Transactions of the Royal Society of Tropical Medicine and Hygiene (2006) **100**, 335–345

www.elsevierhealth.com/journals/trst

Assessments of pharmacokinetic drug interactions and tolerability of albendazole, praziquantel and ivermectin combinations

K. Na-Bangchang[a,*], S. Kietinun[b], K.K. Pawa[b], W. Hanpitakpong[a], C. Na-Bangchang[c], J. Lazdins[d]

[a] *Pharmacology and Toxicology Unit, Faculty of Allied Health Sciences, 99 Mu 18 Thammasat University (Rangsit Campus), Klong Loung, Pathumthani 12121, Thailand*
[b] *Faculty of Medicine, 99 Mu 18 Thammasat University (Rangsit Campus), Klong Loung, Pathumthani 12121, Thailand*
[c] *Department of Pediatrics, Pramongkutklao College of Medicine, 315 Ratchavithee Road, Ratchatevee, Bangkok 10400, Thailand*
[d] *UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, 1211 Geneva 27, Switzerland*

Received 4 February 2005; received in revised form 11 May 2005; accepted 11 May 2005
Available online 2 November 2005

KEYWORDS
Wuchereria bancrofti;
Albendazole;
Albendazole sulphoxide;
Ivermectin;
Praziquantel

Summary The pharmacokinetic interactions and tolerability of albendazole, praziquantel and ivermectin combinations were assessed in 23 healthy Thai volunteers (12 males and 11 females). The study was an open, randomised, three-way crossover design in which each subject attended the study on three separate occasions (Phases I, II and III), of 4 d or 8 d each, with at least 1 or 2 weeks (but not longer than 2 months) between each phase. All subjects received the three study drug regimens as follows: regimen I, oral praziquantel (40 mg/kg body weight); regimen II, oral ivermectin (200 μg/kg body weight) given concurrently with an oral dose of albendazole (400 mg); and regimen III, oral ivermectin given concurrently with albendazole and praziquantel. All treatment regimens showed acceptable tolerability profiles. The incidence of overall drug-related adverse events was significantly higher following regimens I (12/23) and III (7/23) compared with that following regimen II (0/23). Six statistically significant changes in the pharmacokinetic parameters of albendazole sulphoxide (C_{max}, $AUC_{0-\infty}$, V_z/F, CL/F), praziquantel (V_z/F) and ivermectin ($AUC_{0-\infty}$) were observed when the three drugs were given concurrently. However, based on US Food and Drug Administration criteria, these changes were not considered of clinical relevance.

* Corresponding author. Tel.: +66 2 986 9209; fax: +66 2 986 9209.
E-mail address: kesaratmu@yahoo.com (K. Na-Bangchang).

0035-9203/$ – see front matter © 2005 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.trstmh.2005.05.017

1. Introduction

Human lymphatic filariasis caused by *Wuchereria bancrofti* and *Brugia malayi* is a mosquito-borne parasitic infection that affects over 120 million people worldwide, and an estimated 40 million people have filaria-associated lymphoedema or testicular hydrocele, which can lead to enormous medical, social and economic costs (Gyapong et al., 1996). The use of single-dose, once yearly treatment with diethylcarbamazine or ivermectin to reduce microfilaraemia in endemic populations has been perceived as an effective strategy for the control of filariasis with long-term effectiveness for up to 1 year after treatment.

In tropical countries where lymphatic filariasis is endemic, co-infection with intestinal helminths is also an important public health problem, especially among school-age children. Recognition that these infections adversely affect growth, nutrition and even cognitive function has led to school-based distribution programmes of albendazole and other broad-spectrum anthelminthic drugs in several of these countries (Nokes et al., 1992; Stephenson et al., 1993; Thein-Hlaing et al., 1991). The most cost-effective approach to the linking of treatment of filariasis with a school-based control programme for geohelminths would be simultaneous treatment with antifilarial drugs and broad-spectrum anthelminthic drugs. Recent research has therefore been focused on the use of drug combinations, with particular focus on the combination of two out of the three drugs already used in filariasis, namely diethylcarbamazine, ivermectin and albendazole, in the control of lymphatic filariasis for mass therapy (Addiss et al., 1997; Ismail et al., 1998; Moulia-Pelat et al., 1995; Ottesen and Ramachandran, 1995).

In view of its pharmacological activity, ivermectin not only has a potent microfilaricidal activity against *W. bancrofti* (Kumaraswami et al., 1988; Moulia-Pelat et al., 1994), *B. malayi* (Shenoy et al., 1993) and *Loa loa* (Richard-Lenoble et al., 1988), it also has activities against many intestinal nematodes and even ectoparasites such as scabies and lice (Ottesen and Campbell, 1994). Regarding albendazole, apart from its anthelminthic activity, single-dose albendazole is also effective against *W. bancrofti* (Jayakody et al., 1993; Mak et al., 1984). On the other hand, with regard to safety and tolerability, ivermectin has proved much better tolerated than diethylcarbamazine (Carme et al., 1991; Oomen, 1969). Recent observations that albendazole plus ivermectin suppresses bancroftian (Addiss et al., 1997; Ismail et al., 1998), including *B. malayi* (Shenoy et al., 1999), microfilaria for prolonged periods has opened up the possibility of using this drug in large-scale control programmes.

In the present work, we propose the use of a triple-drug combination using an additional dose of another broad-spectrum anthelminthic, praziquantel. Praziquantel possesses activity against intestinal cestodes and trematodes, in addition to the activity on intestinal nematodes covered by albendazole. The triple-drug combination with different modes of action (de Silva et al., 1997; Ottesen and Campbell, 1994) would provide a broader spectrum of activity to cover all common geohelminthic infections. Before further assessment of the clinical efficacy and tolerability of this triple combination in patients with symptomatic and asymptomatic filariasis and, finally, the implementation of worldwide operational programmes in areas where *W. bancrofti* and *B. malayi* are endemic, further research is needed to optimise treatment intervals for the three-drug combination, and co-administration of single doses of all three drugs needs to be investigated. The objective of the proposed study was to investigate the possibility of pharmacokinetic drug interactions and the propensity of enhanced toxicity when albendazole, praziquantel and ivermectin are given concurrently at the recommended doses used for lymphatic filariasis and helminthic infections. The pharmacokinetics of praziquantel in the presence of the other two drugs was compared with the control group when the drug was given alone. Comparison of the pharmacokinetics of albendazole sulphoxide and ivermectin was performed using the data previously reported by Awadzi et al. (2003).

