

ADVERSE REACTIONS TO A SINGLE DOSE OF DIETHYLCARBAMAZINE IN PATIENTS WITH *BRUGIA MALAYI* INFECTION IN RIAU PROVINCE, WEST INDONESIA

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INTRODUCTION

Diethylcarbamazine (DEC) is currently the drug of choice for the treatment of human lymphatic filarial parasites and has been widely used to control infections in individuals and communities (Goodwin, 1984; Partono, 1984). A recent review indicates that not only does DEC have microfilaricidal activity but it also kills adults of *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* (Ottesen, 1984).

The use of DEC has been limited by the adverse reactions which may follow its use. These reactions are of two types, a direct toxic reaction following high doses of DEC and reaction which only occur in patients infected with filarial parasites (Hawking, 1981).

The severity of the adverse reactions varies with the species of the parasite. Very severe reactions or even death may occur, when treating patients infected with *Onchocerca volvulus* (Fuglsang and Anderson, 1974) while less severe reactions, but often necessitating 2-3 days in bed, occur with infections of *B. malayi* (Edeson and Wharton, 1958; Putrali *et al.*, 1975; Seo, 1978) and *B. timori* (Partono *et al.*, 1979). The reactions following treatment of *W. bancrofti* infections are usually milder (Otto *et al.*, 1953). The severity of the reaction is also dose related, less severe reactions occurring with low dose schedules (Seo, 1978). The exact mechanism

of these reactions is not understood although many believe that an immediate hypersensitivity reaction may be involved.

As part of a wider study into the mechanisms of these adverse reactions we have closely examined the clinical reactions in 15 patients, with different *B. malayi* microfilarial densities, after receiving a single dose of DEC.

MATERIALS AND METHODS

In April 1984, a filariasis survey was conducted in the village of Pasirpangarayan, approximately 280 km east of Pekanbaru, Riau province, Sumatera, Indonesia. A total of 712 finger prick blood specimens were collected from the approximately 1,050 inhabitants of the village between 20.00 and 23.00 hours; 117 (16.4%) were found to be infected with nocturnally periodic *B. malayi*.

Fifteen microfilaremic volunteers, in good general health, were selected for this study and hospitalized in Pekanbaru in August 1984. The patients consisted of 4 females (age range 12-35 years) and 11 males (age range 8-47 years) (Table 1). Upon arrival at the hospital, all patients were clinically examined and shown to be in good general health. Temperature, pulse and respiration rates, as well as blood pressure were recorded on 2 separate occasions prior to treatment as control values. Each patient was treated with a single dose of 5 mg DEC/kg body

weight and clinical observations made every 2 hours for the next 48 hours. Particular attention was paid to the time of the onset of any reactions and evidence of symptoms including pruritus, rash, fever, lymph gland enlargement and tenderness, musculoskeletal pains and respiratory and cardiovascular changes. During the observation period, patients were treated with paracetamol when necessary, to reduce the adverse reactions.

RESULTS

All patients taking part in this study were in good physical condition on clinical examination, none of them showed any clinical manifestation of filariasis at the time of the study. After DEC administration all patients exhibited reactions within 10 hours. These are shown in Tables 1 and 2.

In most cases the first reaction seen was fever which commenced $5\frac{1}{2}$ – $9\frac{3}{4}$ hours after treatment. However, in one patient (HAM-6) a rash developed on the face and neck 2 hours post treatment which lasted for approximately 24 hours. No other patient developed a rash. All patients, except the one with the lowest microfilarial count (MID-1) developed fever, defined as an increase in temperature of at least 1°C above control temperature. Individuals with temperature of more than 38.5°C were all given paracetamol for symptomatic relief. It followed, that the peak and duration of fever will be substantially longer or higher if antipyretics were not administered. Maximum increased in temperature of 1.9 to 3.15°C were recorded, with a mean value of $2.6 \pm 0.4^{\circ}\text{C}$, and fever lasted for 48 hours in all patients.

Table 1

Fever response in patients infected with *B. malayi* treated with a single dose of DEC (5 mg/Kg).

