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Diethylcarbamazine in the treatment of patients with onchocerciasis

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Introduction

Onchocerciasis is a filarial disease resulting from infection with *Onchocerca volvulus* and is characterised by the presence of fibrous nodules in the skin and subcutaneous tissues. These represent the repository of adult worms which produce microfilariae responsible for the main, severe clinical manifestation of the disease, blindness. The disease is spread by the bite of the female blackfly, *Simulium* and occurs in a tropical belt in West and Central Africa, Central America and the Middle East. Infective larvae of *O. volvulus* enter the human host after the bite of an infected *Simulium*. The parasites grow into adult worms, mate and produce microfilariae. Female adults live for up to 15 years and produce several thousand microfilariae per day. These have a life span of 1 to 2 years and if ingested by a feed vector they develop into infective larvae which may be transmitted to a new host when the fly bites.

A major breakthrough in the treatment of onchocerciasis has been achieved with the development of ivermectin as a safe, single dose microfilaricide suitable for mass administration. The use of ivermectin as an antiparasitic agent in humans has recently been reviewed (Campbell, 1991). Ivermectin is superior to the established microfilaricide, diethylcarbamazine-citrate (DEC-C) in eliminating high parasite loads without producing severe reactions or ocular deficiency; it also has a more prolonged suppressive effect on skin and ocular microfilariae (Awadzi *et al.*, 1986; Diallo *et al.*, 1986; Greene *et al.*, 1985; Lariviere *et al.*, 1985).

Although ivermectin is now the microfilaricide of choice in onchocerciasis, it is expensive, not yet readily available in many endemic areas, and DEC-C is still widely used. It is therefore pertinent to review the limitations of DEC-C and to outline the methods that have been adopted in an effort to overcome them. Several of these approaches were developed and implemented at the Onchocerciasis Chemotherapy Research Centre (OCRC) at Tamlae, Ghana, in collaboration with the Liverpool School of Tropical Medicine and the Department of Pharmacology and Therapeutics of the University of Liverpool. They represent an attempt to apply the well-established principles of basic and clinical pharmacology to a potent chemotherapeutic agent whose adverse effects were a major drawback to its general acceptance as an agent for mass treatment.

Limitations in the use of diethylcarbamazine for onchocerciasis

Implicit in the administration of DEC-C to onchocerciasis patients is the assumption that reactions are inevitable and could be life threatening in very heavily infected patients. Existing ocular lesions are often aggravated and new lesions precipitated.

Treatment with DEC-C is suppressive as it has little effect on the adult worms; new microfilariae repopulate the skin and eye a few months after the initial treatment. Although repeated dosing is necessary, the reactions to each cycle of administration make DEC-C regimes unpopular and unsustainable (Anderson *et al.*, 1976; Sowa & Sowa, 1978).

Improvements in the use of diethylcarbamazine

Methods employed in attempts to improve the use of DEC-C have included a detailed study of the systemic reactions to treatment and their quantification; trials of various drugs as suppressants of the reactions; assessment of several dose regimes; a detailed study of the clinical pharmacology; modification of the pharmacokinetic profile; topical application and the combination of DEC-C with another microfilaricide, levamisole (Edwards & Breckenridge, 1988).

Reactions to DEC-C

DEC-C has little intrinsic toxicity. Large doses (10–20 mg base kg^{-1}) may cause anorexia, nausea, vomiting, headache and drowsiness. In the onchocerciasis patient

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however, reactions attributable to the death of microfilariae and first described by Mazzotti (1948) are observed. The main clinical features are summarised in Table 1.

The systemic reaction may occur in two phases. A 'primary' phase, a constant feature, commences within 24 h and manifests as a variable combination of increased itching, rash, headache, muscle aches, joint pains; gland tenderness, pain and swelling; hypotension, dizziness, tachycardia, fever and acute respiratory distress.

Severe symptomatic postural hypotension (SSPH) is a distinct feature which is characterised by severe hypotension occurring in the erect position and is usually associated with dizziness, weakness or faintness; syncope may occur or the patient may become restless and confused. The pulse often becomes impalpable. Recovery occurs rapidly in most cases on lying flat when bradycardia, drowsiness and diaphoresis occur.

The severity of the primary reaction to a fixed dose of DEC-C depends on the intensity of infection (Francis *et al.*, 1985); where different doses are given to patients with similar microfilarial loads, the severity increases with increasing dose (*vide infra*); reaction severity is thus related to the number of microfilariae killed.

