

A randomized, double-blind, placebo-controlled study with diethylcarbamazine for the treatment of hydrocoele in an area of Tanzania endemic for lymphatic filariasis

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Abstract

Hydrocoele is common in men in *Wuchereria bancrofti*-endemic areas, the treatment for which is currently surgical intervention. Two community studies have recently suggested that the antifilarial drug diethylcarbamazine (DEC) may have a beneficial effect of reducing the size of hydrocoeles of filarial origin. To test this hypothesis, a double-blind, placebo-controlled study was carried out in 1998 and 1999 in an area of north-eastern Tanzania where microfilaria (mf) carrier rates and hydrocoele prevalence rates were known to be high. Ninety-eight adult male volunteers (aged ≥ 15 years) with chronic hydrocoele received DEC 300 mg per day for 12 days (49 patients), or placebo (49 patients). Circumferential and ultrasonographic measurements of the scrotum, and a serum sample for measuring *W. bancrofti* antigen, were obtained at the onset and after 3, 6 and 12 months. Scrotal size and hydrocoele fluid volume indices were calculated. No statistically significant differences in volumetric measurements between the DEC and placebo groups were found at any of the follow-ups. Separate analyses dividing patients by antigen status, hydrocoele size or presence of thickening of the scrotal skins gave similar results. Geometric mean intensity of *W. bancrofti* antigen was significantly lower in the DEC group than in the placebo group ($P = 0.008$), indicating that lack of compliance was not a significant factor. Two months into the treatment trial, mass treatment with monthly low-dose DEC was given to the rest of the community. We conclude that DEC is not effective in reducing the size of hydrocoele of filarial origin. Interventions to replace or supplement hydrocoelelectomy should be investigated.

Keywords: filariasis, *Wuchereria bancrofti*, chemotherapy, diethylcarbamazine, men, hydrocoele, Tanzania

Introduction

Lymphatic filariasis is endemic in many parts of the tropical world, with an estimated 120 million people suffering from infection and/or clinical illness (MICHAEL *et al.*, 1996). Clinical manifestations include episodes of adenolymphangitis (ADL), hydrocoele, lymphoedema and elephantiasis of legs, arms, breasts, vulva, scrotum and penis, and more rarely chyluria and tropical pulmonary eosinophilia (WHO, 1992a). Hydrocoele may be accompanied by thickening of the spermatic cord and changes in the scrotal skin and subcutaneous tissue including oedema, fibrosis, formation of nodules or ulceration, and oozing of lymph through the skin (JORDAN, 1957). Scrotal swellings vary in size and severity, and may become debilitating, causing reduced mobility, reduced working capacity and sexual incapacitation (DREYER *et al.*, 1997).

Diethylcarbamazine (DEC), currently the treatment of choice for lymphatic filariasis in onchocerciasis-free areas, is a very efficient microfilaricide but less efficient as a macrofilaricide (NORÖES *et al.*, 1997). Some cross-sectional population studies have suggested that community mass treatment with DEC may have a beneficial effect on hydrocoele prevalence in the community and may cause a reduction in the size of smaller hydrocoeles (MEYROWITSCH *et al.*, 1996; BOCKARIE *et al.*, 1998). However, no randomized, placebo-controlled studies have been published about the use of DEC for treatment of filarial hydrocoele. In order to estimate the efficacy of DEC on hydrocoele size in individual patients, we conducted a randomized, double-blind, placebo-controlled treatment trial.

Subjects and Methods

Study area

This study was carried out in 1998 and 1999 in 2 villages located in Muheza District in north-eastern Tanzania, with a total population of about 2400 people.

The villages are highly endemic for *Wuchereria bancrofti* (LEMNGE, 1995; BERNHARD *et al.*, 2000), which is transmitted throughout the year, the main vectors being *Anopheles gambiae s.l.* and *An. funestus* (MBOERA *et al.*, 1997).

Treatment trial

Men (aged ≥ 15 years) with hydrocoele were invited to participate in the study. Study participants were interviewed about the duration and the nature of their symptoms and the degree of disability caused by the hydrocoele. A physical examination was carried out including measurements of the scrotal size by determining the distance from the root of the penis to the bottom of the hydrocoele sac (A) and the horizontal circumference (B) (WHO, 1992b). A scrotal size index was calculated by the formula $A \times B^2 / (4 \times \pi)$ to approximate the actual scrotal volume to a cylinder with height A and circumference B. A blood sample was taken and serum stored at -20°C for later analysis.

