Annals of Tropical Medicine & Parasitology

ISSN: 0003-4983 (Print) 1364-8594 (Online) Journal homepage: https://www.tandfonline.com/loi/ypgh19

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To cite this article: R. K. Shenoy, T. K. Suma, A. John, S. R. Arun, V. Kumaraswami, L. L. Fleckenstein & K. Na-Bangchang (2002) The pharmacokinetics, safety and tolerability of the co-administration of diethylcarbamazine and albendazole, Annals of Tropical Medicine & Parasitology, 96:6, 603-614, DOI: 10.1179/000349802125001663

To link to this article: https://doi.org/10.1179/000349802125001663

Annals of Tropical Medicine & Parasitology, Vol. 96, No. 6, 603–614 (2002)

The pharmacokinetics, safety and tolerability of the co-administration of diethylcarbamazine and albendazole

R. K. SHENOY*, T. K. SUMA†, A. JOHN*, S. R. ARUN*, V. KUMARASWAMI‡, L. L. FLECKENSTEIN§ and K. NA-BANGCHANG¶

**Filariasis Chemotherapy Unit, T.D. Medical College Hospital, Alappuzha – 688 011, India*
†Department of Medicine, T.D. Medical College Hospital, Alappuzha – 688 011, India
‡Tuberculosis Research Centre, Spurtank Road, Chetput, Chennai – 600 031, India
§College of Pharmacy, 427 S, Pharmacy Building, University of Iowa, Iowa City, IA 52242–1123, U.S.A.
¶Faculty of Allied Health Sciences, Thammasat University, 99 Mu 18, Paholyothin Road, Klongluang District, Pathumtani 12121, Thailand

Received 18 June 2002, Accepted 27 June 2002

The pharmacokinetics, safety and tolerability of single, oral doses of diethylcarbamazine (DEC) and albendazole, given alone or in combination, were investigated in a double-blind, randomized and placebo-controlled trial involving 42 amicrofilaraemic subjects living in an area of India where lymphatic filariasis is endemic. The subjects (34 males and eight females, aged 18–52 years and weighing 46–66.5 kg) were randomly allocated to one of the three drug groups. Fourteen were given just DEC (6 mg/kg), another 14 were given just albendazole (400 mg) and the remaining 14 were given both DEC (6 mg/kg) and albendazole (400 mg). Blood samples for pharmacokinetic study were collected at specified intervals before and after drug administration. Plasma concentrations of DEC and albendazole/albendazole sulphoxide were estimated using gas chromatography and HPLC, respectively. The safety and tolerability of the treatments were evaluated through clinical and laboratory assessments.

Both the DEC and albendazole were well tolerated when given alone or in combination, no adverse events being observed. In all three treatment groups, the drugs were rapidly absorbed from the gastro–intestinal tract although there was marked inter-individual variation. The pharmacokinetics of DEC, albendazole and albendazole sulphoxide were similar, whether each drug was given alone or in combination. These results indicate that there is no adverse pharmacokinetic or pharmacodynamic reason why DEC and albendazole should not be co-administered to control lymphatic filariasis.

In many tropical countries, lymphatic filariasis (LF) caused by *Wuchereria bancrofti* or *Brugia malayi* is still a major health problem, affecting nearly 119 million people (Michael *et al.*, 1996). Until recently, control of this disease was largely based on a combination of chemotherapy with diethylcarbamazine (DEC), used in various dosages, and vector control (Andrade *et al.*, 1995). The results of recent trials with DEC and ivermectin have demonstrated that the use of a combination of these two drugs is superior to that of either drug alone, providing sustained clearance of microfilaraemia for as long as 1 year, in both bancroftian (Moulia-Pelat *et al.*, 1995) and brugian (Shenoy *et al.*, 1998) infections. It has also been shown that effective control of the infections can also be achieved using single, annual doses of a combination of albendazole (a broad-spectrum anthelmintic) with DEC or ivermectin. Single doses of albendazole–DEC or albendazole–ivermectin appear equally effective at clearing *W. bancrofti* microfilaraemias for prolonged periods (Addis

Reprint requests to: R. K. Shenoy
E-mail: rkshenoy2000@yahoo.com; fax: +91 477 251353.

DOI: 10.1179/000349802125001663

et al., 1997; Ismail *et al.*, 1998). In brugian microfilaraemia, albendazole–DEC seems more effective than albendazole–ivermectin (Shenoy *et al.*, 1999, 2000). Albendazole appears to be a particularly good drug to use against LF since it not only clears microfilaraemias but also has some adulticidal activity on the filarial parasites and clears intestinal helminths (WHO, 1996).