The dangerous and alarming side effects of DEC-C (Bryceson *et al.*, 1977; Duke & Anderson, 1972, 1975; Fuglsang & Anderson, 1974; Rougemont *et al.*, 1976) result from the cumulative effect of very severe reactions occurring in multiple systems.

A 'secondary' phase may occur 2–6 days after the initiation of therapy. It commonly presents as a severe, symmetrical acute polyarthritis involving predominantly the knees, ankles, wrists, the interphalangeal joints and the shoulders. It is usually accompanied by a recrudescence of fever. Effusions develop, commonly in the knee joints, in which microfilaria *Onchocerca volvulus* can be demonstrated (Awadzi *et al.*, 1982a,b,c; Francis *et al.*, 1985).

Ocular reactions are common in patients with many microfilariae in the eye (Anderson *et al.*, 1976). These include itching, epiphora, photophobia, injection of the conjunctiva, lid swelling (which may completely shut the eye), limbitis and acute iridocyclitis.

Posterior segment changes (optic neuritis, choroidoretinitis) may not be detectable on routine ophthalmoscopy but manifest as loss of the peripheral visual field. Leakage of dye from the optic disc and disturbances of the retinal pigment epithelium are however demonstrable on fluorescein angiography (Bird *et al.*, 1980).

Quantification of reactions to DEC-C

Systemic reactions were quantified by bringing together commonly occurring features and applying to them a scoring system such that the disability experienced by each patient could be expressed numerically. The features which are classified as 'physiological' and 'non-physiological' are listed and scored in Table 2.

Scores for physiological parameters are based on deviations from basal values established during the pretreatment period; scores for non-physiological parameters are based on symptoms and signs. 'Mild' and 'moderate' categories are based on symptoms alone. Higher scores are obtained only when certain precisely defined clinical observations are recorded as well. Scores for rash depend on type as well as extent. The scoring system incorporates an in-built weighting system which highlights reactions that have significant clinical implications (Awadzi, 1980).

The quantification of the Mazzotti reaction was an essential pre-requisite to the assessment of the efficacy of various agents in reducing its severity, to the assessment of the severity of the reaction produced by various dose regimes of DEC-C and to the comparison of the severity of reactions to DEC-C with that of other microfilaricides.

Suppression of the Mazzotti reaction

The pathogenesis of the reaction is little understood. Putative mediators or mechanisms have included serotonin (Salazar Mallen & Chevez Zamora, 1965); histamine, serotonin, bradykinin, slow reacting sub-

Table 1 Common manifestations of the clinical reaction to microfilaricides in onchocerciasis patients (the Mazzotti reaction)

System/Features	*Manifestions*
Dermal	Pruritis
	Lesions – papules, oedema, urticaria, vesicles, scaling; – excoriations, ulcerations, pustules, crusts.
Lymphatic system	Lymphadenitis (pain, tenderness, swelling); lymphoedema.
Musculoskeletal	Headache, myalgia, arthralgia.
Cardiovascular	Tachycardia, hypotension, *SSPH, shock.
Other systemic	Febrile (fever, chills).
	Acute febrile polyarthritis.
Ocular	Epiphora, photophobia, facial oedema; Conjunctival injection, limbitis, anterior uveitis; Choroiodoretinitis, optic neuritis.

*Severe symptomatic postural hypotension.

Table 2 Scoring system for features used in the quantification of the Mazzotti reaction

Feature	*Score* 0	5	10	15	20
Physiological					
Pulse rate (increase min^{-1})	<20	20 to 35	36 to 51	51 to 67	≥68
Fall in MAP* (mm Hg)	<20	20 to <25	25 to 29	30 to 44	≥35 or CNS**
Temperature (°C)	<37.5	37.5 to <38	38 to <38.5	38.5 to <39	≥39
Respiratory rate (increase min^{-1})	<6	6 to <12	12 to <18	18 to <24	≥24
Non-physiological					
Pruritus	Nil	+	++	+++	++++
Gland pain	Nil	+	++	+++	++++
Gland tenderness	Nil	+	++	+++	++++
Joint pains	Nil	+	++	+++	++++
Muscle aches	Nil	+	++	+++	++++
Headache	Nil	+	++	+++	++++

*Mean arterial pressure = $^1/_3$ diastolic pressure + pulse pressure **CNS = Could not stand long enough for pressure to be measured *due to severe postural hypotension.* Pulse rate and blood pressure are scored in the lying and standing positions. + = mild ++ = moderate +++ = very severe ++++ = unbearable. Scoring system for rash not shown.

stance A (SRS-A) and prostaglandins (Henson *et al.*, 1979); generation of immune complexes and complement activation subsequent to microfilarial death (Bryceson *et al.*, 1977); mediators secreted from inflammatory cells, including eosinophils (Guerra-Caceres *et al.*, 1980).

