CLINICAL TRIAL OF TWO REGIMENS OF ALBENDAZOLE AND IVERMECTIN TO TREAT TANZANIAN BANCROFTIAN FILARIASIS AND ONCHOCERCIASIS

W.H. Makunde, J.J. Massaga, F.M. Salum, R.W. Makunde, Savael Z.X. & M.J. Taylor

Abstract: The combination of antifilarial drugs is among the various new therapeutic strategies available for the control of lymphatic filariasis. This combination seems to be the most effective efficacious strategy. In this study we compare the efficacy and safety of albendazole alone and in combination with ivermectin for the treatment of co-infection of bancroftian filariasis and onchocerciasis and single infection of bancroftian filariasis. This is the first time a hospital based double blind placebo controlled clinical trial has been conducted. Forty-one individuals both sex, age between 15 and 55 years old (15 with co-infection of bancroftian filariasis and onchocerciasis and 26 single infection of bancroftian filariasis) with concentration of 108-2231 microfilariae /ml of *Wuchereria bancrofti* and 5-206 microfilariae /skin snip of *Onchocerca volvulus*. The study individuals were randomly assigned to receive single dose treatment of albendazole (400mg) with ivermectin (150mg/kg) or albendazole (400mg) alone. The combination of albendazole plus ivermectin was more effective in mf reduction in both *Onchocerca volvulus* and *Wuchereria bancrofti* than the placebo. In the single infection of bancroftian filariasis, a 99.8% mf reduction was achieved in the combination of albendazole and ivermectin while in albendazole alone a reduction of 69.3% was observed. The adverse reactions observed in this study (co-and single infections) were mild and tolerable.

Combine treatment with albendazole and ivermectin was more effective and rapid in clearing microfilariae in bancroftian filariasis and onchocerciasis than treatment with albendazole alone, without increase in severity and frequency of adverse reactions.

This combination is likely to be the way forward strategy towards elimination of bancroftian filariasis and onchocerciasis and if possible, loiasis when co-exist and that diethylcarbamazine (DEC) can not be used because of the severe systemic adverse reaction.

Introduction

Lymphatic filariasis and onchocerciasis are vector-borne diseases transmitted by *Wuchereria bancrofti* (*W.bancrofti*) and *Onchocerca volvulus* (*O.volvulus*) respectively. These diseases persists as a major cause of clinical morbidity, deformity and disability in the developing world with more than 120 million people affected by *W.bancrofti* and 17.6 million by *O.volvulus* [1 & 2] The chronic pathologies caused by these diseases impose a significant impediment to socio-economic development in the tropics and subtropics [3, 4]. The widely used control measures in most endemic countries are vector management and chemotherapy. Currently the most common strategy adopted is the mass treatment of the whole population using either diethylcarbamazine (DEC) or ivermectin. In areas where

bancroftian filariasis is endemic, it has shown that, mass treatment with DEC or ivermectin either annually or semi-annually is safe and effective [9]. However, there has been drawback in the use of DEC in areas where both bancroftian filariasis and onchocerciasis co-exist because of the associated severe adverse reactions [Mazzotti reaction] in onchocerciasis patients. On the other hand, ivermectin requires periodic repeated administration to achieve long-term effects. Recently albendazole, a benzimidazole derivative has shown to have significant antifilarial activity against several filarial parasites of animals and humans [6, 11, 5, 7, 6, 10 & 12]. This drug when combined with either ivermectin or DEC has been demonstrated to effectively clear bancroftian filariasis microfilaraemics [8 & 13]. There is no available information on the effectiveness of the drug in-patients with co-infection of bancroftian filariasis and onchocerciasis. This study was conducted to determine the safety, tolerability, and efficacy of albendazole alone and in combination with ivermectin for the treatment of two groups of individuals, those with co-infections of bancroftian filariasis and onchocerciasis and those with bancroftian filariasis alone.

Patients and Methods

Screening of study individuals was carried in Maramba A and Mhinduro villages, which are rural communities in Muheza district North eastern Tanzania, where bancroftian filariasis and onchocerciasis co-exist. Individuals with co-infection and, fulfilling the inclusion criteria [asymptomatic, with pre-treatment counts of over 100 mf/ml for bancroftian filariasis and 5 mf /skin snip for onchocerciasis] were recruited for co-infections. Among those screened and positive for *W. bancrofti* only, meeting the inclusion criteria were recruited for single infection. Individuals were admitted at Bombo Regional hospital, Tanga to allow close laboratory investigation, clinical evaluation and monitoring of any adverse effects. Recruitment and admission to hospital was done after informed oral consent was obtained from each individual.

