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Pharmacokinetic investigation of albendazole and praziquantel in Thai children infected with *Giardia intestinalis*

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The pharmacokinetics of albendazole/albendazole sulphoxide and praziquantel were investigated in Thai children with *Giardia* infection. Twenty school-age children were randomly allocated to receive either a single oral dose of albendazole (400 mg/child) or the same dose of albendazole given concurrently with a single oral dose of praziquantel (20 mg/kg). The concentrations of albendazole/albendazole sulphoxide and praziquantel in plasma samples, collected at intervals in the first 24 h post-treatment, were then quantified using HPLC with ultra-violet detection. No significant pharmacokinetic interaction between the albendazole and praziquantel was demonstrated. For albendazole sulphoxide, the active metabolite of albendazole, there was marked inter-individual variation in the maximum plasma concentration and the 'area under the curve'. The pharmacokinetics of albendazole sulphoxide were similar whether albendazole was given alone or in combination with praziquantel.

Albendazole is a potent, broad-spectrum, benzimidazole-carbamate anthelmintic that is effective against several nematodes and cestodes (Horton, 2000). It has also been shown to inhibit the growth of *Giardia intestinalis* trophozoites *in vitro*, the parasite's microtubule-based cytoskeleton and microtubule-associated proteins being the probable targets (Reynoldson *et al.*, 1992). In the treatment of *Giardia* infection in children, Hall and Nahar (1993) found that 5 days of treatment with albendazole, at 400 mg/day, was as effective as metronidazole, leading to a cure 'rate' of 97%. Similarly, when Pungpak *et al.* (1996) treated *Giardia* infections with albendazole daily for 7 days, they cured 96% of their paediatric patients and 100% of the adults. Although 5- to 7-day courses of albendazole therefore appear very effective in the treatment of giardiasis, it seems likely that drug compliance would be a problem if such long regimens were used routinely, especially among children.

Praziquantel is a pyrazino-isoquinoline derivative with anthelmintic activity against both adult and larval cestodes and trematodes. It causes spastic paralysis of the parasite's musculature and vacuolation and degeneration of its integument (Tracy and Webster, 1996). The drug is effective in a single oral dose, and appears very safe, with no serious toxicity reported.

When Homeida *et al.* (1994) gave albendazole and praziquantel concomitantly

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to adult volunteers, they found that the 'area under the curve' — of the plot of plasma concentration *v.* time ($AUC_{0-\infty}$) — for the active metabolite, albendazole sulphoxide, was 4.5-fold higher than when the same dose of albendazole was given alone, without any apparent enhancement of toxicity. This synergistic effect should be beneficial for the treatment of a number of tissue parasites. Although, when given alone, praziquantel was found to cause unexpected and statistically significant reductions in the prevalences of *Entamoeba histolytica* and *G. intestinalis* infection (Flisser *et al.*, 1995), the benefit of using the drug in the treatment of such infections remains unclear. Patient compliance with single-dose treatments with a combination of albendazole and another drug should be better than that achievable with longer regimens of treatment with albendazole alone. The main aim of the present study was to investigate the pharmacokinetic parameters of a single dose of albendazole, when given alone and in combination with a single dose of praziquantel, to Thai children with *Giardia* infection. There appear to have been only two previous pharmacokinetic studies of albendazole in children, one among echinococcosis cases (Okelo *et al.*, 1993) and one among neurocysticercosis cases (Jung *et al.*, 1997).

PATIENTS AND METHODS

The subjects of the present study were 20 Thai children (14 boys and six girls) aged 7–11 years. Each of these subjects had been found stool-positive for *Giardia* cysts in October–November 2000, when admitted to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. The study was approved by the Ethics Committee of Mahidol University's Faculty of Tropical Medicine, and the parents of each child investigated gave their written informed consent before the study began. Each of the 20 children was prospectively and randomly allocated to one of two treatment groups. Each of the 10 children allocated to group 1 was treated with a single oral dose of 400 mg albendazole (Zentel®; GlaxoSmithKline, Uxbridge, U.K.) alone. The other 10 children (group 2) were each given the same dose of albendazole concurrently with a single dose (20 mg/kg) of praziquantel (Biltricide®; Bayer, Newbury, U.K.). The drugs were all administered immediately after each child had drunk 200 ml UHT (ultra-high-temperature) milk, approximately 1 h after breakfast. A 2-ml blood sample was collected from each child, via an indwelling catheter and into a tube with heparin anticoagulant, immediately pre-treatment (0 h) and again 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post-treatment.

