance and U is the amount of sulfoxide excreted in the urine during a dosage interval, U/AUC. Student's "t" test was used for statistical analysis.

TABLE 1. *Dosage schedule and blood sampling times used in the study*

Group I:	Dose: 5 mg/kg, every 8 h				Dose: 7.5 mg/kg, every 12 h			
Days of treatment	1–4	5	6	7	8–10	11	12	13
Sampling time		0800 h	0800 h	0800 h		0800 h	0800 h	0800 h
		1600 h	1000 h	1000 h		2000 h	1000 h	1000 h
		2400 h	1200 h	1200 h			1200 h	1200 h
			1400 h	1400 h			1400 h	1400 h
			1600 h	1600 h			1600 h	1600 h
							2000 h	2000 h
Group II:	Dose: 7.5 mg/kg, every 12 h				Dose: 5 mg/kg, every 8 h			
Days of treatment	1–4	5	6	7	8–10	11	12	13
Sampling time		0800 h	0800 h	0800 h		0800 h	0800 h	0800 h
		2000 h	1000 h	1000 h		1600 h	1000 h	1000 h
			1200 h	1200 h		2400 h	1200 h	1200 h
			1400 h	1400 h			1400 h	1400 h
			1600 h	1600 h			1600 h	1600 h
			2000 h	2000 h				

RESULTS

In humans, albendazole is extensively metabolized following oral administration (8–10). Similarly to previous studies, in the present study albendazole could not be detected in plasma after different doses; only its main metabolite, albendazole sulfoxide, was measured.

The minimum mean plasma concentrations at steady state ($\overline{C}_{p\ min\ ss}$) after the administration of albendazole with both dosage regimens are shown in Fig. 1. There was a large intra- and interindividual variability in steady-state concentrations of albendazole sulfoxide ranging from 0.27 to 2.23 μg/ml when albendazole was administered two times a day and 0.16 to 1.12 μg/ml when administered three times a day. Following t.i.d. dosing of 5 mg/kg, the $\overline{AUC}$ ranged from 1.08 to 11.52 μg/ml/h. In contrast, when albendazole was administered b.i.d. at a dosage of 7.5 mg/kg, the $\overline{AUC}$ ranged from 4.35 to 16.91 μg/ml/h (Table 2). In eight patients from both groups (patients 1, 3, 4, 5, 7, 8, 9, and 10), the $\overline{AUC}$ was increased with this schedule of drug administration but no important changes were observed in patients 2 and 6.

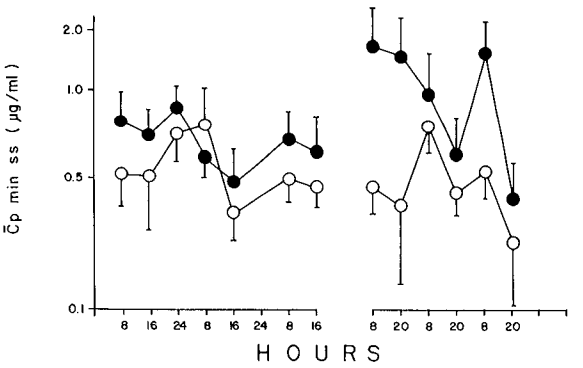

FIG. 1. Minimum mean plasma concentration at steady state, from group I (○—○) and group II (●—●). Each point and vertical bar represents the mean ± SEM of five patients.

TABLE 2. *Pharmacokinetics parameters of albendazole sulfoxide*

Patient	$\overline{AUC}$ (μg/ml/h), T = 8 h/T = 12 h	$\overline{AUC}$/D × 10^{-5}, T = 8 h/T = 12 h	$\overline{Cl}_{t/F}$ (L/kg/h), T = 8 h/T = 12 h	$\overline{Cl}_r$ (L/kg/h), T = 8 h/T = 12 h	U (mg), T = 8 h/T = 12 h	$C_{p\ máx\ ss}$ (μg/ml), T = 8 h/T = 12 h	$t_{máx\ ss}$ (h), T = 8 h/T = 12 h
1	5.23/8.63	1.31/1.44	0.94/0.85	0.03/0.02	13.81/15.56	0.72/0.68	2/2
2	7.39/4.44	1.85/1.11	1.06/1.77	0.04/0.04	13.32/9.02	1.26/0.50	4/2
3	1.48/5.14	0.37/0.86	3.60/1.56	0.03/0.02	2.98/2.16	0.20/0.54	2/4
4	4.12/6.84	1.37/1.37	1.10/1.10	0.02/0.01	5.70/5.60	0.59/0.73	2/2
5	5.36/7.72	2.68/1.93	0.68/0.94	0.01/0.02	3.33/7.31	0.76/0.87	2/2
6	11.52/11.25	2.88/2.81	0.62/0.63	0.02/0.01	10.93/7.18	1.94/1.08	6/4
7	6.36/16.91	2.12/3.38	0.86/0.54	0.01/0.01	2.54/1.52	0.99/1.81	2/2
8	4.31/9.73	2.16/2.43	1.09/0.97	0.02/0.01	3.84/4.02	0.89/1.45	2/2
9	1.08/4.35	0.36/1.09	5.56/1.84	0.02/0.02	1.06/3.30	0.18/0.59	2/4
10	2.32/5.59	1.16/1.40	1.72/1.43	0.01/0.01	2.18/2.77	0.39/0.68	2/4

Group I: patients 1–5; group II: patients 6–10.