The effectiveness of albendazole–DEC offers a new option for countries, such as India, which are not endemic for onchocerciasis or loiasis and where ivermectin is not presently available. However, despite clear evidence of the clinical efficacy of albendazole–DEC, there is no information available on the tolerability of this combination or of the possible pharmacokinetic interactions that may occur when albendazole and DEC are given concurrently. The subjects used in most of the published studies on this combination have been asymptomatic microfilaraemics. In such subjects, it may be impossible to distinguish drug-related adverse events from the inflammatory reactions induced by the microfilaria-killing effect of the drugs. To some extent, the frequency and severity of adverse events (acute pain, fever, and inflammation of scrotal sac and adjacent tissues) following long-term treatment of *W. bancrofti* infections with 600-mg doses of albendazole (Addis *et al.*, 1997; Ismail *et al.*, 1998) have discouraged trials of the use of albendazole (alone or in combination) against LF. The aims of the present study were to determine if there were any detrimental pharmacokinetic interactions when DEC and albendazole were co-administered and to determine the safety and tolerability of the combination.

SUBJECTS AND METHODS

Subjects

During village surveys of LF, the methodology of the present study was explained to the residents of an area of India where lymphatic filariasis is endemic (the Cherthala and Ambalapuzha *taluks* of Alappuzha district), who were then invited to participate. To be enrolled, a subject had to: be aged $\geqslant 18$ years; weigh $\geqslant 35$ kg; be non-pregnant (confirmed by pregnancy test, if necessary) and not lactating; be amicrofilaraemic, asymptomatic and seronegative for HIV and the surface antigen of hepatitis B virus (HBsAg); appear healthy on clinical examination; report that they had not ingested any drugs or herbal treatments (including alcohol or recreational drugs) in the previous 14 days or any antifilarial or anthelmintic drugs in the previous 6 months; have no history of convulsions, other problems associated with the central nervous system, chronic renal, hepatic or cardio-respiratory disease or intolerance of DEC or albendazole; and give laboratory-test results that fell within the ranges considered 'normal' (e.g. $\geqslant 10$ g haemaglobin/dl and a haematocrit of at least 30%; see below). Between 7 June 2000 and 28 September 2000, 34 men and eight women, with a median age of 31.5 years (range = 18–52 years) and a median weight of 57.5 kg (range = 46–66.5 kg), were enrolled after they had given their written, informed consent. The study protocol was approved by the Ethical Committee of T.D. Medical College, Alappuzha, India.

Clinical Evaluation

Before treatment on day 0, each subject was given a detailed clinical assessment and checked for microfilaraemia (by membrane filtration of a sample of 'night' blood), seropositivity in ELISA for HIV or HBsAg, haemoglobin concentration, haematocrit level, leucocyte densities (by total and differential counts), platelet densities, serum concentrations of bilirubin, creatinine, alanine and aspartate aminotransferases and alkaline phosphatase, fasting blood sugar, and blood urea concentration, and by urinalysis.

Each subject was hospitalized for days 0–4 (so that the safety, tolerability and pharmacokinetics of each treatment could be assessed) and asked to return to hospital for a final

follow-up on day 8. On four occasions (24, 48 and 72 h post-treatment and on day 8), a standardized checklist was used to record vital parameters and any signs or symptoms of possible adverse events. The pre-treatment laboratory investigations were repeated on days 3 and 8.

Study Design

The subjects recruited for the study were admitted to the in-patient ward of T.D. Medical College Hospital in batches of three. The subjects in each batch were then randomly allocated, one/treatment group, to the three treatment groups (giving a total of 14 subjects/group). Each subject was then given a single oral dose of DEC (6 mg/kg) plus placebo albendazole, a single oral dose of albendazole (400 mg) plus placebo DEC or a single oral dose of DEC (6 mg/kg) plus albendazole (400 mg).

The drugs used were 50-mg tablets of DEC citrate (Glaxo Wellcome, Research Triangle Park, NC) or placebo DEC (Glaxo Wellcome), and 200-mg tablets of albendazole (SmithKline Beecham, Philadelphia, PA) or placebo albendazole (SmithKline Beecham). As only whole tablets of DEC were used, the total dose given to those receiving DEC was the calculated dose (i.e. that necessary to give 6 mg/kg) $\pm$ 25 mg. Before the treatments, all of the tablets for each subject were placed in a bottle labelled with the randomization code. Since the absorption of albendazole improves with food (Edwards and Breckenridge, 1988), all drug doses were given within 20 min of a standard breakfast. Paracetamol and antihistaminics, where required, were the only other drugs that were permitted during the study period.

Pharmacokinetics

Samples (10 ml) of venous blood were collected in EDTA-coated tubes before drug administration (0 h) and 20, 40, 60 min and 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-treatment. The blood samples taken up to 12 h post-treatment were collected through a cannula left in an antecubetal vein whereas the 24-, 36-, 48- and 72-h samples were each obtained by direct venepuncture. Each sample was centrifuged (1200 $\times$ g, 10 min) immediately after it had been collected and two aliquots of the plasma (each of at least 2.5 ml) were stored in labelled cryostorage tubes (Laxbro, Pune, India) at -20°C until analysis.