All children were closely monitored for 72 h, to detect any adverse effects. Laboratory investigations, including complete blood counts, and measurement of plasma levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and creatinine, were performed prior to and 48 h after treatment, for safety monitoring. Stool samples were collected and examined twice during the post-treatment observation period, on days 1–3 and 10–12 post-treatment, using the technique described by Ritchie (1948). Children found to be still excreting *Giardia* cysts in their stools when the second post-treatment sample of stool was examined were then given a single oral dose of tinidazole (50 mg/kg).

Pharmacokinetic Investigations

The plasma was separated from each blood sample and stored at -70°C until it could be analysed at the Faculty of Allied Health Sciences of Thammasat University in Pathum Thani. The plasma concentrations of albendazole/albendazole sulphoxide and praziquantel were measured using HPLC with ultra-violet detection (Na-Bangchang *et al.*, 1995; Ubalee *et al.*, 1997). For the albendazole analyses, the inter-assay

precision and accuracy, expressed as coefficients of variation, were <10%, and the deviations from the mean were −12.4%, −3.7% and −0.8% at 20, 400 and 600 ng/ml, respectively. For albendazole sulphoxide, the corresponding inter-assay precision and accuracy were also <10%, and the deviations from the mean were 4.9%, −0.01% and 1.6% at 20, 400 and 800 ng/ml, respectively. The quantification limit for both albendazole and albendazole sulphoxide in human plasma was taken to be 3 ng/ml (Ubalee *et al.,* 1997). The inter-assay precision and accuracy for praziquantel analysis, expressed as coefficients of variation, were <7%, and the deviations from the mean were −1.7%, 2.6%, and 0.8% at 120, 1000 and 2000 ng/ml, respectively. The quantification limit for praziquantel in plasma was taken to be 5 ng/ml (Na-Bangchang *et al.*, 1995).

Plots of plasma concentration *v.* time, for albendazole, albendazole sulphoxide and praziquantel, were analysed using the model-independent method of Gibaldi (1991). The time to maximum plasma concentration (t_{max}) and the maximum plasma concentration (C_{max}) were obtained directly from the concentration–time data. Each terminal elimination half-life ($t_{½z}$) was calculated from log–linear regression. The areas under the curve of the plot of plasma concentration *v.* time, from zero time to 24 h ($AUC_{0-24\,h}$), were calculated using the linear trapezoidal rule (for ascending data-points) or the log trapezoidal rule (for descending data-points).

Statistical Analyses

The non-parametric Mann–Whitney *U*-test was use to compare the continuous data whereas χ^2 and Fisher's exact tests were used to compare the categorical data. The differences in the pharmacokinetic parameters of albendazole/albendazole sulphoxide between the two treatment groups were also compared by Mann–Whitney *U*-tests. A *P*-value of <0.05 was considered indicative of a statistically significant difference.

RESULTS

The baseline demographic and clinical data of the children in the two study groups were similar (Table 1). Most of the children (nine of those given albendazole alone and six of those given albendazole–praziquantel) were still excreting *G. intestinalis* cysts when checked on day 10, 11 or 12 post-treatment and where therefore then given tinidazole.

Albendazole and Albendazole Sulphoxide

Albendazole was detectable in plasma samples from eight of the 10 children given

TABLE 1. *Baseline demographic and clinical data in 20 Thai children with giardiasis*

	Given albendazole only	Given albendazole–praziquantel
No. of children	10	10
No. of males:no. of females	7:3	7:3
MEDIAN VALUE AND (RANGE) FOR:		
Age (years)	8.5 (7–11)	9.1 (7–11)
Weight (kg)	21 (17–45)	24 (17–56)
Height (cm)	125.8 (113–139)	130.3 (111–150)
NO. OF CHILDREN WITH HISTORY OF:		
Loss of appetite	3	1
Fatigue	2	1
Abdominal pain	4	4
Abdominal distension	0	1
Loose stools (more than three times/day)	2	4

albendazole alone, with a median C_{max} and (range) of 45.5 (0–172) ng/ml. Plasma concentrations of albendazole were detectable in all 10 patients given a single dose (20 mg/kg) of praziquantel with their albendazole, however, and the median C_{max} in this group was higher, at 82.5 ng/ml (range = 48–150 ng/ml). In the children given albendazole alone and in those given the combination, maximum plasma concentrations of albendazole occurred as early as 60 and 30 min, with median t_{max} values and (ranges) of 1.3 (0–2) and 1.5 (0.5–2) h, respectively.

