TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1998) 92, 94–97

Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis

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Abstract

In a 'blind' trial on 50 male asymptomatic microfilaraemic subjects with *Wuchereria bancrofti* infection, the safety, tolerability and filaricidal efficacy of a single dose of albendazole (alb) 600 mg alone or in combination with ivermectin (iver) 400 μg/kg or diethylcarbamazine citrate (DEC) 6 mg/kg was compared with a single dose of the combination DEC 6 mg/kg and iver 400 μg/kg over a period of 15 months after treatment. All but one subject, with 67 microfilariae (mf)/mL, had pre-treatment counts >100 mf/mL. All 4 treatments significantly reduced mf counts, but alb/iver was the most effective regimen for clearing mf from night blood: 9 of 13 subjects (69%) were amicrofilaraemic by membrane filtration 15 months after treatment compared to one of 12 (8%), 3 of 11 (27%), and 3 of 10 (30%) in the groups treated with alb, alb/DEC, and DEC/iver, respectively. Filarial antigen tests suggested that all 4 treatments had significant activity against adult *W. bancrofti*; alb/DEC had the greatest activity according to this test, with antigen levels decreasing by 77% 15 months after therapy. All 4 regimens were well tolerated and clinically safe, although mild, self-limited systemic reactions were observed in all treatment groups. These results suggest that alb/iver is a safe and effective single dose regimen for suppression of microfilaraemia in bancroftian filariasis that could be considered for control programmes. Additional benefits of this combination are its potent, broad spectrum activity against intestinal helminths and potential relative safety in areas of Africa where DEC cannot be used for filariasis control because of co-endemicity with onchocerciasis or loiasis.

Keywords: filariasis, *Wuchereria bancrofti*, chemotherapy, albendazole, ivermectin, diethylcarbamazine, Sri Lanka

Introduction

Bancroftian filariasis is an important cause of morbidity, deformity and disability in the developing world with over 100 million people affected in more than 70 countries (OTTESEN & RAMACHANDRAN, 1995). Most programmes for control of bancroftian filariasis include mosquito control measures and drug therapy for suppression of microfilaraemia. The 2 most widely employed strategies for drug therapy are mass treatment of entire populations with a 12 d course of diethylcarbamazine citrate (DEC) and selective treatment with the same regimen limited to persons identified by screening to have microfilaraemia and/or clinical filariasis. Both treatment strategies have proved to be cumbersome, difficult to administer, expensive and, in many instances, ineffective.

Filariasis control programmes are increasingly moving toward a strategy of repeated, annual mass therapy of endemic populations with single dose therapy (OTTESEN & RAMACHANDRAN, 1995). Safe and effective single dose regimens should not only improve compliance and coverage of mass therapy programmes, but also decrease costs by simplifying drug distribution. In a review of multicentre trials of single dose ivermectin vs. DEC for bancroftian filariasis, CHODAKEWITZ (1995) observed that ivermectin reduced microfilaria (mf) levels to a greater degree than DEC in the first few months after therapy, but residual mf levels 12 months after therapy were approximately equal after either treatment. Other studies reported that single dose combinations of DEC and ivermectin were more effective for reducing microfilaraemia than either drug alone (DREYER *et al.*, 1995; MOULIA-PELAT *et al.*, 1995). Recent studies have shown that the benzimidazole derivative albendazole has significant antifilarial activity in human onchocerciasis (AWADZI *et al.*, 1991; CLINE *et al.*, 1992), loiasis (KLION, *et al.*, 1993), and bancroftian filariasis (JAYAKODY *et al.*, 1993). Treatment courses in these trials ranged from 7 to 21 d. The present study was performed to determine the safety, tolerability, and efficacy of single dose albendazole, alone or in combination with DEC or ivermectin, as well as DEC with ivermectin for treatment of bancroftian filariasis.

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Patients and Methods

Fifty 'healthy' male asymptomatic microfilaraemic volunteers between the ages of 18 and 58 years (median 35) were admitted to the National Hospital of Sri Lanka in Colombo during May–August 1994, after obtaining informed consent. The pre-treatment mf count was computed in each case by averaging counts of 2 samples, one taken during the week before admission and the other on the pre-study day (day 0) in hospital. Pre-treatment blood samples (1 mL) were diluted 1:4 and 1 mL of the diluted samples was filtered through a 3 μm pore size Nuclepore® membrane for mf counting. After treatment, 1 mL samples of undiluted blood were similarly processed. All but one subject, with 67 mf/mL, had pre-treatment counts of over 100 mf/mL. Albendazole (Zentel®) and DEC (Banocide®) were obtained from SmithKline Beecham, UK and Burroughs Wellcome, India, respectively, while ivermectin tablets were supplied by Merck Sharp & Dohme, France. Patients were stratified according to their pre-treatment mf counts (ADDISS *et al.*, 1993) and randomly allocated to one of 4 single dose treatment groups (Table 1). The study was 'blind' to the extent that patients, clinicians evaluating adverse effects, and laboratory staff carrying out safety tests and measuring mf and antigen levels were unaware of the individual treatment schedules.

All patients were admitted to hospital for 5 d, and therapy was administered after breakfast on day 1. Blood samples for mf counts, laboratory tests and parasite antigen level determination were drawn between 21:00 and 21:30 on days 0, 4 and 14 and months 1, 2, 3, 6, 9, 12 and 15. Laboratory tests (which included white blood cell count and estimation of haemoglobin, haematocrit, serum bilirubin, serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase and serum creatinine) were carried out on days 0, 4 and 14 and thereafter only if necessary. A routine urinalysis was included with the laboratory tests. Electrocardiograms (ECGs) were prepared on day 0 and repeated 36 h after treatment.

All patients were clinically monitored 4 times a day