The concentrations of DEC, albendazole and albendazole sulphoxide (the active metabolite of albendazole) in each sample of plasma were determined, at the University of Iowa's College of Pharmacy (Iowa City, IA), by gas chromatography (GC), GC and HPLC, respectively. The coefficients of variation, calculated as a measure of inter-assay precision and accuracy for the DEC analysis, were $<7\%$ and the deviations from mean were 1.7%, 2.6% and 0.8% at 120, 1000 and 2000 ng DEC/ml, respectively. The lower limit for the estimation of the DEC was taken to be 70 ng/ml. For the albendazole assays, the coefficients of variation for albendazole itself were $<10\%$ and the deviations from the mean were 12.4%, 3.7% and 0.8% at 20, 400 and 600 ng/ml. For albendazole sulphoxide, the coefficients of variation 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 lower limit for the estimation of albendazole or albendazole sulphoxide was taken to be 20 ng/ml.

For each subject, the appropriate pharmacokinetic parameters were estimated from the plots of plasma concentration (of DEC, albendazole or albendazole sulphoxide) *v.* time, using non-compartmental pharmacokinetic analysis (Gibaldi, 1989). The time at the which maximum plasma concentrations occurred (t_{max}) and the maximum plasma concentration (C_{max}) were obtained directly from the concentration–time data. The terminal-phase elimination half-life ($t_{1/2z}$) was calculated as $0.693/\lambda_z$, where λ_z is the elimination rate constant calculated from a log–linear regression of at least four of the

concentration–time data-pairs. The area under the concentration–time curve from zero time to the last observed time (AUC_{0-t}) was calculated using the linear trapezoidal rule (for ascending data points) or the log–linear trapezoidal rule (for descending data points). The area under the concentration–time curve extrapolated from the last data-point to infinity ($AUC_{0-\infty}$) was estimated by dividing the regressed concentration at the last time-point by the estimated elimination rate constant. Oral clearance (CL/F) was estimated as dose/$AUC_{0-\infty}$, and the apparent volume of distribution (V_z/F) was estimated as $[(CL/F)/\lambda_z]$. No values of λ_z, $AUC_{0-\infty}$ or $t_{1/2z}$ were reported and analysed for subjects who did not exhibit a terminal log–linear phase in their concentration–time plot.

Data Analysis

The influence of treatment arm and treatment period (i.e. day of enrollment) was assessed using analysis of variance (ANOVA), the untransformed t_{max}, CL/F, V_z/F and $t_{1/2z}$ data and the logarithmically transformed $AUC_{0-\infty}$ and C_{max} data. Analysis of the pharmacokinetic interactions following the administration of oral doses of DEC and albendazole was performed for all pharmacokinetic parameters in three pairs: the pharmacokinetics of DEC when given alone *v.* when given with albendazole and the pharmacokinetics of albendazole and albendazole sulphoxide when albendazole was given alone *v.* when given with DEC. Since small, consistent, systemic-exposure differences could result in statistical significance without any clinical relevance for the key parameters indicative of absorption (C_{max}) and systemic drug availability ($AUC_{0-\infty}$), evaluation of the drug interaction based on these two parameters was performed according to the recommendations of the United States Food and Drug Administration (Anon., 1999). Based on these recommendations and the pharmacokinetic data already available (Hawking, 1979; Awadzi *et al.*, 1986; Eberhard *et al.*, 1991), a drug–drug interaction was considered significant if the upper limit of the 90% confidence interval (CI) for the (log-transformed) geometric mean value of either C_{max} or $AUC_{0-\infty}$ for the combination treatment was more than 3-fold (DEC) or 5-fold (albendazole and albendazole sulphoxide) higher than the corresponding value for the single-drug treatments. Evaluation of drug–drug interactions using the pharmacokinetic parameters other than C_{max} and $AUC_{0-\infty}$ — t_{max}, V_z/F, CL/F, λ_z and $t_{1/2z}$ — was based on statistical analysis using the Mann–Whitney U-test for non-normally distributed data.

The baseline demographic and clinical data for each treatment group were compared using χ^2 tests (for the qualitative data) or Wilcoxon sign-rank tests (for the quantitative data). The incidences of adverse events in each of the treatment groups were assessed by comparing baseline (0-h) values for each of the 'safety variables' monitored with those recorded at various times post-treatment. For each statistical test, a P-value of <0.05 was taken as an indication of statistical significance.

RESULTS

At enrolment, all of the 42 subjects investigated appeared healthy and clinically normal (as verified by the results of their pre-treatment, clinical and laboratory assessments). Their allocation to one of the treatment groups produced three groups that were similar in terms of the demographic, clinical and laboratory characteristics of their members. At the doses given, both DEC and albendazole were well tolerated. The only adverse events observed — fever, headache, myalgia, cough and blocked nose on days 0–2 in one subject who had received a single oral dose (450 mg) of DEC alone — were attributed to a mild upper respiratory infection.