Albendazole sulphoxide was detectable in the first post-treatment plasma sample from every patient investigated. Figure 1 allows the plots of median plasma concentration *v.* time in the two treatment groups to be compared, for both albendazole and albendazole sulphoxide. The pharmacokinetics of albendazole sulphoxide were similar whether the albendazole was given alone or in combination with praziquantel (Table 2), with median C_{max} and (ranges) of 952 (545–2000) *v.* 730 (525–2300) ng/ml, median $AUC_{0-24\,h}$ and (ranges) of 4951 (2257–14,138) *v.* 3875 (1467–100,088) ng.h/ml, and median $t_{½z}$ and (ranges) of 2.3 (1.7–5.6) *v.* 2.6 (1.2–5.9) h, respectively ($P > 0.05$ for each). Marked inter-individual variation was noted for $AUC_{0-24\,h}$. Median values of t_{max} for both drug groups were exactly the same, at 2 h.

Praziquantel

The plot of median plasma concentration of praziquantel *v.* time, when praziquantel was given with albendazole, is shown in Figure 2. The median t_{max}, C_{max} and $AUC_{0-24\,h}$ values and (ranges) of praziquantel, in the children given praziquantel concurrently with albendazole, were 2 (1.5–2) h, 550 (345–741) ng/ml, and 3551 (1094–4007) ng.h/ml, respectively (Table 2).

Adverse Effects

No adverse effects were noted in any of the 20 children investigated.

DISCUSSION

The present study is probably the first to explore, in children, the pharmacokinetics of albendazole and its active metabolite, albendazole sulphoxide, when albendazole was given in combination with praziquantel. The results indicate that the co-administered praziquantel had no influence on the pharmacokinetics (plasma-concentration–time profile) of albendazole or albendazole sulphoxide.

The pharmacokinetics of albendazole and albendazole sulphoxide observed in the present study, with or without concomitant praziquantel, were generally in accordance with those previously reported and again demonstrate the rapid-elimination characteristics of the parent drug (Marriner *et al.*, 1986; Okelo *et al.*, 1993; Homeida *et al.*, 1994; Jung *et al.*, 1997). The low systemic bio-availability of albendazole may be explained, in part, by its poor gastrointestinal absorption and by its extensive metabolism, by hepatic and mucosal enzymes, to albendazole sulphoxide and, to a lesser extent, other metabolites.

In their study of adult patients with echinococcosis, Lange *et al.* (1988) found that mean plasma concentrations and AUC of albendazole sulphoxide were 4.5 times higher when albendazole was given with breakfast than when the drug was administered to patients in a fasting state. The systemic bio-availabilities of albendazole sulphoxide following the administration of albendazole alone or albendazole with praziquantel appeared to be 8- and 12-fold higher, respectively, when treatment was given with food than those achieved in fasted subjects (Homeida *et al.*, 1994). The presence of neutral fat in the duodenum may increase bile flow and so improve absorption of any ingested albendazole, by increasing the detergent action of the bile acids.

The pharmacokinetic parameters of albendazole sulphoxide in children have now been investigated and reported three times (see Table 3). The maximum plasma levels

