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# Pharmacokinetic Study of Praziquantel Administered Alone and in Combination with Cimetidine in a Single-Day Therapeutic Regimen

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**A brief therapeutic regimen of praziquantel, reduced to a single day, has been effective for treatment of neurocysticercosis. To study its pharmacokinetic characteristics, levels of praziquantel in plasma were determined for eight healthy volunteers after the administration of three oral doses of 25 mg/kg of body weight given at 2-h intervals, alone and with the simultaneous administration of cimetidine. Each volunteer received both regimens in a randomized crossover design. Blood samples were taken during a period of 12 h, and praziquantel concentration was measured by high-performance liquid chromatography. Levels of praziquantel in plasma remained above 300 ng/ml during a period of 12 h; they increased 100% when cimetidine was jointly administered. Compared with other regimens, the high levels obtained and the longer duration of action seem to be advantageous in prolonging the exposure of the parasites to the drug and support previous clinical experience showing that the treatment of neurocysticercosis with praziquantel can be reduced from 2 weeks to 1 day with the drug still retaining its cysticidal properties. Moreover, simultaneous administration of praziquantel and cimetidine could improve further the efficacy of the single-day therapy for cysticercosis and other parasitic diseases, such as schistosomiasis.**

Therapy for parenchymal brain cysticercosis includes two drugs, praziquantel and albendazole (20, 22). Although both are effective, albendazole has been preferred as the drug of first choice mainly due to three features: (i) the current length of treatment with albendazole (1 week) is shorter than that with praziquantel (2 weeks) (19); (ii) albendazole can be used jointly with steroids for concurrent therapy of inflammation (11), whereas simultaneous use of praziquantel and steroids greatly diminishes the levels of the former in plasma (21); and (iii) albendazole is less expensive than praziquantel. To address the above shortcomings of praziquantel, we designed a new schedule for therapy of neurocysticercosis based on the pharmacokinetic characteristics of praziquantel in humans (13), in whom a sharp increase of levels in plasma is achieved 2 h after a single oral administration, falling steadily afterwards with a mean terminal half-life ($t_{1/2}$) of 2.5 h (13). We hypothesized that, if the peak levels of praziquantel in plasma are obtained 2 h after its administration and if this peak declines quickly (2, 13), we could maintain a high concentration of the drug for a long period by giving the whole daily dose in three administrations separated by 2 h each. In this way, we expected to achieve high levels of praziquantel in plasma during the period and therefore to increase the time of exposure of the parasite to cysticidal doses of the drug (2); a preliminary clinical study of a single-day therapy showed a high rate of elimination of parenchymal brain cysticerci (3). To provide pharmacological support for this novel scheme of treatment, in the present study we measured the pharmacokinetic characteristics of praziquantel under a single-day therapeutic regimen. Additionally, as recent reports have described an increase of praziquantel levels in plasma when cimetidine is simultaneously administered (4, 5, 16), we also measured in the same subjects the levels of praziquantel in plasma when administered jointly with cimetidine.

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## MATERIALS AND METHODS

The study was performed with eight healthy male volunteers; mean age was 26 years (range, 23 to 38 years). Each subject underwent physical examination, complete blood count, blood chemistry profile, and urine analysis. The volunteers signed an informed consent after detailed explanation of the purpose, protocol, and risks of the study. The protocol was approved by the local ethics committee. Volunteers were separated into two groups of four subjects each; group I received three oral doses of 25 mg of praziquantel per kg of body weight given at 2-h intervals (at 8 a.m., 10 a.m., and 12 p.m.) as previously reported (3) while group II received the same dosage regimen of praziquantel plus 400 mg of cimetidine 1 h before each praziquantel dose. The schedule for cimetidine administration was chosen on the basis of its peak concentration in plasma being attained within 1 to 2 h and its half-time for elimination being 2 to 3 h (10). Eight days later, the study was repeated in a crossover design. Subjects did not take any other medication or alcohol for at least 15 days prior to the study. Each subject fasted overnight prior to the experiment; fasting was continued for the first 4 h after the first dose of praziquantel, and then a light meal (two chicken sandwiches, one ration of fruit cocktail, and 200 ml of orange juice) was administered. Blood samples were obtained through an indwelling catheter, placed in the antecubital vein, prior to drug administration and at 1, 1.5, 2, 3, 3.5, 4, 5, 5.5, 6, 8, 10, and 12 h after the first dose of praziquantel. Plasma was separated by centrifugation and stored at −4°C until analysis.