Pharmacokinetics

The plasma-concentration–time plots for DEC, following a single oral dose of 6 mg/kg, either alone (14 subjects) or in combination with 400 mg albendazole (14 subjects), are presented in Figure 1. The concentration–time profiles of albendazole and of albendazole sulphoxide, following a single oral dose of 400 mg albendazole alone (14 subjects) or in combination with 6 mg DEC/kg (14 subjects), are presented in Figures 2 and 3, respectively.

Although oral DEC was rapidly absorbed from the gastro–intestinal tract, there was marked inter-individual variation in its absorption. The coefficients of variation for the DEC concentrations measured from 20 min to 72 h post-treatment ranged between 11.7% and 69.7%. In most cases, the drug was detectable in the plasma 20 min post-treatment but fell to undetectable levels within 36–48 h.

Oral albendazole, although absorbed from the gastro–intestinal tract, was rapidly bio-transformed to its active metabolite, albendazole sulphoxide. In three subjects, albendazole concentrations were detectable in the plasma as early as 20 min post-treatment (either when the drug had been given alone or in combination with DEC). Albendazole was only detectable in the plasma within 24 h of treatment and that too at low concentrations (0–209 ng/ml). Albendazole sulphoxide was detectable in plasma from as early as 20 min after treatment (either with albendazole alone or with albendazole and DEC). As with DEC, there were marked inter-individual variations in the plasma concentrations of both albendazole and albendazole sulphoxide, with coefficients of variation varying, over time (20 min–72 h post-treatment), from 6.3% to 66.6% and from 19.2% to 78.4%, respectively.

The pharmacokinetics of DEC, albendazole and albendazole sulphoxide, when DEC and albendazole were given alone or in combination, are summarized in Table 1. When the crude t_{max}, CL/F, V_z/F and $t_{1/2z}$ data and the logarithmically transformed C_{max} and $AUC_{0-\infty}$ data were subjected to an ANOVA, the results did not indicate any influence of treatment arm or period on any of the pharmacokinetic parameters. Considerable inter-individual variation was observed in most of the pharmacokinetic parameters of DEC, albendazole and albendazole sulphoxide, the associated coefficients of variation ranging from 11.7% to 67.9%, 25.5% to 114.5% and 19.6% to 70.3%, respectively. Less than 15% of each value of $AUC_{0-\infty}$ fell below the extrapolated part of the plot. The t_{max}, CL/F, V_z/F and $t_{1/2z}$ values for DEC, albendazole and albendazole sulphoxide when DEC or albendazole was given alone were the same as when the two drugs were co-administered ($P > 0.05$ for each comparison). In terms of the key pharmacokinetic parameters indicative of absorption (C_{max}) and systemic availability ($AUC_{0-\infty}$; Table 2), there was no evidence that DEC or albendazole had any influence on any of the pharmacokinetic parameters of the other (when the drugs were given in combination) or on those of albendazole sulphoxide.

No λ_z, $AUC_{0-\infty}$ or $t_{1/2z}$ values were reported or analysed for eight subjects (two who had received albendazole alone and six who had been given albendazole with DEC) who had albendazole concentrations during the terminal elimination phase that fell below the limit of quantification.

DISCUSSION

The present article appears to be the first published in which the pharmacokinetics of the combined administration of DEC and albendazole is described. The propensity of these drugs for pharmacokinetic (concentration–time) and pharmacodynamic (adverse reaction) interactions when given concurrently has also been assessed.