Hydrocoele fluid volume was estimated by ultrasound examination using an Aloka SSD-500 scanner (Aloka Co., Japan), a 3.5-MHz Aloka curved array transducer, and a Sony Videographic printer (UP-890CE; Sony Electronics Inc., Japan). A hydrocoele fluid volume index was calculated by multiplying the longest measures of height, width and depth of the hydrocoele sac, and in bilateral cases adding the results from the 2 sides. Volumes of the largest hydrocoeles could not be estimated using ultrasound.

Patients were randomly assigned to either active treatment with DEC 300 mg per day in 3 divided doses for 12 days (WHO, 1992a), or to vitamin B complex which was used as placebo. Randomization was done in 3 strata according to hydrocoele size: small (measurement $A < 8$ cm), intermediate ($A = 8-11$ cm), and large ($A > 11$ cm). In the analysis small and intermediate hydrocoeles were combined, since there were only a few individuals with small hydrocoeles. Measurements were repeated after 3, 6 and 12 months. *W. bancrofti* filarial antigen was measured with the TropBio ELISA test for serum specimens (Tropical Biotechnology Pty, Australia). Three specially trained male village assistants

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supervised tablet intake and checked for the occurrence of adverse reactions.

Two months after beginning the trial, monthly low-dose DEC was distributed for 1 year to village residents aged ≥ 1 year who were not part of the present study.

Data analysis

SPSS 8.0 for Windows was used for statistical analysis. Normally distributed values were compared using *t*-test, categorical and not normally distributed values using non-parametric tests, and proportions using χ^2 .

Ethical considerations

The study was reviewed and approved by the Tanzanian Commission for Science and Technology, by the Medical Research Co-ordinating Committee of the National Institute for Medical Research in Tanzania, and by the Central Scientific-Ethical Committee of Denmark. The study was conducted in accordance with the principles of the Helsinki II Declaration. Oral consent for participation was obtained from all participants. At the end of the study, untreated participants testing positive for *W. bancrofti* antigen were given DEC treatment.

Results

The main characteristics of the 98 study participants are shown in Table 1. mf counts ranged from 0 to 14 960 mf/mL, scrotal volume index from 184 to 4203 mL and hydrocoele fluid volume index from 17 to 2094 mL, with no significant difference between the DEC and the placebo group. The proportion of patients positive for *W. bancrofti* antigen was significantly higher in the DEC group than in the placebo group.

Seventy-two (73%) patients attended all 3 follow-up examinations. The effect of DEC and placebo on scrotal size and hydrocoele fluid volume is shown in Table 2, stratified for antigen status. There was a statistically significant reduction in scrotal size in the DEC group (antigen-positive and -negative individuals combined) after 3 months ($P < 0.0001$) and 6 months ($P = 0.02$)

but not after 12 months, and in the placebo group a statistically significant reduction at 3, 6 and 12 months ($P < 0.0001$, $P = 0.0150$ and $P = 0.0055$, respectively). Hydrocoele fluid volume remained constant in the DEC group throughout the study, and in the placebo group after 3 and 6 months, but showed a statistically significant increase in the placebo group after 12 months ($P = 0.0242$). There was no statistically significant difference between DEC and placebo at any of the time points for either of the measurements. This was true even when analysing separately by antigen status, by hydrocoele size (measurement A smaller or larger than 11 cm) or by presence or absence of scrotal skin thickening.

No severe adverse reactions were recorded. The most common complaints were fever, headache, joint pains and abdominal pains. There was no significant difference in the occurrence of adverse events in patients receiving DEC or placebo.

Six percent of individuals reported mild incapacitation when working, and 7% mild incapacitation during movement. Both work and movement incapacitation were significantly associated with scrotal size ($P = 0.021$ and $P = 0.023$ respectively), but not with age or *W. bancrofti* antigen status. Of 85 individuals responding to the question, 11 reported mild, 11 moderate, and 7 severe sexual incapacitation, with a significant association between degree of sexual incapacitation and increasing age ($P = 0.002$) and increasing scrotal size ($P = 0.039$), but not with *W. bancrofti* antigen status.

The geometric mean intensities (GMIs) of *W. bancrofti* antigen decreased in antigen-positive individuals receiving DEC and increased in the placebo group throughout the observation period (Table 3). After 12 months GMI in the DEC group was significantly lower than in the placebo group ($P = 0.008$).