2. Materials and methods

2.1. Subjects and study design

The study was an open, randomised, three-way crossover design in which each subject attended the study on three separate occasions. Approval of the study protocol was obtained from the Ethics Committee of the Faculty of Medicine, Thammasat University. A total of 23 healthy Thai subjects (12 males, 11 non-pregnant females), aged between 18 years and 55 years, weighing 40—65 kg, who were non-smokers and non-alcohol drinkers and were residents of Bangkok or suburb areas were recruited into the study. Exclusion criteria included those with (i) hepatic or renal diseases, (ii) history of using any drug or herbal medicine within the past 14 days, except antipyretic or anti-emetic drugs or (iii) history of intolerance to albendazole, praziquantel or ivermectin.

After written informed consent for study participation was obtained, the pre-study screening was carried out. Pre-study investigation to confirm the suitability of the study subjects (according to the inclusion/exclusion criteria) included physical examination, electrocardiogram (ECG) monitoring and laboratory investigations (haematology, biochemistry, urinalysis and pregnancy status). All subjects were admitted to the ward at Thammasat Chalerm Prakiat Hospital for inpatient observation during the first 4 d or 8 d investigation period, depending on the allocated drug regimens.

2.2. Drug administration

On the first occasion, subjects were randomised to receive one of the three study drug regimens as follows: regimen I, a single oral dose of praziquantel (40 mg/kg body weight; 600 mg per tablet; Government Pharmaceutical Organization of Thailand, Bangkok, Thailand); regimen II, a single oral dose of ivermectin (200 μg/kg body weight; Mectizan® 3 mg per tablet; Merck and Co., Ltd, Whitehouse Station, NJ, USA), given concurrently with a single oral dose of albendazole (400 mg; 400 mg per tablet; GlaxoSmithKline, Brentford, Middlesex, UK); or regimen III, a single oral dose of ivermectin (200 μg/kg body weight), given concurrently with albendazole (400 mg) and praziquantel (40 mg/kg body weight). On the following occasions, subjects were randomised to receive treatment with the remaining regimens. The wash-out period was at least 1 week following regimen I, and at least 2 weeks following regimens II and III (the maximum wash-out period on all occasions was not longer than 2 months).

Although previous data demonstrated the improved absorption of albendazole by 4—5-fold when the drug was given with a fatty meal (Awadzi et al., 1994), in the present study subjects were fasted for 6 h before drug administration on any occasion to avoid any complicated interaction between food and drugs. No food or solids were consumed, although alcohol-free and xanthine-free fluids were permissible the night prior to the study. Drug dosage was taken with 150 ml water.

Only analgesics/antipyretics and anti-emetics were allowed in cases of fever and nausea. No other drugs, especially those with potential interactions with the study drugs (anticonvulsants: phenobarbital, phenytoin, carbamazepine; and corticosteroids: dexamethasone and cimetidine) were allowed during the study period (Bittencourt et al., 1992; Masimirembwa et al., 1993; Vazquez et al., 1987).

2.3. Assessments of safety and tolerability

Safety and tolerability of the three drug regimens were assessed based on clinical and laboratory assessments during follow-up, according to NIH/NCI Common Toxicity Criteria (CTC) Grading System for Adverse Events (National Cancer Institute, 2003). Clinical assessments included physical examination, and monitoring of vital signs and adverse events. Information on the occurrence of all adverse events was obtained by questioning plus results recorded at physical examination. Routine laboratory assessments (haematology, biochemistry, urinalysis) were done prior to dosing on day 1 and on day 4 (following regimen I) or day 8 (following regimens II and III) after drug administration on each occasion. Pregnancy test (β-human chorionic gonadotropin test) was repeated before dosing at each phase. Any abnormal laboratory result was followed-up with repeat checks every week until it returned to normal. Laboratory abnormalities (outside the normal ranges) that first occurred or increased in intensity during follow-up were evaluated.

2.4. Blood sample collection for pharmacokinetic investigation

Serial venous blood samples were collected through an indwelling i.v. Teflon™ catheter, inserted into a forearm vein of the subject during the 24 h of frequent blood sampling; patency was maintained with sodium-heparinised saline. Blood sampling after 24 h was obtained by direct venipuncture. Following regimen I (praziquantel alone), a total of 19 venous blood samples (3 ml each) were drawn for pharmacokinetic investigation into heparin-coated plastic tubes: before drug administration at 0 h (day 1), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 (day 2), 30, 36, 48 (day 3), 60 and 72 (day 4) h after drug administration. Following regimens II and III, blood sample collection (5—7 ml each) was extended to 84, 96 (day 5), 108, 120 (day 6), 144 (day 7) and 168 (day 8) h, giving a total of 25 samples.

Immediately after blood sampling, the blood drawn was centrifuged at 1200 × *g* for 15 min and plasma samples were collected in plain plastic tubes without anticoagulant and stored at −80 °C until analysis.

2.5. Determination of drug concentrations in plasma

Plasma concentrations of albendazole and its active metabolite, albendazole sulphoxide, as well as

ivermectin and praziquantel were measured using HPLC, according to the methods of de Montigny et al. (1990), Hanpitakpong et al. (2004) and Ubalee et al. (1997), with modifications.

2.6. Pharmacokinetic analysis

The appropriate pharmacokinetic parameters were estimated from the obtained plasma concentration–time profiles of albendazole sulphoxide, praziquantel and ivermectin using non-compartmental pharmacokinetic analysis (Gibaldi, 1991). No pharmacokinetic analysis was performed for albendazole plasma concentration–time profiles obtained from all subjects on all occasions as no persistent plasma concentrations were observed.

2.7. Criteria for pharmacokinetic drug interaction

Since small, consistent systemic exposure differences could result in statistical significance without any clinical relevance, the conclusion on the clinically relevant pharmacokinetic drug interactions was based on the criteria of the US Food and Drug Administration (1999), focusing only on the key parameters indicative of absorption, namely C_{max} (the maximum measured plasma concentration over the timespan specified, obtained directly from the plasma concentration–time data) and t_{max} (the time of the maximum measured plasma concentration obtained directly from the plasma concentration–time data; in the case that the maximum value occurred at more than one time point, t_{max} was defined as the first time point with this value), and of systemic drug availability, $AUC_{0-\infty}$ (the area under the plasma concentration–time curve from time 0 to infinity; $AUC_{0-\infty}$ was calculated as the sum of the area under the plasma concentration–time curve from time 0 to the last measurable concentration as calculated by the linear trapezoidal method (AUC_{0-t}) plus the ratio of the last measurable plasma concentration to the elimination rate constant). Briefly, the geometric mean ratios (GMR: the ratio of the value of the parameter for the drug when used in combination to the corresponding value for the drug used alone), and the 90% CI about the GMR were determined. The pharmacokinetic parameters defined previously for albendazole and ivermectin when used alone (Awadzi et al., 2003) were used as historic controls. It was concluded that a clinically significant pharmacokinetic drug interaction had occurred whenever the 90% CI for a systemic exposure ratio fell entirely outside the equivalence range of 0.8–1.25 (Longshore et al., 1999).