Analysis of praziquantel in plasma was performed by a high-performance liquid chromatographic method (8) as follows. To 1 ml of plasma, 100 μl of a solution containing the 2-cycloheptyl analog of praziquantel (10 μg/ml) plus 1 ml of 0.2 M sodium hydroxide was added, shaken on a vortex mixer for 15 s, and extracted by passage through a Sep Pack $C_{18}$ cartridge. The sample was washed with 20 ml of phosphate buffer. The compounds were then eluted twice with 3 ml of ethyl acetate-diisopropyl ether (70:30 [vol/vol]). The two fractions were evaporated to dryness under a nitrogen stream at 25°C. The residue was dissolved in 100 μl of the mobile phase of acetonitrile-water (45:55). Aliquots of 20 μl were injected into a Hewlett-Packard high-performance liquid chromatography system with a Lichrospher 100 RP-18 column (250 by 4 mm in inside diameter; particle size, 5 μm) with UV detection at 217 nm. A linear relationship between peak height ratio and praziquantel was obtained in the range of 0.062 to 8 μg/ml. Sensitivity of the assay under these conditions was 0.062 μg/ml. The maximum within-day coefficient of variation was 6.58% at 0.125 μg/ml, and the mean value

TABLE 1. Praziquantel levels in CSF and cysticercus fluid[a]

| Time (h) | Plasma level[b] | CSF level[b] | Cysticercus content[b] | Cysticidal effect[d] |
|---|---|---|---|---|
| 1 | 317/384 | 48/52 | 5/5 | −/− |
| 2 | 229/501 | 34/75 | 3/8 | −/− |
| 3 | 388/809 | 58/121 | 6/12 | −/+ |
| 4 | 430/968 | 64/145 | 7/15 | −/+ |
| 5 | 1,819/3,705 | 273/556 | 27/56 | +/+ |
| 6 | 1,561/2,445 | 234/367 | 23/37 | +/+ |
| 7 | 1,092/1,840[c] | 164/276 | 16/28 | +/+ |
| 8 | 611/1,272 | 92/191 | 9/19 | −/+ |
| 9 | 560/990[c] | 84/149 | 8/15 | −/+ |
| 10 | 458/695 | 69/104 | 7/10 | −/+ |
| 11 | 413/533[c] | 62/80 | 6/8 | −/− |
| 12 | 403/415 | 60/62 | 6/6 | −/− |

[a] Calculated from levels in plasma obtained when praziquantel was administered alone or with cimetidine in a single-day therapeutic regimen. The mathematical model assumes that the permeable fraction in CSF is 15% of levels in plasma, that the drug content in cysticercus fluid is 10% of levels in CSF, and that the minimal effective cysticidal concentration of praziquantel in the cystic fluid is 10 ng/ml.

[b] Values represent ratios of mean levels (in nanograms per milliliter) of praziquantel ($n = 8$) when given alone to those when given with cimetidine.

[c] Mean levels were derived by pharmacokinetic calculations.

[d] − and + indicate absence and presence of cysticidal effect, respectively, for praziquantel given alone (first symbol) and with cimetidine (second symbol).

was 4.6% in the concentration range of 0.062 to 8 μg/ml. The maximum interday reproducibility was 7.77% at 0.250 μg/ml, and the mean was 7.10% in the range of 0.125 to 8 μg/ml. There was no chromatographic interference from endogenous compounds or cimetidine. The recovery ranged between 95 and 100%.