Discussion

Lymphatic filariasis is probably the single most common cause of hydrocoele in endemic areas, and possibly worldwide, with an estimated 27 million men suffering from this condition (MICHAEL *et al.*, 1996). In lymphatic

Table 1. Baseline characteristics of the study participants

Group	n ^a	Mean age (years)	Mean duration of hydrocoele (years)	Percentage of men with:			
				<i>W. bancrofti</i> microfilaraemia	<i>W. bancrofti</i> antigenaemia	Scrotal hernia	Thickening of scrotal skin
DEC	49	50.7 (15-88)	11.3 (0-48)	38%	61%*	4%	29%
Placebo	49	48.4 (18-87)	13.2 (0-53)	24%	35%*	12%	35%

^aNumber of patients at baseline. * $P = 0.009$ (χ^2 test). The range of values is given in parentheses.

Table 2. Mean scrotal size and mean hydrocoele fluid volume in filariasis patients given diethylcarbamazine or placebo: percentage volume reductions since treatment start (baseline) are given in parentheses for each follow-up

	n ^a	Scrotal size (mL) ^b				Hydrocoele fluid volume (mL)			
		Baseline	3 month	6 month	12 month	Baseline	3 month	6 month	12 month
Antigen-positive individuals									
DEC	30	667	618 (10%)	663 (9%)	644 (7%)	372	384 (-7%)	378 (-10%)	379 (-2%)
Placebo	17	941	825 (12%)	830 (12%)	765 (10%)	256	264 (-6%)	260 (-9%)	303 (-29%)
Antigen-negative individuals									
DEC	19	1042	996 (11%)	982 (7%)	1046 (3%)	518	491 (-2%)	545 (-9%)	578 (-23%)
Placebo	32	754	640 (10%)	644 (5%)	660 (6%)	356	366 (-4%)	391 (-10%)	407 (-22%)

The mean volumes are those of patients present at the given follow-up time, and the percentage changes in volumes (positive for a reduction and negative for an increase) are the differences between initial and follow-up mean volumes of those individuals only.

^aNumber of patients at baseline.

^b8 patients with scrotal hernia were excluded from analysis of scrotal size reductions. DEC, diethylcarbamazine.

Table 3. Geometric mean intensity (/mL) of the concentration of *W. bancrofti* antigen of the 36 antigen-positive individuals with hydrocoele who were present at all follow-ups (percentage of initial value in parentheses)

Group	n*	Baseline	3 months	6 months	12 months
DEC	24	1367	1078 (79%)	882 (65%)	571 (42%)
Placebo	12	1363	1590 (117%)	1557 (114%)	2051 (150%)

*Number of patients at baseline.

filariasis the primary mechanism for development of hydrocoele is impeded flow of lymph fluid resulting from lymphangiectasia and inflammatory damage caused by adult worms (JUNGSMANN *et al.*, 1991). Lymphatic damage may subsequently be aggravated by infections, e.g., epididymo-orchitis.

Two papers report a beneficial effect on small hydrocoeles of community mass DEC treatment (MEYROWITSCH *et al.*, 1996; BOCKARIE *et al.*, 1998). The present study could not demonstrate any beneficial effect of DEC treatment on hydrocoeles, and, although only a few individuals with small hydrocoeles were included in this study, there was no indication of them benefiting from DEC treatment. The effect of DEC in reducing concentrations of *W. bancrofti* antigen rules out non-compliance or drug ineffectiveness as the cause of the lack of effect of DEC on hydrocoele size. It is undoubtedly true that continuous community mass treatment with antifilarial drugs eventually will reduce the prevalence of hydrocoele in the community, and in many cases the reduced burden of adult worms in the lymphatic system may lead to a slow improvement of the hydrocoele. This theory seems to be corroborated by FAN *et al.* (1995) who studied previously mf-positive individuals many years after eradication of lymphatic filariasis in an area. It was found that more individuals had experienced improvement or disappearance of hydrocoele than had experienced no change or aggravation.

Considerable fluctuations in scrotal size were observed during the study period which were similar for both treatment groups, and were probably attributable to external factors such as variations in ambient temperature, work load and type, and nutritional status. This finding stresses the importance of a control group when studying hydrocoele treatment responses.

Many patients complained of sexual dysfunction, a condition which has been reported in the literature (DREYER *et al.*, 1997), but not previously quantified. No studies of the underlying mechanisms for sexual dysfunction or of its frequency in hydrocoele patients compared to the general population have been published.

Hydrocoelelectomy remains the treatment of choice, but is a relatively expensive and like all surgical interventions potentially dangerous procedure, and alternative treatment strategies need to be investigated. These might include repeated aspiration of hydrocoele fluid from the scrotum, or aspiration followed by injection of a sclerosing substance in the tunica vaginalis (MUSA *et al.*, 1995; BRASLIS & MOSS, 1996). The long-term effects of community mass antifilarial treatment on individual hydrocoele size and on prevalence of hydrocoele also remain to be determined.

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