One approach to the prevention of the development of the Mazzotti reaction is the use of antagonists to the putative mediators. Antihistamines have been used extensively with little success although only a few individual cases have been described (Fuglsang & Anderson, 1974). There have been conflicting reports regarding the prophylatic value of cyproheptadine, an antihistamine as well as an antiserotonin agent (Salazar Mallen *et al.*, 1962); Villamayor, 1963) and of methysergide, an antiserotonin agent used alone or in combination with indomethacin, an inhibitor of prostaglandin synthesis (Fuglsang & Anderson, 1976; Lagraulet *et al.*, 1974; Salazar Mallen & Chevez Zamora, 1965; Villamayor, 1970).

On the other hand, corticosteroids (given as cortisone, prednisone, triamcinolone, dexamethasone or betamethasone) either alone or in combination with other agents have been found to be effective in suppressing most of the reactions to DEC-C (Bernhard *et al.*, 1964; Duke & Anderson, 1972, 1975; Garcia Manzo *et al.*, 1965; Markel & Turner, 1957; Salazar Mallen *et al.*, 1962; Torroella, 1964).

In order to examine rigorously the role of mediators in the pathogenesis of the reaction, a number of double-blind placebo controlled studies were carried out at the OCRC from 1978 to 1980 (Awadzi *et al.*, 1982a,b,c). Candidate drugs included cyproheptadine, indomethacin, prednisone, and a combination of a short course (3 days) of prednisone with cyproheptadine. These drugs were started 12–24 h before DEC-C, except in the combination study when cyproheptadine or placebo preceded DEC-C by 45 min. DEC-C was given in a total dose of 1400 to 2400 mg over 7–10 days and systemic reactions to treatment were quantified.

A marked suppresion of the mean total reaction score occurred only in the group treated with the full course of prednisone (Awadzi *et al.*, 1982b). This effect is illustrated in Figure 1. Prednisone, however, had little effect on the severity of the itching; it delayed the onset but did not affect the extent of the rash and did not prevent the occurrence of the acute febrile polyarthritis of the secondary reaction. These results suggest that histamine, prostaglandins and serotonin release are not primarily involved in the reaction to DEC-C.

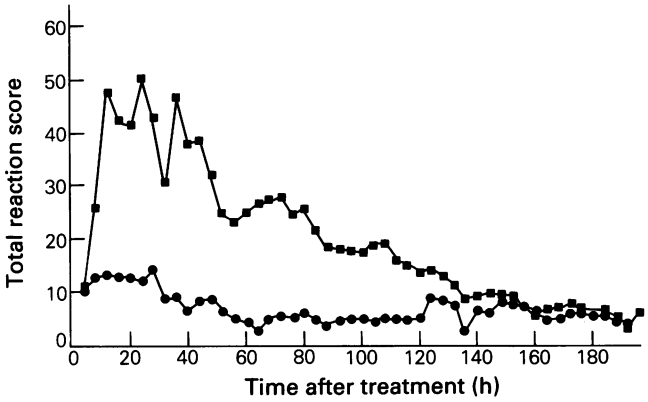

Figure 1 The effect of prednisone (n = 23, •——•) and placebo (n = 21, ■——■) on the overall Mazzotti reaction pattern in patients with onchocerciasis treated with diethylcarbamazine.
Note: reactions were scored in 4 hourly time intervals.

Dosage schemes of DEC-C

An 'ideal' dose regime of DEC-C is one that eliminates most of the initial microfilarial load, defines how therapy should be initiated, the total dose to be given and the period over which it should be administered, determines when and at what dose level subsequent DEC-C therapy should be given, avoids severe reactions both at the initial and subsequent phases of therapy and is amenable to mass distribution.