2.8. Statistical analysis

Statistical analysis of the data was performed with SPSS for Windows Software version 12 (SPSS software, Gorichem, The Netherlands). Comparison of the incidence of subjects with adverse events between two groups was performed using the χ^2 test. Analysis of variance (ANOVA) included the appropriate statistical tests of the effect (i.e. group allocation) in the model. An ANOVA was carried out on the untransformed t_{max}, CL/F (the total body clearance, where F is the fraction of dose absorbed, calculated as dose/$AUC_{0-\infty}$), V_z/F (the volume of distribution based on the terminal phase elimination, calculated from $(CL/F)/\lambda_z$), λ_z (the apparent first-order elimination or terminal rate constant, calculated from a semi-log plot of the plasma concentration–time curve; the parameter was calculated by linear least-squares regression analysis using the last three (or more) non-zero plasma concentrations) and $t_{1/2z}$ (the elimination or terminal half-life, calculated as $0.693/\lambda_z$) data, and on the logarithmically transformed AUC and C_{max} data. Comparison of the pharmacokinetic parameters (C_{max}, $AUC_{0-\infty}$, t_{max}, V_z/F, CL/F and $t_{1/2z}$) between two drug regimens was done using the Wilcoxon signed-rank test. Statistical significance level was set at $\alpha = 0.05$ for all tests.

3. Results

Demographic and baseline laboratory data of all 23 volunteers are summarised in Table 1. All subjects were healthy as verified by results of clinical (physical examination, vital signs, ECG) and laboratory assessments. One subject had a common cold and took a single oral dose of 500 mg paracetamol 5 d before screening and the other had fever 1 week before screening and took a single oral dose of 500 mg paracetamol.

3.1. Pharmacokinetics of albendazole sulphoxide, praziquantel and ivermectin

Results of an ANOVA analysis indicate no influence of treatment allocation on any of the pharmacokinetic parameters of albendazole sulphoxide, praziquantel and ivermectin following drug administration on all occasions.

3.1.1. Albendazole sulphoxide

Figure 1b depicts median plasma concentration–time profiles of albendazole sulphoxide in all subjects following the administration of regimens II

Table 1 Demographics, and admission clinical and laboratory data of 23 healthy Thai study subjects (12 males, 11 females)

	Median (95% CI)
Age (years)	21 (19—25)
Body weight (kg)	53.1 (43—63.1)
Haemoglobin (g/dl)	14.0 (12.0—16.2)
Haematocrit (%)	40.0 (38.0—50.0)
WBC ($\times 10^9$/l)	7.0 (5.0—12.2)
Neutrophils (%)	58 (50—70)
Lymphocytes (%)	36 (25—45)
Monocytes (%)	4 (0—8)
Eosinophils (%)	2 (0—4)
Basophils (%)	0 (0—1)
RBC ($\times 10^{12}$/l)	4.77 (4.12—5.98)
Platelets ($\times 10^9$/l)	135 (160—420)
Total bilirubin (mg/dl)	0.8 (0.3—1.1)
Direct bilirubin (mg/dl)	0.3 (0.1—0.6)
Alkaline phosphatase (U/L)	71 (37—75)
AST (U/L)	23 (16—36)
ALT (U/L)	17 (7—40)
Glucose (mg/dl)	80 (65—91)
Creatinine (mg/dl)	0.90 (0.60—1.10)
BUN (mg/dl)	10 (6—17)
Total protein (g/dl)	7.8 (6.8—8.3)
Albumin (g/dl)	4.7 (3.7—4.6)
Urine specific gravity	1.024 (1.005—1.034)
Urinary pH	6.0 (5.0—8.0)

WBC: white blood cells; RBC: red blood cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen.

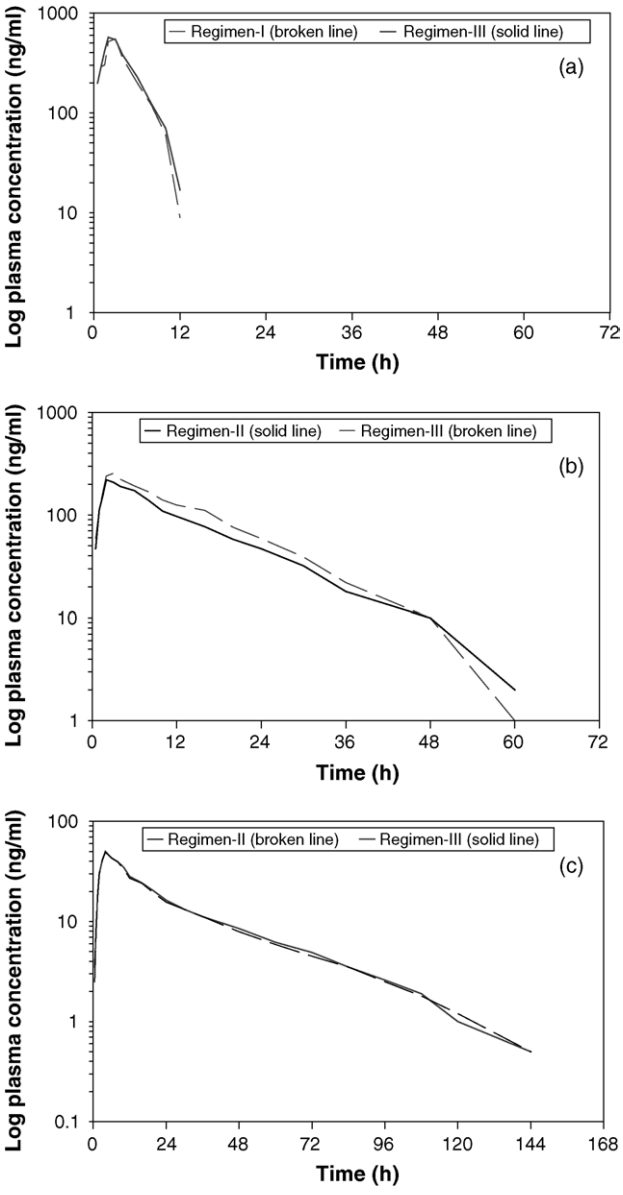

Figure 1 Median plots (log-scale) of plasma concentration—time profiles of (a) praziquantel, (b) albendazole sulphoxide and (c) ivermectin in 23 healthy subjects (12 males, 11 females) following regimen I (a single oral dose of 400 mg/kg body weight praziquantel), regimen II (single oral doses of 400 mg albendazole and 200 μg/kg body weight ivermectin) and regimen III (single oral doses of 40 mg/kg body weight praziquantel and 400 mg albendazole and 200 μg/kg body weight ivermectin).