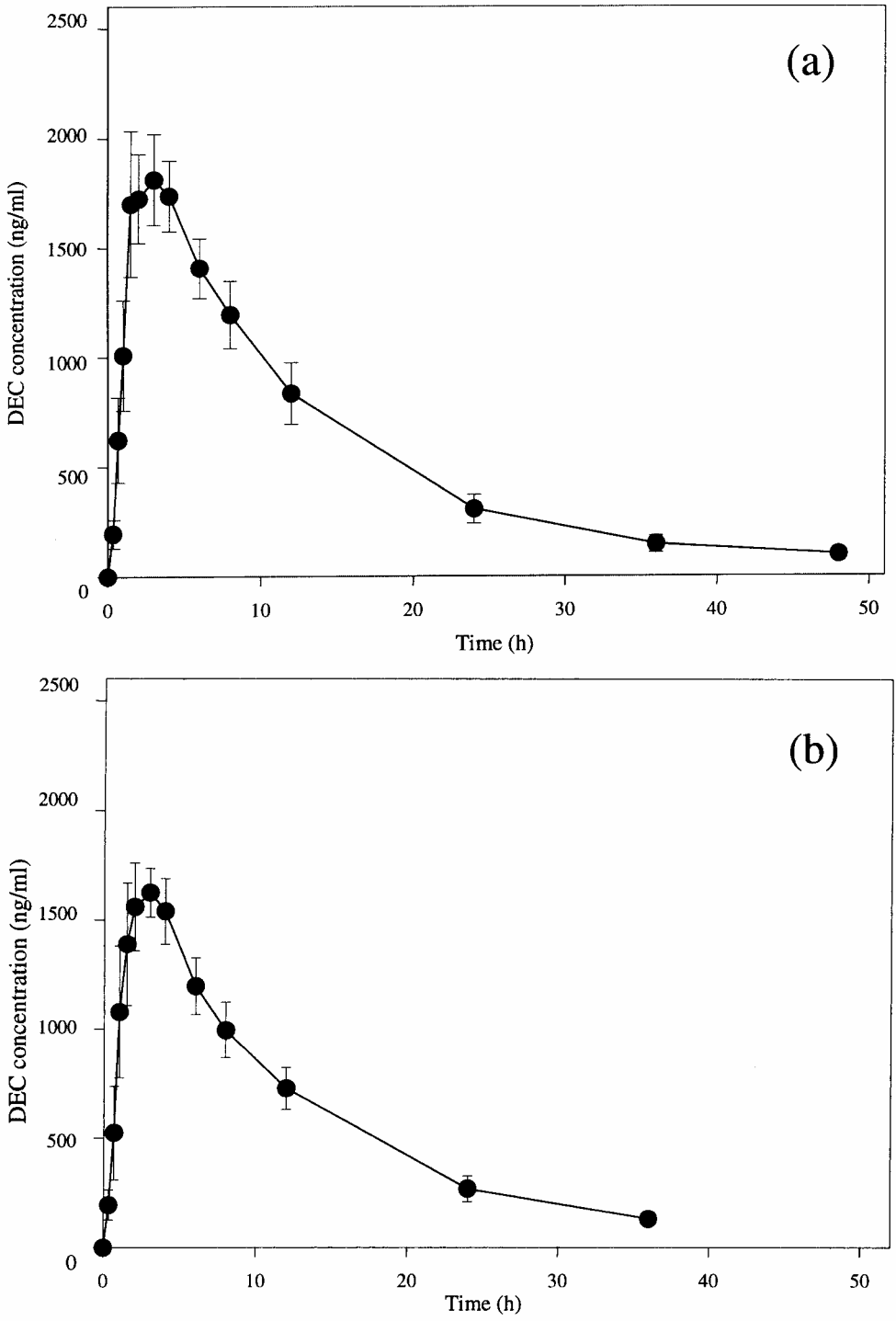

FIG. 1. Plots of the mean plasma concentrations of diethylcarbamazine (DEC) *v.* time post-treatment, observed when the subjects were treated with DEC alone (a) or in combination with albendazole (b). Vertical lines indicate S.D.