Maximum concentration in plasma after each dose of praziquantel and time to attainment of maximum concentration ($t_{max}$) in both conditions, with and without cimetidine, were determined directly from the individual plasma concentration profiles. The terminal first-order rate constant ($k_{el}$) was estimated with the nonlinear regression fitting program PCNONLIN (17). The corresponding half-lives ($t_{1/2}$) were calculated as $0.693/k_{el}$. The area under the plasma concentration-time curve ($AUC_{0-t}$) was calculated by linear trapezoidal rule and was determined after each dose. The statistical analysis was performed with the SigmaStat program (Statistical Software version 1.0, 1992 to 1994; Jandel Corporation) by using the analysis of variance test and the Wilcoxon signed rank test. Differences were considered statistically significant with $P < 0.05$. Through the values obtained in plasma, a mathematical model was used to calculate praziquantel contents in cerebrospinal fluid (CSF) and in cysticercus fluid. Praziquantel crosses the subarachnoideal space by passive diffusion, with ranges in CSF being between 15 and 24% of drug concentration in plasma (12). Considering the lower value (15%) and assuming that an effective cysticidal concentration of 100 ng/ml in CSF must be attained and that cysts must be exposed to the drug for at least 1 h in order to be effectively destroyed (1, 18), calculations were made in order to determine the levels of the drug in CSF and the duration of cystocidal doses of praziquantel within the subarachnoid space (Table 1).

## RESULTS

For administration alone, the mean plasma profile versus time after the administration of three doses of 25 mg/kg of praziquantel each 2 h is illustrated in Fig. 1. A large interindividual variability was found. Mean levels of praziquantel in plasma 1 h after the first, second, and third doses were 317, 388, and 1,819 ng/ml, respectively (Fig. 1). When cimetidine was administered together with praziquantel, mean maximum levels of the latter in plasma 1 h after the first, second, and third doses were 348, 809, and 3,705 ng/ml, respectively. The concentration of praziquantel in plasma increased about 100% when given with cimetidine in comparison to the levels achieved when given alone ($P < 0.05$) (Fig. 1). All volunteers tolerated both treatments; side effects were mild and mainly included slight dizziness and headache. Pharmacokinetic parameters with and without cimetidine are shown in Table 2. $t_{1/2}$ ranged between 1.2 and 2.7 h when praziquantel was administered alone and 1.8 to 2.4 h when it was administered with

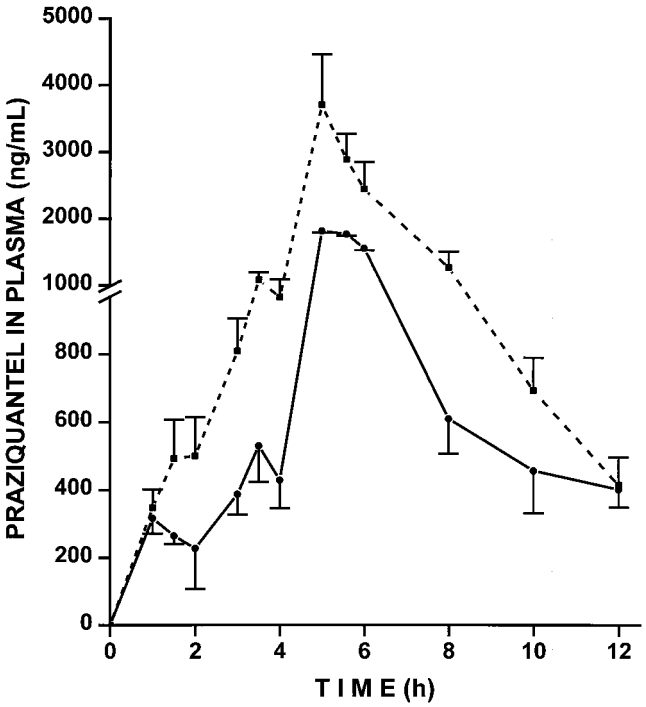


FIG. 1. Mean levels of praziquantel in plasma after three oral doses of 25 mg/kg administered at 2-h intervals, when praziquantel was given alone (solid line) and when 400 mg of cimetidine was given 1 h before each dose of praziquantel (dashed line).