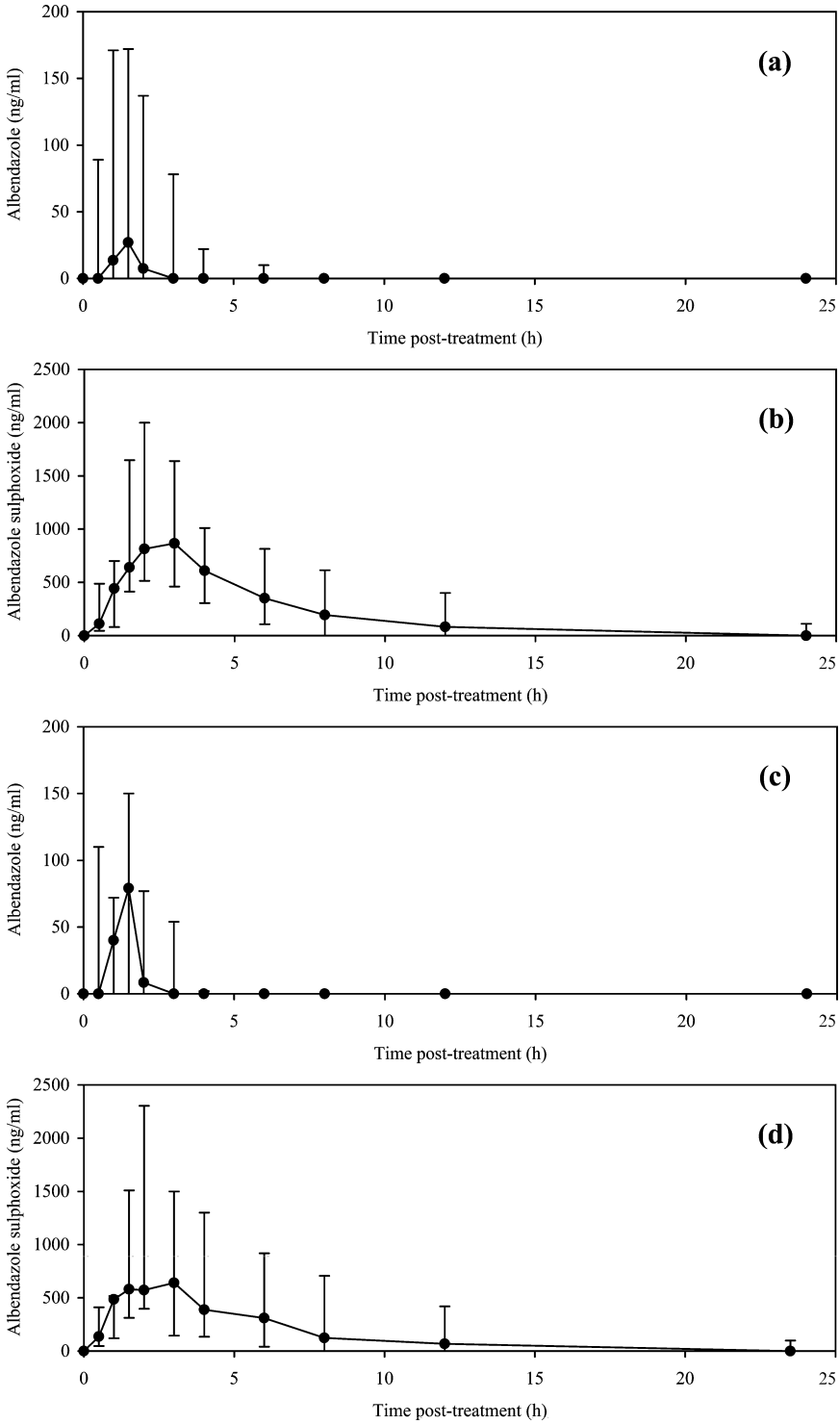

FIG. 1. Plots of median plasma concentration *v.* time, for albendazole (a) and albendazole sulphoxide (b) in the children given albendazole only, and for albendazole (c) and albendazole sulphoxide (d) in the children given albendazole–praziquantel. The vertical lines indicate the ranges.

TABLE 2. *The median pharmacokinetic parameters, and (ranges), of albendazole, albendazole sulphoxide and praziquantel in Thai children infected with* Giardia intestinalis, *when albendazole was given alone (400 mg) or in combination with praziquantel (20 mg/kg)*