$\overline{AUC}$: mean area under the curve; $\overline{AUC}$/D: mean area under the curve/dose; $\overline{Cl}_t$/F: mean apparent clearance; $\overline{Cl}_r$: mean renal clearance; U: total amount in urine; $C_{p\ máx\ ss}$: maximum plasma concentration at steady state; $t_{máx\ ss}$: maximum time at steady state to reach $C_{p\ máx\ ss}$.

Renal and total clearances of albendazole sulfoxide ranged from 0.01 to 0.04 and 0.54 to 5.56 L/kg/h, respectively (Table 2). Values for the renal clearance are in close agreement with those previously determined (9). The drug was well tolerated at both dosage regimens in all patients.

DISCUSSION

As expected, $C_{p\ min\ ss}$ values were lower after the dosage of 5 mg/kg than after the 7.5 mg/kg dose; however, fluctuations were large with both regimens. There were no statistically significant differences in $C_{p\ min\ ss}$ between regimens. Although not significant, it was noted that albendazole sulfoxide levels were higher in patients from group II than in patients from group I with both schedules of drug administration.

Our results showed a great interindividual variability in AUC. This variability has also been found in earlier studies (6,9,10). No significant differences were found by the Student's "*t*" test when correcting the $\overline{AUC}$ by the dose ($p < 0.05$). The results of this study showed no differences in the extent of absorption between the two dosage regimens. Also, no differences were found when the drug was given first every 8 h and then every 12 h or vice versa. Our results for the AUC at steady state were similar to those obtained after a single oral dose (6). Patients had breakfast 1 h after intake of the first dose; by correcting the AUC values obtained by Lange (10) after the administration of a 400 mg oral dose, our results are similar to those obtained after administration of a single oral dose together with breakfast.

As expected, the maximum plasma concentration at steady state ($C_{p\ máx\ ss}$) was higher for the b.i.d. dosage regimen; however, the maximum time at steady state to reach $C_{p\ máx\ ss}$ ($t_{máx\ ss}$) was similar with both regimens (Table 2); $C_{p\ máx\ ss}$ showed a great interindividual variability that could be due to differences in drug absorption. $\overline{Cl}_r$ values were similar for both dosage regimens and similar to those reported by Marriner et al. (9). Patients 3 and 9 showed greater total clearance values after albendazole administration three times a day. These data would suggest an increased metabolic rate; however, individual absorption was unknown, and the great inter- and intraindividual variability of albendazole absorption in the gastrointestinal tract makes a further statement impossible.

The data suggest that a 7.5 mg/kg b.i.d. dosage regimen produces slightly higher levels and can be used instead of the usual 5.0 mg/kg t.i.d. regimen. We do not suggest reducing the currently used dosage of 15 mg/kg/day, which has proved to be highly effective (11,12), but our results support the idea of a simplified administration twice a day. The modified regimen is expected to decrease the number of prescriptions and costs of drug administration and increase patient compliance.

REFERENCES

1. Escobedo F, Sotelo J, Penagos P, Rodríguez J, Del Brutto OH. Albendazole therapy for human neurocysticercosis, a controlled study with computerized tomography and magnetic resonance. *Acta Leiden* 1989;57:247–54.
2. Escobedo F, Penagos P, Rodríguez J, Sotelo J. Albendazole therapy for neurocysticercosis. *Arch Intern Med* 1987;147:738–41.

3. Saimot AG, Cremieux AC, Hay JM, et al. Albendazole as a potential treatment for human hydatidosis. *Lancet* 1983;2:652–6.
4. Sotelo J. Cysticercosis. In: Vinken PJ, Bruyn GW, Klawaus HL, eds. *Handbook of clinical neurology,* Vol. 52. Amsterdam: Elsevier Science Publishers B.V., 1988:529–34.
5. Sotelo J, Penagos P, Escobedo F, Del Brutto OH. Short course of albendazole therapy for neurocysticercosis. *Arch Neurol* 1988;45:1130–3.
6. Jung H, Hurtado M, Sánchez M, Medina MT, Sotelo J. Clinical pharmacokinetics of albendazole in patients with brain cysticercosis. *J Clin Pharmacol* 1992;32:28–31.
7. Hurtado M, Medina MT, Sotelo J, Jung H. Sensitive high-performance liquid chromatographic assay for albendazole and its main metabolite albendazole sulphoxide in plasma and cerebrospinal fluid. *J Chromatogr* 1989;494:403–7.
8. Penicaut B, Maugein PH, Maisonneuve H, Rossignol JF. Pharmacocinétique et métabolisme urinaire de l'albendazole chez l'homme. *Bull Soc Pathol Exp* 1983;76:698–708.
9. Marriner SE, Morris DL, Dickson B, Bogan JA. Pharmacokinetics of albendazole in man. *Eur J Clin Pharmacol* 1986;30:705–8.
10. Lange H, Eggers R, Bircher J. Increased systemic availability of albendazole when taken with a fatty meal. *Eur J Clin Pharmacol* 1988;34:315–7.
11. Del Brutto OH, Sotelo J. Albendazole therapy for subarachnoid and ventricular cysticercosis. *J Neurosurg* 1990;72:816–7.
12. Sotelo J, Del Brutto OH, Penagos P, et al. Comparison of therapeutic regimen of anticysticercal drugs for parenchymal brain cysticercosis. *J Neurol* 1990;237:69–72.