Several studies have been undertaken in pursuance of the ideal dose regimen for DEC-C; recent ones include those of Phillipon *et al.* (1981), Prod'Hon *et al.* (1979a,b), Rougemont *et al.* (1976), Sowa & Sowa, (1978). This problem was again examined at the OCRC at Tamale in the savanna area of northern Ghana where reinfection was unlikely due to vector control activities.

The aim of the studies was to outline a dose schedule of DEC-C which satisfied 'ideal' requirements by determining the response to a number of dose regimes in heavily infected patients. Features quantified included the microfilaricidal effect, the severity of the systemic reactions evoked and the rate of return of microfilariae to the skin.

Ten separate studies were conducted between 1978 and 1983 and the pooled data related to 401 patients and 20 treatment regimes. Patients were selected on the basis of high microfilarial counts and were followed up for up to 2 years after treatment. Total dose of DEC-C ranged from 100–6600 mg. In order to investigate the dose-response relationship five dosage groups were defined (Table 3).

The dose-response curve at one week after completion of treatment (a measure of microfilaricidal efficacy) for a 'standard patient' with an initial skin microfilarial load of 270/4 mg (as determined from the outer canthus, scapula, iliac crest and calf on the left side of the body) age 30 years and weight 54 kg is shown in Figure 2. The estimated overall total reaction is presented in Figure 3 and the re-population of the skin by microfilariae after a total dose of 1085 mg of DEC-C over 8 days is shown in Figure 4. The definition of a 'standard patient' is based on the approximate mean values observed in the data. Detailed analyses of the data have been presented by Fulford *et al.* (1987).

The findings from these studies as illustrated in Figures 2–4, may be stated as follows: a) a total dose of 2000 mg of DEC-C can reduce the microfilarial density from 240/4 mg to 10/4 mg, increasing the dose beyond this has little additional effect; b) only a minor increase in microfilaricidal efficacy occurs when the total dose is increased from 1300 mg to 2000 mg; c) the ED_{90} (the dose that will reduce the initial microfilarial load by 90% at 1 week) is approximately 500–600 mg; d) total reaction increases with total dose, the reaction to the 6600 mg dose being significantly greater than to the 2000 mg dose although the reductions achieved in skin microfilarial counts were similar; e) with a total dose exceeding 1000 mg skin microfilarial counts will not increase above 40/4 mg for approximately 4 months. DEC-C can thus be repeated at this time since severe systemic side effects are uncommon at this level of

Table 3 Dose schemes of DEC-C-grouping of the total dose administered

Group	*Total dose of DEC-C (mg)*	*Number of patients*
1	100	21
	200	29
2	500	21
	600	30
	625	25
3	1200	30
	1250	25
	1400	86
4	2000	41
	2400	73
5	6600	20
	Total	401

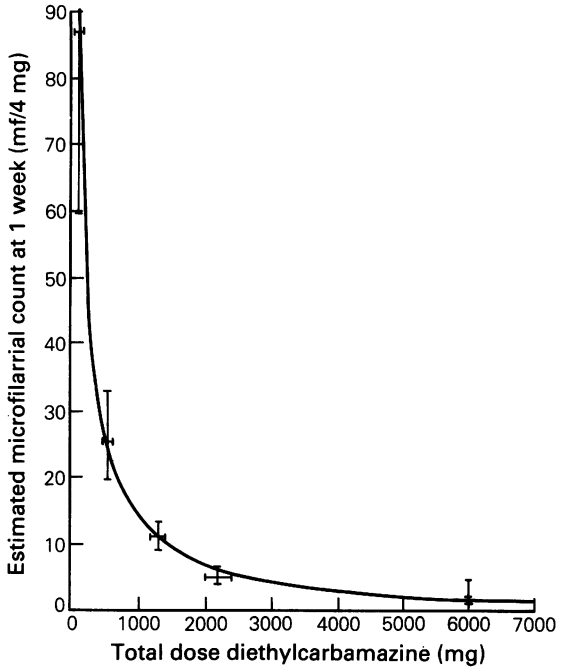

Figure 2 Dose-response curve for diethylcarbamazine at 1 week post-treatment (for a standard patient with an initial microfilarial load of 270 $(4\ mg)^{-1}$ (left outer canthus, scapula, iliac crest and calf) and an age of 30 years.
Note: vertical bars represent 95% confidence intervals for mean microfilarial count at each dosage level. Horizontal bars indicate range of doses used at each microfilarial count level (see Table 3). The smooth curve represents estimated microfilarial counts fitted to dose as a continuous variable. (From Fulford *et al.*, 1987, with permission).