and III. Albendazole was almost undetectable in the plasma of all subjects. Plasma concentrations varied between 0 ng/ml and 71 ng/ml during 0—6 h of drug administration. Albendazole sulphoxide was detected at the first time of blood sampling (0.5 h), with the levels varying between 6 ng/ml and 113 ng/ml. In most cases, concentrations were measurable until 48 h of drug administration, with levels varying between 6 ng/ml and 688 ng/ml. The pharmacokinetics of albendazole sulphoxide when albendazole was given at a single oral dose of 400 mg in combination with ivermectin (regimen II) are summarised in Table 2. Interindividual variation was observed for most pharmacokinetic parameters, ranging from 9.6% to 19.1%. Four statistically significant differences in the pharmacokinetic parameters of albendazole sulphoxide were observed when albendazole was given at a single oral dose of 400 mg in combination with only ivermectin (regimen II) compared with when given in combination with both ivermectin and praziquantel (regimen III). C_{max} and $AUC_{0-\infty}$ were significantly higher (8% and 31%, respectively) following regimen III compared with regimen II ($P = 0.0196$, 95% CI 26.5—62 for C_{max}; and $P = 0.0011$, 95% CI 248—1929 for $AUC_{0-\infty}$). Furthermore, V_z/F and CL/F were significantly lower when albendazole was given in combination with praziquantel and ivermectin (regimen III) ($P = 0.0042$, 95% CI 3.4—9.3 for V_z/F; and $P = 0.0039$, 95% CI 1.8—11.1 for CL/F). The t_{max} and $t_{1/2z}$ were comparable.

Table 2 Pharmacokinetics of albendazole sulphoxide in 23 healthy subjects (12 males, 11 females) following regimen II (single oral doses of 200 μg/kg body weight ivermectin and 400 mg albendazole) and regimen III (single oral doses of 200 μg/kg body weight ivermectin and 400 mg albendazole and 40 mg/kg body weight praziquantel)

Pharmacokinetic parameter	Median (95% CI)	
	Regimen II ($N = 23$)	Regimen III ($N = 23$)
C_{max} (ng/ml)[a]	245 (119–571)	264 (148–688)
t_{max} (h)	2.0 (2.0–3.0)	2.0 (2.0–3.0)
AUC_{0-t} (ng.h/ml)	2920 (1166–6961)	3919 (1897–7672)
$AUC_{0-\infty}$ (ng.h/ml)[b]	2998 (1222–7005)	3943 (1905–7696)
V_z/F (l/kg)[c]	27.3 (10.7–58.6)	24.5 (12.3–45.0)
CL/F (ml/min/kg)[d]	39.0 (18.5–92.4)	35.6 (15.5–69.9)
λ_z (/h)	0.082 (0.060–0.259)	0.083 (0.057–0.126)
$t_{1/2z}$ (h)	8.4 (4.6–11.5)	8.1 (5.5–12.0)

Note: Statistical comparison was done for C_{max}, t_{max}, $AUC_{0-\infty}$, V_z/F, CL/F and $t_{1/2z}$.
[a] Statistically significant difference between regimens II and III ($P = 0.0196$, 95% CI 26.5–62.0).
[b] Statistically significant difference between regimens II and III ($P = 0.0011$, 95% CI 248–1929).
[c] Statistically significant difference between regimens II and III ($P = 0.0042$, 95% CI 3.4–9.3).
[d] Statistically significant difference between regimens II and III ($P = 0.0039$, 95% CI 1.85–11.1).

3.1.2. Praziquantel

Figure 1a depicts median plasma concentration–time profiles of praziquantel in all subjects following the administration of regimens I and III. Praziquantel was detected in plasma at the first time of blood sampling (0.5 h), with the levels varying between 45 ng/ml and 296 ng/ml. In most cases, concentrations were measurable until 12 h of drug administration, with the levels varying between 10 ng/ml and 102 ng/ml. The pharmacokinetics of praziquantel when given alone (regimen I) and in combination with albendazole and ivermectin (regimen III) are summarised in Table 3. A statistically significant difference in pharmacokinetic parameters was observed with V_z/F, which was significantly lower (10%) when praziquantel was given in combination with albendazole and ivermectin (regimen III) ($P = 0.0017$, 95% CI 3.95–163.4).

3.1.3. Ivermectin

Figure 1c depicts median plasma concentration–time profiles of ivermectin in all subjects following the administration of regimens II and III. Ivermectin was detected in plasma at the first time of blood sampling (0.5 h), with the levels varying between 1.4 ng/ml and 12.5 ng/ml. In most cases, concentrations were measurable until 144 h of drug administration, with the levels varying between 0.1 ng/ml and 1.6 ng/ml. The pharmacokinetics of ivermectin when given in combination with albendazole at a single oral dose of 200 μg/kg body weight (regimen II) and in combination with both albendazole and praziquantel (regimen III) are summarised in Table 4. A statistically significant difference in pharmacokinetic parameters was observed with $AUC_{0-\infty}$, which was significantly lower (4.4%) when ivermectin was given in

Table 3 Pharmacokinetics of praziquantel in 23 healthy subjects (12 males, 11 females) following regimen I (single oral dose of 40 mg/kg body weight praziquantel) and regimen III (single oral doses of 200 μg/kg body weight ivermectin and 400 mg albendazole and 40 mg/kg body weight praziquantel)

Pharmacokinetic parameter	Median (95% CI)	
	Regimen I ($N = 23$)	Regimen III ($N = 23$)
C_{max} (ng/ml)	783 (204–1414)	768 (318–1518)
t_{max} (h)	2.0 (0.5–3.0)	2.5 (0.5–3.0)
AUC_{0-t} (ng.h/ml)	3614 (602–7484)	3366 (910–7782)
$AUC_{0-\infty}$ (ng.h/ml)	3615 (610–7484)	3366 (924–7813)
V_z/F (l/kg)[a]	27.9 (17.5–137.2)	25.1 (18.1–93.6)
CL/F (ml/min/kg)	199 (89–1091)	197 (85–728)
λ_z (/h)	0.408 (0.226–0.874)	0.417 (0.244–1.1)
$t_{1/2z}$ (h)	1.7 (0.8–3.1)	1.6 (0.6–2.8)

Note: Statistical comparison was done for C_{max}, t_{max}, $AUC_{0-\infty}$, V_z/F, CL/F and $t_{1/2z}$.
[a] Statistically significant difference between regimens I and III ($P = 0.0017$, 95% CI 3.95–163.4).