Parameter	Given albendazole only	Given albendazole–praziquantel
ALBENDAZOLE		
t_{max} (h)	1.3 (0–2)	1.5 (0.5–2)
C_{max} (ng/ml)	45.5 (0–172)	82.5 (48–150)
ALBENDAZOLE SULPHOXIDE		
t_{max} (h)	2 (1.5–3.0)	2 (1.5–3.0)
C_{max} (ng/ml)	952 (545–2000)	730 (525–2300)
$t_{½z}$ (h)	2.3 (1.7–5.6)	2.6 (1.2–5.9)
$AUC_{0–24\,h}$ (ng.h/ml)	4951 (2257–14,138)	3875 (1467–100,088)
PRAZIQUANTEL		
t_{max} (h)		2 (1.5–2.0)
C_{max} (ng/ml)		550 (345–741)
$t_{½z}$ (h)		3.1 (1.5–4.3)
$AUC_{0–24\,h}$ (ng.h/ml)		3551 (1094–4007)

t_{max}, Time to reach maximum plasma concentration; C_{max}, maximum plasma drug concentration; $t_{½z}$, terminal elimination half-life; $AUC_{0–24\,h}$, area under the plot of plasma concentration *v.* time, from time zero to the last observation (24 h post-treatment).

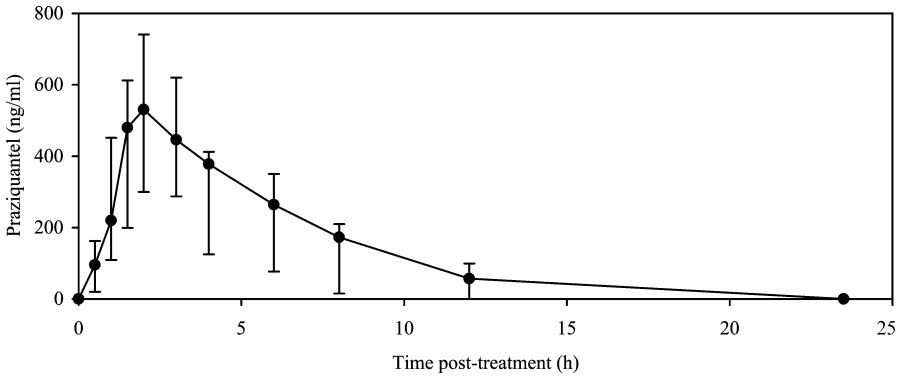

FIG. 2. The plot of the median plasma concentration of praziquantel *v.* time, in the children given albendazole–praziquantel. The vertical lines indicate the ranges.

TABLE 3. *Pharmacokinetic parameters of albendazole sulphoxide in children given albendazole: the results of three studies*

Underlying condition	No. of children	Albendazole dose (mg/kg)	t_{max} (h)	C_{max} (ng/ml)	$t_{½z}$ (h)	AUC (ng.h/ml)	Reference
Cystic echinococcosis	5	10	2.0–3.0	200–680	6.4–9.8	1740–6090	Okelo *et al.* (1993)
Neurocysticercosis	8	15	ND	200–1000	2.3–8.3	ND	Jung *et al.* (1997)
Giardia infection	10	9–24	1.5–3.0	545–2000	1.7–5.6	2257–14,138	Present study

t_{max}, Time to reach maximum plasma concentration; C_{max}, maximum plasma drug concentration; $t_{½z}$, terminal elimination half-life; $AUC_{0–24\,h}$, area under the plot of plasma concentration *v.* time, from time zero to the last observation; ND, not determined.

of albendazole sulphoxide observed in the present study, in the children who each received 400 mg (i.e. approximately 9–24 mg/kg) albendazole alone, are generally higher than those recorded in children with brain cysticercosis given albendazole at 15 mg/kg (Jung *et al.*, 1997). Moreover, the albendazole-sulphoxide C_{max} and $AUC_{0-\infty}$ values recorded in the present study (in the children not given praziquantel) are 2- to 3-fold higher than those seen in the five paediatric patients with cystic echinococcosis who were each given 200 or 300 mg albendazole by Okelo *et al.* (1993). Some of the inter-study variation may be the result of variation in the timing of treatment in relation to food, or in the composition of the food taken near treatment. Even within the present study, however, there was marked inter-individual variation in the pharmacokinetics. There is no evidence of dose-dependent bio-availability for albendazole (Schipper *et al.*, 2000) but the way in which the drug is metabolised, and the speed with which it is metabolised, may vary with the individual.