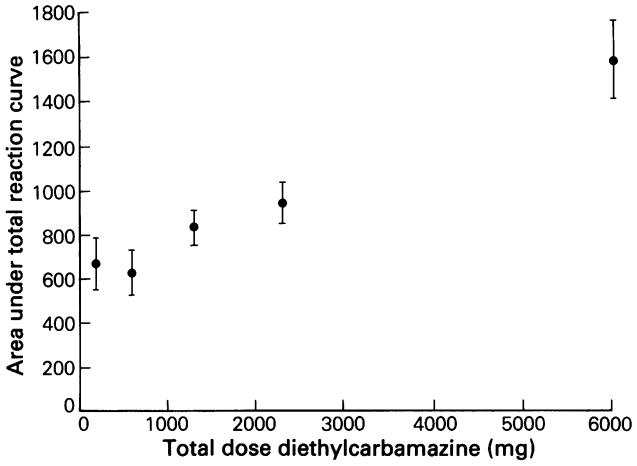

Figure 3 Reaction scores from five dose groups of diethylcarbamazine in a standard patient with an initial microfilarial load of 270 $(4\ mg)^{-1}$ and an age of 30 years.
Note: vertical bars represent 95% conficence intervals for mean area under total reaction curve at each dosage level (Table 3).

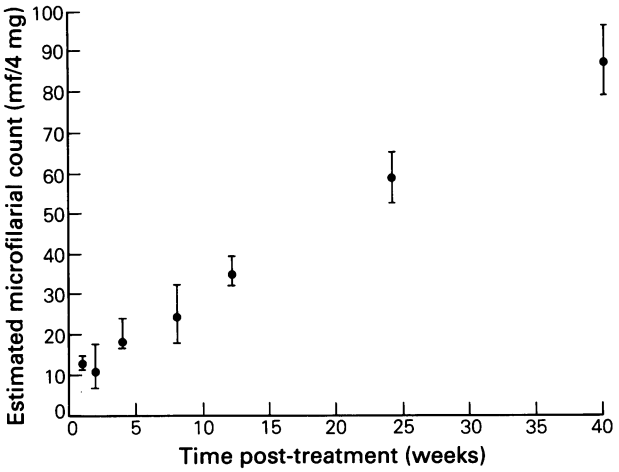

Figure 4 Repopulation graph of microfilarial load after treatment with diethylcarbamazine (for a standard patient with an initial microfilarial load of 270 $(4\ mg)^{-1}$, a total dose of 1085 mg, treatment duration 8 days and an age of 30 years. Note: vertical bars represent 95% confidence intervals for mean microfilarial count at each time point. (From Fulford *et al.*, 1987, with permission)

infection intensity and with an initial dose of 50 mg (Awadzi, personal observation).

A recommended dose regime of DEC-C for a 50 kg adult based on these studies could be as follows: initial dose 50 mg day 1; build-up 50 mg twice daily on day 2; maintenance 100 mg twice daily days 3 to 8; total dose 1350 mg; duration of therapy, 8 days; repeat dosage at 4 months.

The clinical pharmacology of DEC-C

The disposition of ^{14}C-labelled DEC-C after a single oral administration to onchocerciasis patients in northern Ghana was studied by Edwards *et al.* (1981a). The drug was rapidly and almost completely absorbed and peak plasma concentrations were achieved in 1–2 h. Elimination was also rapid and occurred by both renal and extra-renal routes with a half-life of 12 h. Most of the drug was excreted unchanged in the urine with only a small proportion as the *N*-oxide.

DEC-C is a basic compound and changes in urinary pH would be expected to alter the excretion of the drug. This effect was demonstrated by a significant increase in the elimination half-life and total body load of DEC-C and a significant diminution in renal clearance and total urinary excretion when an alkaline urine was maintained as opposed to an acidic urine (Edwards *et al.*, 1981b).