Table 4 Pharmacokinetics of ivermectin in 23 healthy subjects (12 males, 11 females) following regimen II (single oral doses of 200 μg/kg body weight ivermectin and 400 mg albendazole) and regimen III (single oral doses of 200 μg/kg body weight ivermectin and 400 mg albendazole and 40 mg/kg body weight praziquantel)

Pharmacokinetic parameter	Median (95% CI)	
	Regimen II ($N = 23$)	Regimen III ($N = 23$)
C_{max} (ng/ml)	50.1 (32.3—62.2)	49.2 (32—64.2)
t_{max} (h)	4.0 (3.0—4.0)	4.0 (3.0—6.0)
AUC_{0-t} (ng.h/ml)	1338 (705—1881)	1290 (678—1825)
$AUC_{0-\infty}$ (ng.h/ml)[a]	1361 (710—1922)	1301 (681—1861)
V_z/F (l/kg)	5.4 (3.8—10.1)	5.3 (4.0—10.4)
CL/F (ml/min/kg)	2.4 (1.7—4.6)	2.5 (1.9—5.5)
λ_z (/h)	0.029 (0.020—0.039)	0.029 (0.021—0.045)
$t_{1/2z}$ (h)	23.8 (17.4—33.2)	23.5 (15.2—31.9)

Note: Statistical comparison was done for C_{max}, t_{max}, $AUC_{0-\infty}$, V_z/F, CL/F and $t_{1/2z}$.
[a] Statistically significant difference between regimens II and III ($P = 0.0015$, 95% CI 30—71).

combination with albendazole and praziquantel (regimen III) ($P = 0.0015$, 95% CI 30—71).

3.2. Evaluation of pharmacokinetic drug interactions

Evaluation of the differences in all pharmacokinetic parameters of albendazole sulphoxide, ivermectin and praziquantel between the treatment groups are described in Table 5. Based on the criteria set by the US Food and Drug Administration (1999), no significant drug interaction was observed when albendazole, ivermectin and praziquantel were given concurrently as single oral doses (regimen III) or when albendazole was given concurrently with only ivermectin (regimen II). The changes in pharmacokinetic parameters of each drug, particularly $AUC_{0-\infty}$, C_{max} and t_{max}, did not reach the level that would be considered a pharmacokinetic drug interaction. The GMRs and the related 90% CIs for the $AUC_{0-\infty}$, C_{max} and t_{max} are summarised for each paired drug combination, together with the equivalence range, in Figure 2. GMRs together with 90% CIs for albendazole/ivermectin (regimen II) and albendazole/ivermectin/praziquantel (regimen III) combinations lie within the acceptable range (0.8—1.25).

3.3. Safety and tolerability assessments following drug administration

Adverse events observed following the three drug regimens included dizziness, bitter taste, fever, abdominal pain/epigastric pain, nausea, syncope, low back pain, palpitation, fatigue, diarrhoea, axillary abscess, running nose, nasal congestion and headache. However, these symptoms were self-limiting and did not interfere with daily activity. No subjects had vomiting following the administration of any drug regimen. No serious adverse events or adverse events with severity of CTC grade 3 or 4 were observed in any subject following the administration of all treatment regimens. No subjects had abnormal ECG following each treatment regimen, although a non-clinically significant increase in QT interval (uncorrected) was observed in two subjects (19% and 25% increase) at 2 h following the administration of regimens I and II.

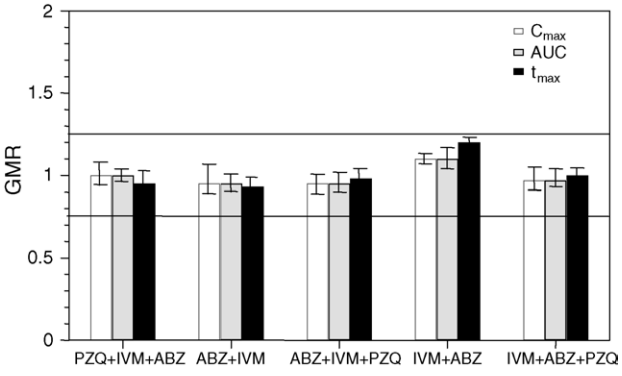

Figure 2 Geometric mean ratio (GMR) for the pharmacokinetic parameters AUC, C_{max} and t_{max} for praziquantel when given with ivermectin and albendazole (regimen III, PZQ + IVM + ABZ), albendazole sulphoxide when albendazole was given with ivermectin (regimen II, ABZ + IVM), albendazole sulphoxide when albendazole was given with ivermectin and praziquantel (regimen III, ABZ + IVM + PZQ), ivermectin when given with albendazole (regimen II, IVM + ABZ) and ivermectin when given with albendazole and praziquantel (regimen III, IVM + ABZ + PZQ). The horizontal lines indicate the equivalence range (0.8—1.25). Whenever the vertical lines, which indicate the 90% CIs, lie entirely outside of the equivalence range, a clinically significant drug—drug interaction is indicated.

Table 5 Evaluation of drug interactions based on the key pharmacokinetic parameters (C_{max}, t_{max} and $AUC_{0-\infty}$) of albendazole sulphoxide, praziquantel and ivermectin

Pharmacokinetic parameter	Albendazole sulphoxide, when albendazole was given:			Praziquantel, when praziquantel was given:		Ivermectin, when ivermectin was given:		
	Alone[a]	+ IVM (regimen II)	+ IVM + PZQ (regimen III)	Alone (regimen I)	+ IVM + ABZ (regimen III)	Alone[a]	+ ABZ (regimen II)	+ ABZ + PZQ (regimen III)
C_{max} (ng/ml)	153 (52)	281 (123)	310 (123)	784 (381)	765 (351)	23 (12)	49.2 (73)	49.8 (78)
$AUC_{0-\infty}$ (ng.h/ml)	3581 (1432)	3962 (1604)	4523 (1967)	3282 (1732)	3308 (1705)	527 (309)	1281 (308)	1237 (313)
t_{max} (h)	3.0 (1.6)	2.5 (0.7)	2.4 (0.5)	2.0 (0.9)	2.1 (0.9)	2.0 (3.5)	4.0 (0.2)	4.0 (0.4)

Data are presented as arithmetic mean (SD).
[a] 'Historical' data of Awadzi et al. (2003).