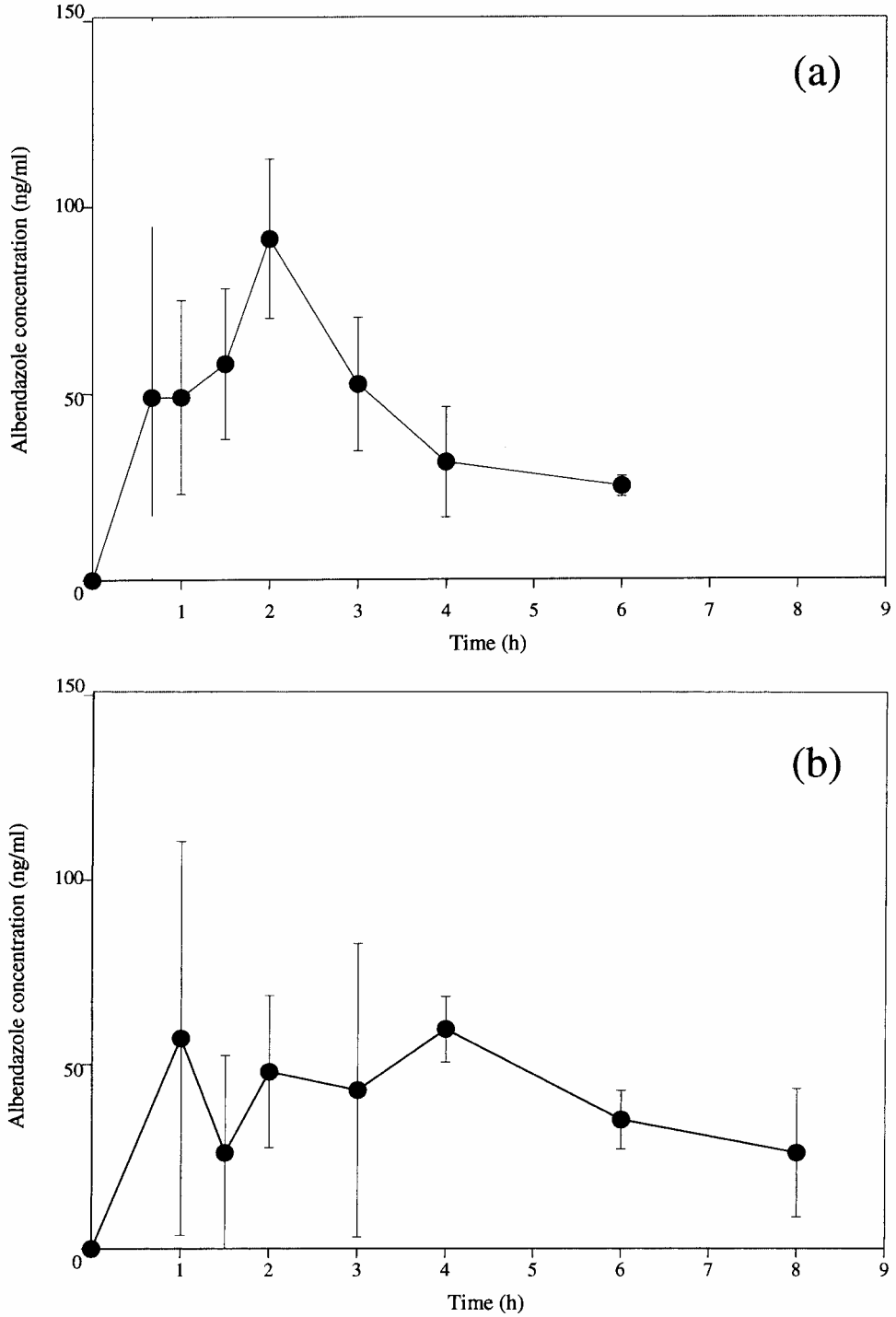

FIG. 2. Plots of the mean plasma concentrations of albendazole *v.* time post-treatment, observed when the subjects were treated with albendazole alone (a) or in combination with diethylcarbamazine (b). Vertical lines indicate S.D.