Clinical and Laboratory Procedures

Each individual was subjected to physical examination prior to specimen sampling. Specimen collection was done at night between 21:00 and 01:00hrs and were collected on admission day, D0, and on Day 2, 3, and 7 during the hospitalisation period. Study patients were clinically monitored every six hours during the first 48 hours following treatment. Adverse effects were assigned a score of (0=no alteration), (1= mild alteration), (2=moderate alteration) and (3=severe alteration). The pre-treatment microfilariae count was computed in each case by averaging counts of two samples, one collected three days before admission and the other on day 0 pre-drug administration at the hospital.

Results

Forty-seven individuals aged between 15 and 55 years were screened for dual infection of bancroftian filariasis and onchocerciasis and single infection of bancroftian filariasis respectively (15 females and 32 males). Forty-one individuals completed the seven-day admission period, whereas 40 of the recruited individuals completed 12 months. Sixteen apparently health, (13 males and 3 females) asymptomatic, microfilaraemics and microfilaridermics with dual infections of bancroftian filariasis and onchocerciasis were recruited for the trial but only fifteen individuals (3 females & 12 males) completed the 12 months follow up. In the single infection 30 apparently health microfilaraemics (10 females and 16 males) with single infection of bancroftian filariasis were recruited, only 25 individuals were analysed at the end of the study.

Pre-treatment Examination in co-infection

The pre-treatment mf counts in the studied individuals ranged from 108-2231/ml in bancroftian filariasis, whereas in onchocerciasis was from 5-206 mf /skin snip. The microfilarial geometric mean intensity [GMI] for *O.vulvulus* was 47-mf/skin snip and 12-mf/skin snip for the albendazole plus ivermectin and placebo treatment group respectively. In *W.bancrofti*, the GMI was 361 in the albendazole plus ivermectin treatment regimen and 473 mf/ml of blood in placebo group. The difference was significant in *O.volvulus* infection, however, the difference in *W.bancrofti* was not significant. The biochemical serum levels and haematological indices were within normal range, during pre-treatment period in co and single infections respectively. However, clinically, there was no significant variation in blood pressure, both systolic and diastolic between the two treatment regimens, placebo and the combination of albendazole plus ivermectin and albendazole alone. Whereas in single infection, the mf count in the studied group ranged from 108-2340/ml. The microfilarial geometric mean intensity [GMI] was 507.0 and 507.0 mf /ml for *W.bancrofti* in the single dose albendazole alone and the combination of albendazole plus ivermectin respectively.

Microfilarial Clearance Rates

The mean intensities for each treatment regimen in the two treatment groups, albendazole plus ivermectin against placebo have shown that, the combination regimen, reduced *O.volvulus* by 96.4% whereas in the placebo the reduction was by 25.8% by day 7 post-treatment. However, the mean clearance in *W.bancrofti* was 99.7% in the albendazole plus ivermectin combination therapy, while in the placebo a reduction of 54.1% was achieved by day seven post-treatment. A 99.0% reduction in [GMI] mf in the single infection of bancroftian filariasis was observed within 72 hours of the administration of ivermectin plus albendazole. In the single dose of albendazole, a reduction of 81.6% was observed. On the other hand 69.3 % and 99.8% reduction was achieved in the single regimen of albendazole alone and the combination of albendazole plus ivermectin respectively by day seven post-treatment.

Post-treatment Evaluation

Post-treatment levels of the functional tests and haematological indices between the two treatment regimens, placebo and the combination of albendazole plus ivermectin were all within the normal range. Nonetheless, the rest of the parameters assessed, blood pressure, heart frequency and body weight were within the normal range between the two treatment regimens of albendazole plus ivermectin, in both single and dual infections.

Adverse Reactions

The adverse reactions in the majority of the individuals first occurred between 24, 48 hours and on day 6 post-treatment. These effects generally lasted for 48 hours. The commonly reported adverse reactions were fever, itching, pruritus, oedema and palpitation. Adverse reactions were generally mild in intensity and tolerable with mean score of one in both single and co-infection. There was no treatment given except paracetamol 500mg tablets to alleviate the reactions. In the co-infection of bancroftian filariasis and onchocerciasis 9 (60%) individuals experienced adverse reaction. In single infection adverse reactions were reported in 11 (42.3%) of the studied individuals.

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