A number of subjects had laboratory values (haematology, biochemistry) outside the normal range at baseline and on day 4 or day 8 following drug administration. All of these changes were of severity of CTC grade 1 and 2. No statistically significant difference in incidence of abnormal laboratory findings was observed between the three treatment regimens both on day 1 or on day 4 or day 8 following drug administration. The incidence of adverse events either unrelated or related to treatment regimens was significantly higher following regimens I and III compared with regimen II. With respect to drug-related adverse events, the incidence of overall events following regimen I (12/23, 52.2%) was significantly higher than that following regimen II (0/23, 0%) ($P = 0.0002$, 95% CI 0.004—0.251). In addition, the incidence of overall events following regimen III (7/23, 30.4%) was significantly higher than that following regimen II (0/23, 0%) ($P = 0.01$, 95% CI 0.009—0.64). However, the incidence of each drug-related adverse event was found to be significantly different; the incidence of dizziness following regimen I (7/23, 30.4%) was significantly higher than that following regimen II (0/23, 0%) ($P = 0.004$, 95% CI 0.0095—0.64).

4. Discussion

The present study is the first report that describes the pharmacokinetic (plasma drug concentration—time profiles) and pharmacodynamic (adverse reactions) interactions when albendazole, ivermectin and praziquantel are given concurrently as single oral doses. The study was carried out in healthy Thai volunteers in a fasting condition to avoid the complex interaction between drugs and food (Guzzo et al., 2002; Homeida et al., 1994). The study design was a three-way crossover to minimise interindividual variation of drug handling. It would have been ideal to conduct a seven-way crossover design to detect interaction of all components in the same individuals, but this is not practical and ethical as there are quite a few pharmacokinetic studies of albendazole alone, ivermectin alone, and drug interaction studies of praziquantel and ivermectin, as well as praziquantel and albendazole. The use of pharmacokinetic data previously reported for albendazole sulphoxide and ivermectin when used alone as historic controls should provide sufficient information to allow interpretation on the interaction of each component of the three-drug combination, although higher variability in the pharmacokinetics would be expected.

The pharmacokinetics of albendazole sulphoxide and ivermectin observed in this study were in general agreement with those reported previously following the same or equivalent doses (Awadzi et al., 1994, 2003; Guzzo et al., 2002; Homeida et al., 1994; Mandour et al., 1990; Pengsaa et al., 2004; Shenoy et al., 2002). However, the following should be noted: (i) in most studies, including the present study, albendazole was unmeasurable, but some studies reported significant levels of albendazole in plasma following an equivalent dose (Pengsaa et al., 2004; Shenoy et al., 2002); (ii) plasma albendazole sulphoxide concentrations were approximately double in one reported study following the same dose (400 mg) of albendazole when given with food, either alone or with diethylcarbamazine (Shenoy et al., 2002); and (iii) the apparent terminal phase elimination half-life estimates for ivermectin in various studies varied somewhat with dose and method of administration, from approximately 15 h to 50 h in fasting or fed conditions.

There were no significant changes in the pharmacokinetics of praziquantel and ivermectin when given together with albendazole (regimen III). However, the systemic availability of albendazole sulphoxide (major plasma active metabolite of albendazole) was increased compared with regimen II (albendazole plus ivermectin). This is in agreement with data in healthy Sudanese volunteers who received the same dose of praziquantel and albendazole (without ivermectin) (Homeida et al., 1994). It was clear from that study that praziquantel altered the kinetics of albendazole and, in contrast, albendazole had no affect on the kinetics of praziquantel. Thus, the change in systemic availability of albendazole sulphoxide in the present study is unlikely to be due to ivermectin. This is supported by a study in African patients with onchocerciasis where the same doses of ivermectin and albendazole were used; no changes in the pharmacokinetics of albendazole or ivermectin were seen in that study (Awadzi et al., 2003). The pharmacokinetics of albendazole sulphoxide observed in regimen II (albendazole and ivermectin) was also in general agreement with that observed in other studies following the same dose (Awadzi et al., 1994, 2003; Homeida et al., 1994; Shenoy et al., 2002). With these supporting studies, it is concluded that the pharmacokinetic interactions observed with albendazole/albendazole sulphoxide were due to the effect of praziquantel but not ivermectin. The change in the pharmacokinetics of albendazole sulphoxide could be explained by the effect of praziquantel on absorption, or inhibition of metabolism of albendazole and/or albendazole sulphoxide by hepatic or intestinal cytochrome P450. However, despite these pharmacokinetic changes, no clinically relevant pharmacokinetic drug interaction was observed. The increase in the absorption (C_{max}) and systemic availability ($AUC_{0-\infty}$) of plasma albendazole sulphoxide did not reach the level that would be considered a pharmacokinetic drug interaction (US Food and Drug Administration, 1999). This was supported by the clinical evidence that despite an increase in the $AUC_{0-\infty}$ of albendazole sulphoxide, the incidence of adverse events that were likely to be associated with the administration of the combination of the three drugs was not higher than that after the administration of a single-dose regimen (regimen I, praziquantel alone).

Administration of all treatment regimens, either as a single dose (regimen I) or a combination of two (regimen II) or three (regimen III) drugs, generally showed acceptable tolerability profiles. No serious adverse effects or adverse effects with severity of CTC grade 3 or 4 were observed in any subject. Adverse events that were likely to be attributable to drug administration (drug-related adverse events) in all regimens included dizziness, nausea, abdominal/epigastric pain, palpitation and bitter taste. These were mild, transient and did not interfere with daily activity. The incidence of these drug-related adverse events was greatest following regimen I (12 occurrences in 10 subjects), followed by regimen III (7 occurrences in 5 subjects), which were significantly higher than regimen II (none). The high incidence following praziquantel alone was rather unexpected. The distribution of these events was equal in both sexes. Praziquantel has been shown to be relatively devoid of adverse effects (EMEA, 1996; Reynolds, 1993; PDR, 2001; Shen et al., 1983). It should be noted that the number of subjects included in this study was too small to draw any definitive conclusion on this matter. Nevertheless, the adverse effects were likely to be due to the pharmacodynamic effect of praziquantel, although it was noted that systemic bioavailability of albendazole sulphoxide (C_{max}, $AUC_{0-\infty}$) following the administration of regimen III was significantly higher than following regimen II. The incidence of these adverse effects was higher in regimens containing praziquantel, both when the drug was given alone (regimen I) or in combination with the other drugs (regimen III), whilst no drug-related adverse events were observed following regimen II. Only slight and insignificant changes (CTC grade 1) in laboratory parameters (haematology and biochemistry) from normal ranges were observed following all treatment regimens, and there was no significant difference

in the incidence among the three treatment groups.