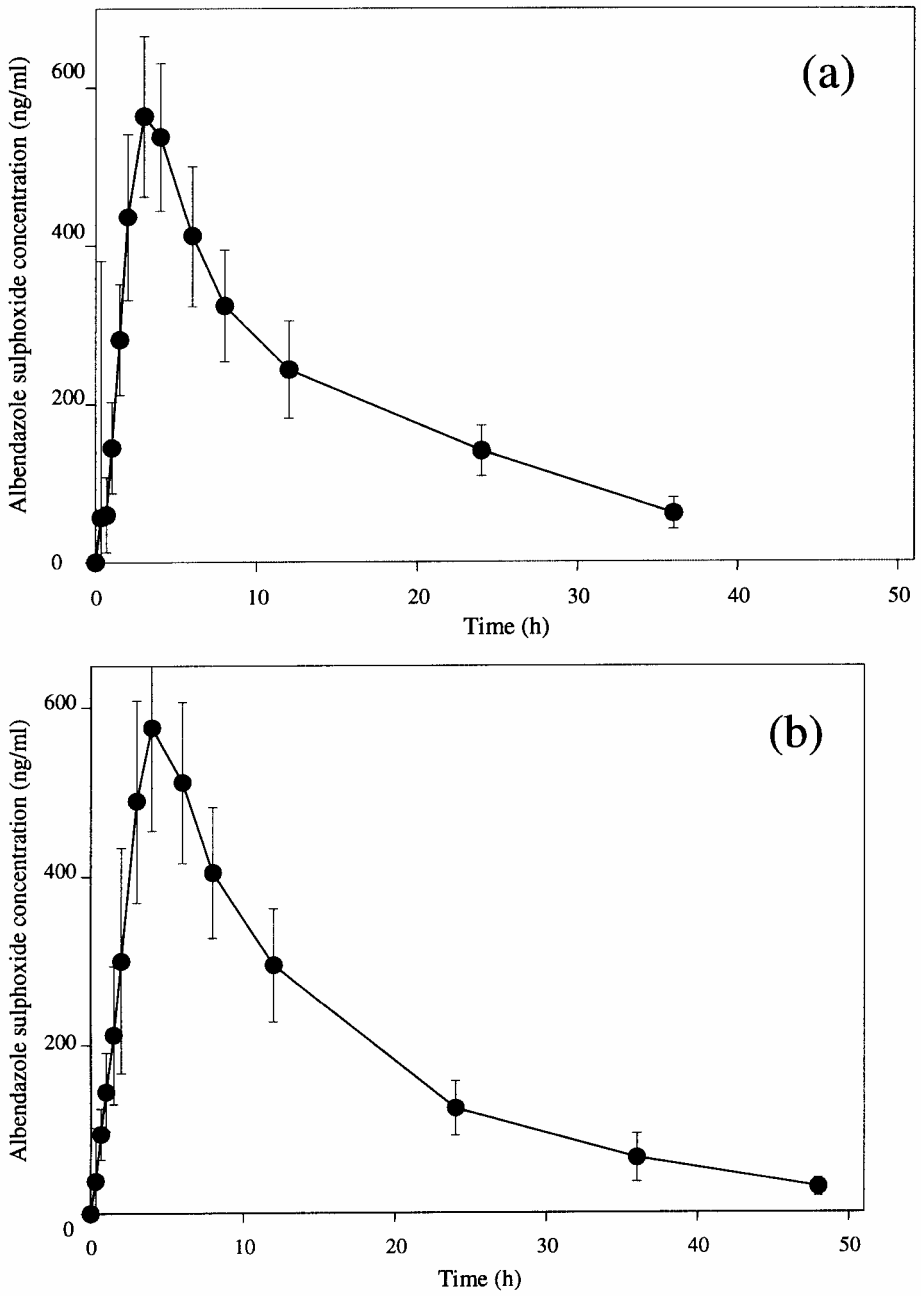

FIG. 3. Plots of the mean plasma concentrations of albendazole sulphoxide *v.* time post-treatment, observed when the subjects were treated with albendazole alone (a) or in combination with diethylcarbamazine (b). Vertical lines indicate S.D.

For each drug, the absorption and disposition phases when that drug had been given alone appeared very similar to those observed when the drug had been given in a combination. The pharmacokinetics of albendazole and its major plasma metabolite albendazole sulphoxide observed in the present study were in accordance with those

TABLE 1. *The pharmacokinetic parameters of diethylcarbamazine (DEC), albendazole (ALB) and albendazole sulphoxide when DEC (6 mg/kg) and ALB (400 mg) were given alone or in combination*

	DEC, in those treated with:		ALB, in those treated with:		ALB sulphoxide, in those treated with:	
Parameter*	DEC alone	ALB–DEC	ALB alone	ALB–DEC	ALB alone	ALB–DEC
C_{max} (ng/ml)						
Geometric mean and (95% CI)	1930 (1813–2093)	1813 (1751–1886)	79 (66–680)	63 (50–101)	583 (526–680)	573 (508–712)
No. of subjects	14	14	13	11	14	14
t_{max} (h)						
Median and (95% CI)	3.0 (2.0–3.0)	2.5 (2.0–3.0)	2.0 (2.0–2.0)	3.0 (2.0–3.0)	3.0 (2.0–4.0)	3.0 (3.0–4.0)
No. of subjects	14	14	13	11	14	14
AUC_{0-t} (ng.h/ml)						
Geometric mean and (95% CI)	23,850 (21,648–28,090)	21,514 (19,779–24,171)	189 (151–9488)	154 (125–351)	6830 (6047–9488)	6630 (5949–9118)
No. of subjects	14	14	12	8	14	14
$AUC_{0-\infty}$ (ng.h/ml)						
Geometric mean and (95% CI)	25,643 (23,352–29,666)	23,318 (21,565–25,872)	295 (226–1017)	430 (356–553)	7461 (6610–10,172)	7222 (6484–9780)
No. of subjects	14	14	12	8	14	14
V_z/F (litre)						
Median and (95% CI)	182.0 (141.3–204.7)	187.9 (159.9–204.8)	3628 (2322–5592)	3098 (970–8861)	739.6 (559.9–905.8)	711.6 (542.2–1063.7)
No. of subjects	14	14	12	8	14	14
CL/F (litre/h)						
Median and (95% CI)	14.5 (10.9–17.6)	14.3 (12.8–16.8)	1429 (985–2478)	1000 (459–1253)	48.7 (38.0–80.0)	44.4 (35.2–105.1)
No. of subjects	14	14	12	8	14	14
$t_{1/2z}$ (h)						
Median and (95% CI)	9.0 (7.6–10.2)	8.7 (7.5–8.7)	1.5 (1.1–2.6)	2.6 (0.7–7.5)	10.2 (7.1–12.3)	10.3 (7.0–13.5)
No. of subjects	14	14	12	8	14	14

CI, Confidence interval.
*The pharmacokinetic parameters recorded when each drug was used alone were all similar to those observed when the drugs were used in combination (Mann–Whitney U-test; $P > 0.05$ for each).