The practical implications of these pharmacokinetic studies for onchocerciasis chemotherapy include the following: a) the administration of DEC-C in twice daily dosage should provide significant blood drug concentration over a 24 h period, more frequent dosing is unnecessary; b) the rapid and almost complete absorption of DEC-C after oral administration and the attainment of high peaks in plasma concentration may contribute to the severe reactions that occur during treatment; c) manipulations of urinary pH may permit the administration of DEC-C in small doses which do not produce high peaks but persist for much longer periods, thereby producing a gradual but sustained microfilarial elimination without violent reactions; d) variations in the response to therapy—clinical and parasitological—in similar patients given the same dose of DEC-C may be related to differences in urinary pH such as may be determined by dietary factors.

Moderate urine alkalinization and low dose therapy with DEC-C

The effect of moderate urine alkalinization on low dose DEC-C therapy was investigated in 21 onchocerciasis patients at Tamale. In 11 patients an alkaline urine (pH > 7.5) was maintained during most of the treatment period by administering 2 g of sodium bicarbonate 6 hourly for three doses daily beginning 1 day before DEC-C. Ten patients acted as controls (pH < 7.0 during most of the treatment period). The dose of DEC-C was 25 mg twice daily for 10 days (total dose 500 mg).

The mean pre-dose plasma DEC-C concentration during treatment and the mean plasma DEC-C half-life were significantly higher and total urinary excretion of DEC-C was significantly less in bicarbonate treated patients as compared to controls.

These pharmacokinetic differences were reflected in a significantly higher reduction in skin microfilarial counts in the bicarbonate treated group at 1 week but at the expense of a higher, but not statistically significant, total clinical reaction. There was however no significant difference in microfilaricidal activity between the two groups at 1 month and neither regime affected the adult worms. Thus manipulation of the urinary pH was of little practical value in the therapy of onchocerciasis with low dose DEC-C (Awadzi *et al.*, 1986).

Local therapy with DEC-C

Onchocerciasis affects mainly the skin and the eye and it is logical that application of DEC-C be limited to these sites in order to avoid the severe reactions that result from systemic administration.

Transdermal application of DEC-C as a 1–2% lotion cleared most of the skin microfilariae in the treated areas in lightly infected patients without serious side effects (Langham *et al.*, 1978). In heavily infected patients this resulted in very severe local and systemic reactions and was less effective against the microfilariae than oral DEC-C (Hutchinson *et al.*, 1979). Furthermore, controlled studies using oral DEC-C and DEC-C lotion, showed that the latter was less well tolerated as well as being less effective against skin and ocular microfilariae (Taylor *et al.*, 1980).

The evolution of a dose scheme which was lethal to intra-ocular microfilariae but which produced few adverse reactions was investigated by the application of half-log dilutions of DEC-C from 1.0 to 0.0001% to the cornea (Jones *et al.*, 1978). Microfilariae were killed by

delivery rates as low as 0.1 μg h^{-1}. Dose related adverse reactions – itching, redness and globular infiltrates occurred at delivery rates as low as 0.6 μg h^{-1}. More severe reactions, such as vasculitis, were only seen with delivery rates of or above 1.0 μg h^{-1}. This raised the possibility of eliminating ocular microfilariae without inducing severe reactions by continuous non-pulsed delivery of DEC-C either by direct application to the eye or by a transdermal system. Previous investigations using topical DEC-C in the eye have been carried out by Anderson & Fuglsang (1973), Aviel & David (1972) and Ben-Sira *et al.* (1970).

Combination of DEC-C with levamisole

Prodhorn *et al.* (1979a,b) investigated the use of DEC-C in combination with levamisole. The aim was to evolve a regime which would reduce skin microfilarial counts below a level which can affect sight but which was acceptable on mass administration.

A dose regime of 200 mg DEC-C plus 120 mg levamisole given daily for 14 days followed by DEC-C 200 mg plus levamisole 60 mg at 1 month and up to five times during the subsequent year was found to provide adequate suppression of skin microfilarial counts with minimal clinical effects.

Conclusions

Despite reports of *apparent* clinical cure in lightly infected patients (Ree, 1977), and of the presence of degenerate worms in nodules after treatment (Martinez Baez, 1952, 1953; Sowa & Sowa, 1978;), it is generally accepted that DEC-C is not a macrofilaricide for *O. volvulus*. This remains true even after repeated, prolonged or high dosage (Adams & Woodruff, 1953; Albiez *et al.*, 1988; Duke, 1957, 1968; Hawking, 1952; Mazzotti, 1951; Taylor *et al.*, 1990).