cimetidine. The approximate duration of cysticidal concentrations in plasma in a single-day scheme was more than 12 h when praziquantel was administered with or without cimetidine; in CSF, cysticidal concentrations lasted approximately 3 h when praziquantel was given alone and 8 h when it was given with cimetidine ($P < 0.05$) (Table 1). These results are in contrast with the pharmacokinetics of praziquantel when administered in a single dose of 50 mg/kg, for which cysticidal concentrations lasted less than 2 h in plasma and only a few minutes in CSF (2, 12, 13).

TABLE 2. Pharmacokinetic parameters of praziquantel with and without cimetidine

| Subject no. | Value for drug: | | | | | |
|---|---|---|---|---|---|---|
| | Praziquantel | | | Praziquantel plus cimetidine | | |
| | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) | $AUC_{0-t}$ (ng/ml/h) | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) | $AUC_{0-t}$ (ng/ml/h) |
| 1 | 0.41 | 1.7 | 5,870 | 0.39 | 1.8 | 15,770 |
| 2 | 0.25 | 2.7 | 11,930 | 0.28 | 2.4 | 21,690 |
| 3 | 0.39 | 1.7 | 7,850 | 0.38 | 1.8 | 15,770 |
| 4 | 0.41 | 1.7 | 2,720 | 0.30 | 2.3 | 8,340 |
| 5 | 0.32 | 2.1 | 8,620 | 0.29 | 2.4 | 8,950 |
| 6 | 0.38 | 1.8 | 7,490 | 0.36 | 1.9 | 10,370 |
| 7 | 0.57 | 1.2 | 7,410 | 0.31 | 2.2 | 16,180 |
| 8 | 0.39 | 1.8 | 12,340 | 0.29 | 2.4 | 16,580 |
| Mean | 0.39 | 1.8 | 7,410 | 0.33 | 2.2 | 14,210[a] |
| SD | 0.09 | 0.4 | 2,780 | 0.04 | 0.3 | 4,590 |

[a] $P < 0.05$ compared with praziquantel group.

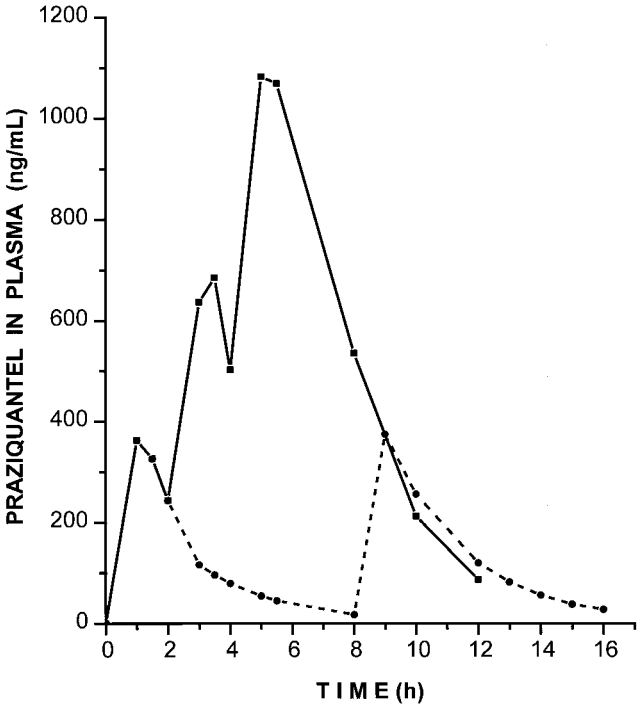


FIG. 2. Levels of praziquantel in plasma of volunteer 8 after the administration of three doses of 25 mg/kg every 2 h. Dashed lines correspond to simulated pharmacokinetic data for a single dose of 25 mg/kg being administered every 8 h as in the usual regimen.