Albendazole, praziquantel and ivermectin are generally safe drugs at therapeutic doses (Edwards and Breckenridge, 1988). Adverse events observed following the three treatment regimens included dizziness, nausea, headache, abdominal/epigastric pain, diarrhoea, fever, bitter taste, syncope, low back pain, palpitation, fatigue, axillary abscess, running nose, nasal congestion and laboratory changes (elevated levels of alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, total protein and albumin). The elevated levels of all the biochemistry tests occurred on day 4 or day 8 of drug administration and returned to normal within 7 d. In spite of the increase in systemic availability of albendazole sulphoxide observed with regimen III, no association between the incidence of these adverse events and plasma albendazole sulphoxide concentrations were seen in this study. However, it should also be kept in mind that the absorption of these drugs could be enhanced significantly when co-administered with food (Guzzo et al., 2002; Homeida et al., 1994; Mandour et al., 1990), although results from a previous study showed no significant adverse effects whilst the systemic bioavailability of albendazole sulphoxide was increased 4.5-fold when albendazole was given in a fed condition, 8-fold when co-administered with praziquantel and 12-fold when co-administered with food and praziquantel (Homeida et al., 1994). This might increase the incidence of adverse effects that are seen now in this study but should still be within a tolerance limit. However, care should still be taken when these three drugs are given concurrently with food.

5. Conclusion

The results of the present study suggest that there is no clinically relevant drug interaction between praziquantel, ivermectin and albendazole when given concurrently as single oral doses in healthy Thai volunteers. The data observed in this study in healthy Thai volunteers are similar to those in African (Sudanese) healthy volunteers and African (Ghanaian) patients with onchocerciasis; thus, they could be extrapolated to the African population without greater values of variation.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

Acknowledgements

The study was supported by UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. We thank Dr Juntra Karbwang, Clinical Co-ordinator, Product Research and Development, for her technical support and comments during the study. We are grateful to the staff of Thammasat Chalermprakiet Hospital for their assistance during the clinical phase of the study.

References

Addiss, D.G., Beach, M.J., Streit, T.G., Lutwick, S., LeConte, F.H., Lafontant, J.G., Hightower, A.W., Lammie, P.J., 1997. Randomised placebo-controlled comparison of ivermectin and albendazole alone and in combination for *Wuchereria bancrofti* microfilaraemia in Haitian children. Lancet 350, 480—484.

Awadzi, K., Hero, M., Opoku, N.O., Buttner, D.W., Coventry, P.A., Prime, M.A., Orme, M.L., Edwards, G., 1994. The chemotherapy of onchocerciasis XVII. A clinical evaluation of albendazole in patients with onchocerciasis; effects of food and pretreatment with ivermectin on drug response and pharmacokinetics. Trop. Med. Parasitol. 45, 203—208.

Awadzi, K., Edwards, G., Duke, B.O., Opoku, N.O., Attah, S.K., Addy, E.T., Ardrey, A.E., Quartey, B.T., 2003. The co-administration of ivermectin and albendazole — safety, pharmacokinetics and efficacy against *Onchocerca volvulus*. Ann. Trop. Med. Parasitol. 97, 165—178.

Bittencourt, P.R., Gracia, C.M., Martins, R., Fernandes, A.G., Diekmann, H.W., Jung, W., 1992. Phenytoin and carbamazepine decreased oral bioavailability of praziquantel. Neurology 42, 492—496.

Carme, B., Boulesteix, J., Boutes, H., Puruehnce, M.F., 1991. Five cases of encephalitis during treatment of loiasis with diethylcarbamazine. Am. J. Trop. Med. Hyg. 44, 684—690.

de Montigny, P., Shim, J.S., Pivnichny, J.V., 1990. Liquid chromatographic determination of ivermectin in animal plasma with trifluoroacetic anhydride and N-methylimidazole as the derivatization reagent. J. Pharm. Biomed. Anal. 8, 507—510.

de Silva, N., Guyatt, H., Bundy, D., 1997. Anthelmintics. A comparative review of their clinical pharmacology. Drugs 53, 769—788.

Edwards, G., Breckenridge, A.M., 1988. Clinical pharmacokinetics of anthelmintic drugs. Clin. Pharmacokinet. 15, 67—93.

EMEA, 1996. Praziquantel Summary Report by CVMP. European Medicines Evaluation Agency, London, EMEA/MRL/141/96 September 1996.

Gibaldi, M., 1991. Biopharmaceutics and Clinical Pharmacokinetics, fourth ed. Lea and Febriger, Philadelphia, PA, pp. 14—23.

Guzzo, C.A., Furtek, C.I., Porras, A.G., Chen, C., Tipping, R., Clineschmidt, C.M., Sciberras, D.G., Hsieh, J.Y., Lasseter, K.C., 2002. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J. Clin. Pharmacol. 42, 1122—1133.

Gyapong, J.O., Gyapong, M., Adjei, S., 1996. The epidemiology of acute adenolymphangitis due to lymphatic filariasis in northern Ghana. Am. J. Trop. Med. Hyg. 54, 591—595.

Hanpitakpong, W., Banmairuroi, V., Kamanikom, B., Choemung, A., Na-Bangchang, K., 2004. A high-performance liquid

chromatographic method for determination of praziquantel in plasma. J. Pharm. Biomed. Anal. 36, 871–876.

Homeida, M., Leahy, W., Copeland, S., Ali, M.M., Harron, D.W., 1994. Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. Ann. Trop. Med. Parasitol. 88, 551–559.

Ismail, M.M., Jayakody, R.L., Weil, G.J., Nirmalan, N., Jayasinghe, K.S., Abeyewickrema, W., Rezvi Sheriff, M.H., Rajaratnam, H.N., Amarasekera, N., de Silva, D.C., Michalski, M.L., Dissanaike, A.S., 1998. Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. Trans. R. Soc. Trop. Med. Hyg. 92, 94–97.