TABLE 2. *Evaluation of the interactions between albendazole (ALB) and diethylcarbamazine (DEC), based on the 90% confidence intervals for the geometric mean values (CI-GM) of the key pharmacokinetic parameters* C_{max} *and* $AUC_{0-\infty}$*, for DEC, ALB, albendazole sulphoxide, observed when the drugs were given alone or in combination**

	DEC		ALB		Albendazole sulphoxide	
Parameter	Threshold for DEC alone	CI-GM for ALB–DEC	Threshold for ALB alone	CI-GM for ALB–DEC	Threshold for ALB alone	CI-GM for ALB–DEC
C_{max}(ng/ml)	5790	1751–1886	237	50–101	1749	508–712
$AUC_{0-\infty}$(ng.h/ml)	76,929	21,565–25,872	885	356–553	22,383	6484–9780

*For a drug interaction to be considered significant, the upper limit of the CI-GM for the combination had to exceed a certain threshold. The thresholds were set as the (upper limit of the CI-GM seen when the drug was used alone) multiplied by 5 (for DEC) or 3 (for albendazole).

reported previously, in which the rapid elimination of the parent drug was demonstrated (Penicaut *et al.*, 1983; Marriner *et al.*, 1986; Guan *et al.*, 1990; Orme *et al.*, 1990; Edwards *et al.*, 1994; Jung *et al.*, 1997). The absorption of albendazole has been found to be enhanced in the presence of food (Edwards and Breckenridge, 1988). In the present study, however, although the drug was always taken with food, albendazole itself was poorly absorbed from the gastro–intestinal tract and was almost undetectable in the plasma. The low systemic availability of albendazole may be attributed not only to the drug's poor gastro–intestinal absorption but also to its extensive metabolism by hepatic and mucosal enzymes, to albendazole sulphoxide and, to a lesser extent, other metabolites (Bogan and Marriner, 1980; Edwards and Breckenridge, 1988). Albendazole sulphoxide is the pharmacologically active substance which contributes much of the antiparasitic activity of albendazole (Dollery, 1991). When 400 mg albendazole were given, either alone or concurrently with DEC, the C_{max} of albendazole sulphoxide from 2–3 h post-treatment was 220–250 ng/ml. The estimated terminal-phase half-life ($t_{1/2z}$) for the metabolite was 8–9 h. Albendazole sulphoxide was detectable in plasma within 20 min of the treatment and its t_{max} (2–6 h) almost coincided with that of the parent drug (1–4 h). The wide variation seen in the systemic exposure to albendazole sulphoxide may reflect inter-individual variation in the extent and/or rate of absorption from the gastro–intestinal tract, including the extent of first-pass metabolism of albendazole.

The rate of absorption of DEC from the gastro–intestinal tract was more rapid than that of albendazole and its elimination was much slower (with median $t_{1/2z}$ of 8.0–9.0 h for DEC and only 1.5–2.5 h for albendazole). The disposition kinetics of DEC seen in the present study were similar to those already reported (Bogan and Marriner, 1980; Edwards *et al.*, 1981*a*, *b*; Adjepon-Yamoah *et al.*, 1982; Edwards and Breckenridge, 1988), whether the drug was given alone or with albendazole. A single dose of DEC at 6 mg/kg bodyweight produced a median peak plasma concentration of 1254–2348 ng/ml in 2–4 h. This level is higher than the blood concentration believed to be required for antifilarial activity (800–1000 ng/ml; Stephenson and Wiselka, 2000). The drug was widely distributed in all tissues and therefore its apparent volume of distribution (V_z/F) was large.

The present results indicate that the pharmacokinetics and pharmacodynamics of a single oral dose of DEC (6 mg/kg) are unaffected by the co-administration of a single oral dose of albendazole (400 mg), and *vice versa*. Both drugs were well tolerated and no drug-related adverse effects were seen either when they were given alone or in combination. In view of the clinical efficacy

of these agents, the use of an annual, single, combined dose of DEC plus albendazole can be recommended, even on a mass scale, for preventing the transmission of the parasites causing LF. The combination should result in improved treatment without any fear of increasing the severity or incidence of adverse reactions to either drug. The inclusion of albendazole would not only help to clear microfilaraemias but would also have the added advantage of clearing intestinal helminths from the treated population (WHO, 1996). This might offer a public-health impact that is far greater than the elimination of LF alone and improve compliance (Ottesen *et al.*, 1997). Use of drug combinations rather than single drugs in filariasis-elimination programmes may also slow the development of resistance to the individual drugs. The pharmacokinetic profiles of DEC and albendazole sulphoxide (the active, antifilarial metabolite of albendazole) appear generally well matched in terms of their half-lives. These are, however, subjects that merit further investigation. Adjustment of the dose regimen, to take account of the pharmacokinetic and pharmacodynamic characteristics of DEC and albendazole/albendazole sulphoxide, could improve the clinical efficacy of the DEC–albendazole combination.

ACKNOWLEDGEMENTS. We gratefully acknowledge the sociological help received from P. V. Jaykala and V. Sunitha, the laboratory assistance of S. Bindhu Thomas, and the secretarial assistance of S. Sindhu. Our thanks are also due to the Principal and Superintendent of T.D. Medical College and Hospital, for their support and encouragement. This investigation received financial support from the African Programme for Onchocerciasis Control, the Onchocerciasis Control Programme in West Africa, and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

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