In the present study, when albendazole was taken concurrently with praziquantel after breakfast, the C_{max} of albendazole sulphoxide was between 525 and 2300 ng/ml. Under these conditions, the estimated terminal-phase elimination half-life ($t_{½Z}$) of the albendazole sulphoxide was 1.2–5.9 h. This metabolite was detectable in the plasma within 30 min of treatment and its t_{max} values (1.5–3.0 h) almost coincided with those of the parent drug (0.5–2 h). The large inter-individual variation seen in systemic exposure to albendazole sulphoxide could reflect a variable extent or rate of drug absorption from the gastro-intestinal tract (including the extent of the first-pass metabolism of albendazole), and the physiological differences between children and adults.

Ingested praziquantel is rapidly absorbed and hydroxylated to mono- and di-hydroxylated products, with 80% of the total dose excreted as metabolites in the urine (Patzschke *et al.*, 1979). The bio-availability of praziquantel, like that of albendazole sulphoxide, is significantly influenced by concomitant food intake, whether that food is normal, high-fat or high-carbohydrate (Mandour *et al.*, 1990; Homeida *et al.*, 1994; Castro *et al.*, 2000). Mandour *et al.* (1990) suggested that high-carbohydrate diets may inhibit cytochrome P450, which is responsible for the hydroxylation of praziquantel. The median C_{max} of praziquantel observed in the present study (550 ng/ml) is higher than the mean value seen in adult volunteers given a single dose of 1800 mg (i.e. approximately 30–36 mg/kg) after 10 h of fasting (319 ng/ml) but lower than the values obtained, with the same dose in similar volunteers, when high-fat (1095 ng/ml) or high-carbohydrate diets (1962 ng/ml) were given (Castro *et al.*, 2000).

Interestingly, the median C_{max} of praziquantel observed in the present patients (550 ng/ml), after they had been given a dose of 20 mg praziquantel/kg, was less than half the maximum concentration (1200 ng/ml) observed in adults with mild *Schistosoma* infection who were given only a slightly higher dose, of 25 mg/kg (Valencia *et al.*, 1994). The rapid clearance of unchanged praziquantel within 12 h of treatment was, however, noted in both the present study and that of Valencia *et al.* (1994). Relatively high oral doses, of 40 and 46 mg praziquantel/kg, yielded peak serum concentrations of 1000 and 1700 ng/ml, respectively (Patzschke *et al.*, 1979; Homeida *et al.*, 1994). The present results, in indicating the rapid metabolism of praziquantel and its pronounced first-pass metabolism ($t_{max} = 1.5$–2 h), are in agreement with the data reported by Leopold *et al.* (1978), who also showed that the pharmacokinetics of praziquantel appeared to be dose-dependent.

Curiously, although no pharmacokinetic interaction between albendazole and praziquantel was generally apparent in the present study, Homeida *et al.* (1994) observed a 5-fold increase in the $AUC_{0-\infty}$ of albendazole sulphoxide when praziquantel was co-administered with albendazole. This

inter-study variation may be attributable to differences in the drug dosages used and in the study population. In the present study, praziquantel appeared to enhance the activity of albendazole in just one patient, a boy who, after receiving both albendazole and praziquantel, had particularly high values of C_{max} (2300 ng/ml) and $AUC_{0-24\,h}$ (110,088 ng.h/ml) for albendazole sulphoxide.

Both the albendazole and praziquantel were well tolerated in the present study, with no reports of adverse effects attributable to either drug. Albendazole and praziquantel are generally safe drugs when used in therapeutic doses and only a few, mild and transient adverse effects (headache, malaise, anorexia, weakness, nausea, vomiting and sleepiness) have been occasionally observed (Vanijanonta *et al.*, 1991; Horton, 2000; Pengsaa *et al.*, 2002). In the treatment of intestinal parasites (unlike the treatment of tissue parasites, where the pharmacokinetics of the drugs are paramount in determining adequate plasma concentrations and thus adequate drug concentrations at the target sites), a pharmacodynamic (synergistic) effect of using two or more drugs in combination may be particularly relevant. This subject merits further investigation, with emphasis on the administration of albendazole on an empty stomach (in order to reduce its absorption) in the treatment of intestinal parasites.

In conclusion, no significant pharmacokinetic interaction between albendazole and praziquantel was observed when the two drugs were given concurrently to children with *Giardia* infection.

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