## DISCUSSION

Pharmacokinetics of praziquantel when administered in a single dose show disappearance of the drug in plasma within 3 h (2, 13). In contrast, our results showed that with the schedule of three doses given at 2-h intervals high levels in plasma are maintained for several hours. Instead of a fast drop of the drug 2 h after the initial dose, a continuous rise was obtained with the subsequent doses; levels in plasma increased from 317 to 388 ng/ml 1 h after the second dose, after the third dose a further increase to 1,819 ng/ml was achieved, and even at 12 h levels in plasma remained above 400 ng/ml (Fig. 1). Considering that the usual dosage of praziquantel in other regimens is every 8 h, we made simulations based on the estimated elimination half-life for each volunteer. These simulations showed that with the three-times-daily dosage regimen, levels in plasma at 8 h would be in the range of 30 to 60 ng/ml, far below cysticidal range. For instance, the data obtained from volunteer 8 after the scheme used in this study and the simulated data if the volunteer received a single oral dose of 25 mg/kg every 8 h as in the usual regimen (Fig. 2) show that, by decreasing the time interval of praziquantel administration, higher levels are obtained for a prolonged time, thus preventing the drop in concentrations in plasma that occurs with the currently used therapeutic schedule.

The elevation of levels of praziquantel in plasma after the third dose was higher than expected; this could be due either to the fact that after this dose the volunteers received a standard lunch, influencing the bioavailability of praziquantel, as reported by Mandour et al. who found higher concentrations of praziquantel in plasma when given with meals (15) or to the possibility that the clearance of the drug could be saturated under the proposed dosage regimen by Michaelis-Menten kinetics (14). However, these speculations need further study.

Many patients with neurocysticercosis cannot afford the cost of praziquantel, or the duration of conventional therapy is not properly followed. In others, the fear of secondary reactions prompts the physician to administer steroids simultaneously with praziquantel therapy with the possibility of a diminution of its cysticidal effectiveness (21). The therapeutic scheme proposed in this study offers several advantages: the cost and total dose of therapy are reduced 10-fold in comparison with the currently used scheme, and thus it becomes available to the economically underprivileged, who constitute the great majority of cysticercosis patients. The duration of therapy is reduced from 15 days to a single day and allows supervision for strict compliance with the therapeutic schedule at the outpatient clinic, obviating, in most cases, the need for hospitalization (22). The rational therapy for both features of neurocysticercosis, the parasitic infection and its ensuing inflammation, can be sequentially covered without the simultaneous use of both therapies. The cysticidal treatment is given first to induce cyst destruction; a few hours later, steroids such as dexamethasone can be administered to treat the inflammatory reaction triggered by the acute destruction of the parasites (6). With this sequence, the therapeutic actions of praziquantel and dexamethasone are separated in order to avoid pharmacological interference with one another (9, 21).

A single-day treatment with praziquantel has been successfully used for another parasitic disease of the brain, cerebral schistosomiasis (23). Occasionally, in asymptomatic subjects who receive a single dose of praziquantel as intestinal antihelminthic therapy, neurological symptoms develop as a manifestation of acute destruction of dormant brain cysticerci (7). These anecdotal cases support the idea that a brief therapeutic course, designed in accordance with the pharmacokinetic properties of praziquantel, can accomplish the cysticidal effects achieved with longer courses.

The present data, together with the observations of a previous clinical study (3), suggest that the proposed dosage is an adequate alternative to the currently used regimen that would lead to a lowering of total dose, time, and costs of cysticercosis treatment. Also, although further clinical studies are required, our results suggest that joint administration of praziquantel and cimetidine (4, 16) could lead to a further improvement of the effectiveness of praziquantel therapy administered in a single day.

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