Since the innate resistance of adult *O. volvulus* could not be altered, efforts to improve the use of DEC-C have been directed mainly at attenuating the reactions to treatment. These are such a regular feature that they form the basis of a diagnostic test for onchocerciasis – the Mazzotti test.

Mazzotti (1948) suggested that the reaction to DEC-C may be useful in the diagnosis of onchocerciasis in cases where nodules are absent and where infection is so light that microfilariae cannot be demonstrated in skin snips, provided a coincidental infection with *Wuchereria bancrofti* can be excluded. The test which continues to be extremely useful (WHO, 1987) highlights the occurrence of reactions as being central to the problem of DEC-C treatment of onchocerciasis.

Initial attempts to improve the use of DEC-C involved the use of agents to prevent the reactions from occurring. Despite the variety of agents used – antihistamines, antiserotonins, inhibitors of prostaglandin synthesis and corticosteroids – only the latter are consistently of benefit.

Corticosteroids however cannot be used on a mass scale owing to their considerable side effects, the absence of qualified medical personnel and the co-existence of a wide variety of communicable diseases in endemic areas which would normally preclude their use. Furthermore, steroids do not affect itching (Awadzi *et al.*, 1982b) which is a major reason for non-compliance with DEC-C treatment regimes.

A major determinant of the severity of the reaction is the number of microfilariae killed; this in turn depends on the intensity of infection and the dose of DEC-C employed such that alarming reactions occur in the heavily infected and with high initial doses. Any improvement in the use of DEC-C must therefore address the problem of the heavily infected patient.

The OCRC dose-finding studies administered varying doses of DEC-C to a 'relatively fixed' high level of intensity of infection. The quantification of the reactions to treatment permitted a mathematical relationship to be derived between the reduction in microfilarial counts and the severity of the reaction evoked as well between the dose administered, and the rate of return of microfilariae to the skin. A dose regime of DEC-C was evolved on the basis of these studies.

The OCRC dose regime, like many others before it, did not completely solve the problem of DEC-C reactions since the employment of a similar regime subsequently resulted in ocular deficiency in 2 out of 20 patients (Dadzie *et al.*, 1987). These studies however defined upper dose limits, and ED_{90} and a dose response curve for DEC-C (Figure 2). Ocular reactions were not quantified in the dose finding studies. A system analogous to that for systemic reactions was subsequently developed at the OCRC for ocular reactions (Hero *et al.*, 1992).

The pharmacological studies provided useful information to guide the dose finding studies; they also prompted the use of moderate urine alkalinisation in an attempt to combine optimal microfilarial killing with minimal reactions. The total dose of DEC-C employed (500 mg) was equivalent to the ED_{90} as determined from the dose finding studies. Although the clinical reaction and the initial reduction in skin microfilarial counts were consistent with the kinetic findings, there was no long term benefit.

The transdermal approach to DEC-C administration (Langham *et al.*, 1978) has been shown to be inferior to oral DEC-C (Hutchinson *et al.*, 1979; Taylor *et al.*, 1980) and hence does not offer a solution to the problem of DEC-C reactions in onchocerciasis. It may however be acceptable to lightly infected communities to whom the direct application of DEC-C lotion to an obviously affected area of skin may seem more logical than the ingestion of tablets. The practical value of the dose-response studies of DEC-C eye drops (Jones *et al.*, 1980) are yet to be determined.

Despite intensive studies, it has not been possible to develop safe dose regimes for DEC-C applicable to mass distribution. Hence the recommended indications for the use of DEC-C are still based on detailed clinical, opthalmological and parasitological criteria which are well beyond the capacity of most hospitals in endemic areas (WHO, 1987).

Unfortunately, DEC-C is cheap and widely available to paramedical personnel in endemic areas who form

the backbone of the health care delivery system. Unsupervised DEC-C administration occurs, often with serious consequences. Reactions to treatment are sometimes regarded as an indication of the 'power' and effectiveness of the drug. Any resulting ocular deficiency is often attributed to progression of the natural disease; several patients are often quite unaware of the restriction in their visual fields.

It is for these reasons that the advent of ivermectin is of such fundamental importance in onchocerciasis chemotherapy. Ivermectin invalidates the old concepts of the performance of microfilaricides (un-avoidable severe reactions, precipitation of ocular deficiency and non-feasibility of mass therapy) and should be widely available wherever onchocerciasis is endemic.

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