Jayakody, R.L., de Silva, C.S.S., Weerasinghe, W.M.T., 1993. Treatment of bancroftian filariasis with albendazole: evaluation of efficacy and adverse reactions. Trop. Biomed. 10, 19–24.

Kumaraswami, V., Ottesen, E.A., Vijayasekaran, V., Devi, U., Swaminathan, M., Aziz, M.A., Sarma, G.R., Prabhakar, R., Tripathy, S.P., 1988. Ivermectin for the treatment of *Wuchereria bancrofti* filariasis. Efficacy and adverse reactions. JAMA 259, 3150–3153.

Longshore, D., Grills, C., Annon, K., 1999. Effects of a culturally congruent intervention on cognitive factors related to drug-use recovery. Subst. Use Misuse 34, 1223–1241.

Mak, J.W., Sim, B.K.L., Yen, P.K.F., 1984. Experimental infection of the leaf-monkey. *P. melalophos* with subperiodic *B. malayi*. Trop. Biomed. 1, 21–27.

Mandour, M.E., el Turabi, H., Homeida, M.M., el Sadig, T., Ali, H.M., Bennett, J.L., Leahey, W.J., Harron, D.W., 1990. Pharmacokinetics of praziquantel in healthy volunteers and patients with schistosomiasis. Trans. R. Soc. Trop. Med. Hyg. 84, 389–393.

Masimirembwa, C.M., Naik, Y.S., Hasler, J.A., 1993. Effects of phenobarbital and 3-methylcholanthrene pretreatment on the pharmacokinetics of praziquantel in rats. Eur. J. Drug Metab. Pharmacokinet. 18, 261–264.

Moulia-Pelat, J.P., Glaziou, P., Nguyen, L.N., Chanteau, S., Plichart, R., Beylier, I., Martin, P.M., Cartel, J.L., 1994. Ivermectin 400 μg/kg: long-term suppression of microfilariae in Bancroftian filariasis. Trans. R. Soc. Trop. Med. Hyg. 88, 107–109.

Moulia-Pelat, J.P., Glaziou, P., Weil, G.J., Nguyen, L.N., Gaxotte, P., Nicolas, L., 1995. Combination ivermectin plus diethylcarbamazine, a new effective tool for control of lymphatic filariasis. Trop. Med. Parasitol. 46, 9–12.

National Cancer Institute, 2003. Common Terminology Criteria For Adverse Events, version 3.0, 31 March 2003. US Department of Health and Human Services, National Institutes of Health, Bethesda, MD.

Nokes, C., Grantham-McGregor, S.M., Sawyer, A.W., Cooper, E.S., Robinson, B.A., Bundy, D.A., 1992. Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican school children. Parasitology 104, 539–547.

Oomen, A.P., 1969. Fatalities after treatment of onchocerciasis with diethylcarbamazine. Trans. R. Soc. Trop. Med. Hyg. 63, 548.

Ottesen, E.A., Campbell, W.C., 1994. Ivermectin in human medicine. J. Antimicrob. Chemother. 34, 195–203.

Ottesen, E.A., Ramachandran, C.P., 1995. Lymphatic filariasis infection and disease: control strategies. Parasitol. Today 11, 129–131.

PDR, 2001. Albenza™, in: Physicians' Desk Reference, 55th ed. Medical Economics Co., Montvale, NJ, pp. 3058–3059.

Pengsaa, K., Na-Bangchang, K., Limkittikul, K., Kabkaew, K., Lapphra, K., Sirivichayakul, C., Wisetsing, P., Pojjaroen-Anant, C., Chanthavanich, P., Subchareon, A., 2004. Pharmacokinetic investigation of albendazole and praziquantel in Thai children infected with *Giardia intestinalis*. Ann. Trop. Med. Parasitol. 98, 349–357.

Reynolds, J.R. (Ed.), 1993. Albendazole, in: Martindale: The Extra Pharmacopoeia, 30th ed. Pharmaceutical Press, London, p. 4.

Richard-Lenoble, D., Kombila, M., Rupp, E.A., Pappayliou, E.S., Gaxotte, P., Nguiri, C., Aziz, M.A., 1988. Ivermectin in loiasis and concomitant *O. volvulus* and *M. perstans* infections. Am. J. Trop. Med. Hyg. 39, 480–483.

Shen, G.R., Zhang, C.E., Zhou, X.Q., You, B.Y., Yang, Y., 1983. [Clinical observations on the effect of pyquiton on hepatic function]. Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi (Journal of Parasitology and Parasitic Diseases) 1, 37–39 [in Chinese].

Shenoy, R.K., Kumaraswami, V., Rajan, K., Thankom, S., Jalajakumari, 1993. A comparative study of the efficacy and tolerability of single and split doses of ivermectin and diethylcarbamazine in periodic brugian filariasis. Ann. Trop. Med. Parasitol. 87, 459–467.

Shenoy, R.K., Dalia, S., John, A., Suma, T.K., Kumaraswami, V., 1999. Treatment of the microfilaraemia of asymptomatic brugian filariasis with single doses of ivermectin, diethylcarbamazine or albendazole, in various combinations. Ann. Trop. Med. Parasitol. 93, 643–651.

Shenoy, R.K., Suma, T.K., John, A., Arun, S.R., Kumaraswami, V., Fleckenstein, L.L., Na-Bangchang, K., 2002. The pharmacokinetics, safety and tolerability of the co-administration of diethylcarbamazine and albendazole. Ann. Trop. Med. Parasitol. 96, 603–614.

Stephenson, L.S., Latham, M.C., Adams, E.J., Kinoti, S.N., Pertet, A., 1993. Physical fitness, growth and appetite of Kenyan school boys with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved four months after a single dose of albendazole. J. Nutr. 123, 1036–1046.

Thein-Hlaing, Thane-Toe, Than-Saw, Myat-Lay-Kyin, Myint-Lwin, 1991. A controlled chemotherapeutic intervention trial on the relationship between *Ascaris lumbricoides* infection and malnutrition in children. Trans. R. Soc. Trop. Med. Hyg. 85, 523–528.

Ubalee, R., Thanavibul, A., Banmmairuroi, V., Kamanikom, B., Na-Bangchang, K., Karbwang, J., 1997. A simple high performance liquid chromatographic method for simultaneous determination of albendazole and albendazole sulfoxide in biological fluids. J. Trop. Med. Parasitol. 20, 36–39.

US Food and Drug Administration, 1999. Guidance for Industry: In vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Rockville, MD, November 1999.

Vazquez, M.L., Jung, H., Sotelo, J., 1987. Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. Neurology 37, 1561–1562.