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The effect of eight half-yearly single-dose treatments with DEC on *Wuchereria bancrofti* circulating antigenaemia

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Summary The effect of eight half-yearly treatment rounds with diethylcarbamazine (DEC; 6 mg/kg bodyweight) on *Wuchereria bancrofti*-specific circulating filarial antigen (CFA), a marker of adult worm infection, was followed in 79 individuals who were CFA-positive before start of treatment. Half of these were also microfilariae (mf)-positive. Microfilaraemia decreased rapidly after onset of treatment and became undetectable after four treatments. Circulating antigenaemia also decreased progressively, but at a much slower rate. After two, four and eight treatment rounds, the mean CFA intensity was reduced by 81, 94 and 98%, and the prevalence of CFA positivity was 85, 66 and 57%, compared with pre-treatment, respectively. CFA clearance rates were negatively related to pre-treatment CFA intensities, and were higher among pre-treatment mf-negative individuals than among pre-treatment mf-positive individuals. Even among patients who had pre-treatment CFA intensities above the upper measuring level (32 000 antigen units), and who continued to have intensities above this level after treatment, a decrease in post-treatment CFA intensities was obvious from a continuous decrease in ELISA optical

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density values. Repeated DEC therapy thus appears to have a slow but profound and persistent macrofilaricidal effect, which in the long run may be beneficial to populations undergoing DEC-based control interventions by reducing the probability of future morbidity development.

1. Introduction

Diethylcarbamazine (DEC) has for many years been the most widely used drug for treatment and control of lymphatic filariasis (Melrose, 2003), which on the African continent results from infection with the mosquito-borne filarial parasite *Wuchereria bancrofti*. DEC is an effective microfilaricide, which rapidly reduces the microfilarial load from the blood of infected humans, as well as the prevalence and intensity of microfilaraemia in treated communities (Meyrowitsch and Simonsen, 1998; Simonsen et al., 2004). In most African countries, where DEC may provoke severe adverse reactions in patients with onchocerciasis, a combination of ivermectin and albendazole has now replaced DEC for control within the Global Programme for the Elimination of Lymphatic Filariasis (GPELF), whereas repeated mass treatment with DEC or its combination with albendazole are the key measures applied for control of lymphatic filariasis in other parts of the world (Molyneux and Zagaria, 2002; Ottesen, 2000).

The effectiveness of DEC in killing adult filarial worms, being responsible for most pathology in lymphatic filariasis, is less clear. The recovery of dead and degenerating adult worms in excised nodules appearing after DEC treatment is evidence that at least some adult worms are killed (Figueredo-Silva et al., 1996; Ottesen, 1985). Ultrasound studies of worm nests in vivo (Norões et al., 1997) have similarly shown that the 'filaria dance sign' becomes undetectable in a proportion of nests after DEC treatment, and that palpable nodules subsequently develop around the quiet nests contain degenerating adult worms. However, in a significant proportion of nests, the 'filaria dance sign' was not affected by the DEC treatment, indicating that many adult worms were not killed by DEC during the study period.

Diagnosis of lymphatic filariasis has been considerably improved in recent years through development of methods for detection of *W. bancrofti*-specific circulating filarial antigens (CFA) in human blood, and two brands of test kits based on this technology have been marketed for sensitive and specific diagnosis of *W. bancrofti* infection (Melrose et al., 2004). One of these is the qualitative Binax Filariasis NOW® rapid card test [http://www.binax.com], which gives a yes/no answer, and the other is the semi-quantitative TropBio Og4C3 ELISA [http://www.tropbio.com.au], which measures CFA intensity in arbitrary antigen units. The antigen detected by both of these tests is primarily of adult worm origin, and a CFA-positive response is a marker of adult worm infection (Chanteau et al., 1994). Several studies have shown that DEC treatment of *W. bancrofti*-infected individuals induces a decrease in CFA intensity, but generally the observed decrease is small and few or no individuals revert to a CFA-negative status within a period of 1–2 years after treatment (Eberhard et al., 1997; Kazura et al., 1993; Nicolas et al., 1997; Ramzy et al., 2002; Schuetz et al., 2000; Weil et al., 1988). Even very aggressive treatment with DEC over a 2 year period resulted in limited CFA clearance (Freedman et al., 2001). This has raised the issue of whether some adult filarial worms are insensitive to DEC.

We have previously reported on the early effect of half-yearly DEC mass treatment on *W. bancrofti* infection in two East African communities with different levels of endemicity (Simonsen et al., 2004). To quantify the effect of repeated treatments with DEC on circulating antigenaemia over a longer period, and to assess to what extent clearance occurs, we followed the CFA intensity in 79 individuals from a high-endemicity community in Tanzania (Masaika village) who were CFA-positive at pre-treatment and who complied with eight half-yearly treatments with DEC.

2. Materials and methods

2.1. Study design

The study was carried out in Masaika village, about 25 km inland from the Indian Ocean coast in Pangani District (Tanga Region), northeastern Tanzania. A description of the village is given by Simonsen et al. (2002), and results from pre-treatment examination for *W. bancrofti* infection of the inhabitants in July 1999 were presented by Simonsen et al.