| Patient | Age (Years) Sex | Mf count (20 mm ³) | Initial Temperature* ($^{\circ}\text{C}$) | Time to fever** (hours) | Max temp ($^{\circ}\text{C}$) | Change in temperature ($^{\circ}\text{C}$) |
|-----------------|-----------------------|-----------------------------------|---|-------------------------------|---------------------------------------|--|
| Mid | – 1 20 F | 3 | 36.8 | – | – | – |
| EW | – 2 16 M | 5 | 36.7 | 9 | 39.5 | 2.8 |
| Has | – 3 30 M | 16 | 36.15 | 6.25 | 39.0 | 2.85 |
| Bus | – 4 12 M | 28 | 36.7 | 9.2 | 38.6 | 1.9 |
| Mus | – 5 15 M | 29 | 36.6 | 9 | 38.5 | 1.9 |
| Ham | – 6 47 M | 30 | 36.9 | 6.25 | 39.8 | 2.9 |
| Len | – 7 12 F | 35 | 36.7 | 9 | 39.5 | 2.8 |
| Sya | – 8 16 M | 35 | 36.2 | 9 | 39.3 | 3.1 |
| Ibr | – 9 33 M | 40 | 36.35 | 9.75 | 38.8 | 2.45 |
| Said | – 10 8 M | 80 | 37.05 | 6 | 39.3 | 2.25 |
| Naa | – 11 12 M | 116 | 37.15 | 8.75 | 39.6 | 2.45 |
| AH | – 12 12 M | 117 | 36.8 | 5.5 | 39.7 | 2.9 |
| Sum | – 13 35 M | 174 | 36.35 | 8.5 | 39.5 | 3.15 |
| Sal | – 14 14 F | 244 | 36.6 | 6.5 | 39.0 | 2.4 |
| Iros | – 15 35 F | 305 | 36.8 | 8 | 39.3 | 2.9 |
| Mean \pm S.D. | | | 36.66 ± 0.29 | 7.9 ± 1.4 | 39.24 ± 0.41 | 2.63 ± 0.41 |
| Range | 8 – 47 | 3 – 305 | 36.2 – 37.15 | 5.5 – 9.75 | 38.5 – 39.8 | 1.9 – 3.15 |

*Mean of two values

**Fever = 1°C rise above pretreatment temperature.

Table 2

Adverse reactions in 15 patients infected with *B. malayi* treated with a single dose of DEC (5 mg/kg).

| Patient | Mf count (20 mm ³) | fever | gland pain | head ache | Joints pain | muscles ache | abdominal pain | nausea and vomitus | anorexia | collapse on standing |
|--------------|--------------------------------------|-------|---------------|--------------|----------------|-----------------|-------------------|--------------------------|----------|----------------------------|
| Mid - 1 | 3 | - | + | + | - | - | - | - | - | - |
| EW - 2 | 5 | + | - | + | - | - | - | - | + | + |
| Has - 3* | 16 | + | + | + | + | + | - | + | + | - |
| Bus - 4 | 28 | + | - | + | + | - | + | - | + | - |
| Mus - 5 | 29 | + | - | + | - | + | - | - | + | + |
| Ham - 6** | 30 | + | - | + | - | + | - | - | - | - |
| Len - 7 | 35 | + | - | + | - | - | + | + | + | - |
| Sya - 8 | 35 | + | - | - | - | - | + | - | + | + |
| Ibr - 9 | 40 | + | + | + | + | + | - | - | - | - |
| Said - 10 | 80 | + | - | + | - | - | - | + | + | - |
| Naa - 11 | 116 | + | - | + | - | - | - | - | + | - |
| AH - 12 | 117 | + | - | - | - | - | + | - | + | - |
| Sum - 13 | 174 | + | - | + | + | + | - | - | + | - |
| Sal - 14 | 244 | + | - | + | - | - | - | + | + | - |
| Iros - 15*** | 305 | + | - | - | + | - | + | - | + | - |
| | | 14 | 3 | 12 | 5 | 5 | 5 | 4 | 12 | 2 |

*Diarrhoea

**Rash

***Respiratory distress.

No significant changes in blood pressure were seen in any of these patients and respiration rates paralleled body temperature. A summary of the symptoms occurring in these 15 patients are shown in Table 2. Apart from fever, anorexia and headache were the two commonest signs, both found in 80% of patients. Three of the anorexic patients exhibited vomiting while one showed both vomiting and diarrhoea. Joint and muscle pains were each reported in 5 patients (33%). Abdominal pain, 4 on the upper left quadrant and 1 on the upper right quadrant, also occurred. Two patients (HAS-3 and SUM-13) with microfilarial of 13 and 174 per 20 mm³ reported both joint and muscle pain.

Approximately 24 hours after drug treatment 3 persons developed local swelling of lymph glands. These patients had microfilarial counts of 3, 16 and 40 microfilariae per 20 mm³ of blood.

Postural hypotension occurred in 2 patients (MUS-5 and SYA-8) both of whom collapsed on standing on the day following treatment. The patient (IROS-15) with the largest number of microfilariae in the blood, experienced respiratory distress for approximately 1 hour, 16 hours after treatment. She was extremely restless, although still awake, with rapid shallow breathing of 40 per minute, increase pulse rate of 144 per minute and fever of 38.8°C.

DISCUSSION

The adverse reactions which may occur in microfilaraemic patients infected with *B. malayi* following DEC treatment have been reported from Malaysia (Wilson, 1950; Edson and Wharton, 1958), Korea (Seo, 1978) and Indonesia (Putrali *et al.*, 1975). Similar reactions to *B. timori* (Partono *et al.*, 1979) and *W. bancrofti* (Sasa *et al.*, 1963; Van Dijk, 1961) have also been reported. Although the clinical symptoms are similar, the severity differs. There has been considerable debate as to whether the severity of the reactions for a particular case is associated with the microfilarial count (Partono *et al.*, 1979). In this study, although there was a wide range of mf. densities in the blood of patients (3 to 305 per 20 mm³), there was no absolute association between parasite counts and severity of reactions.

Clinically the 4 patients who exhibited the most severe reactions to DEC were HAM-6, LEN-7, AH-12 and IROS-15 having microfilarial counts of 30, 35, 117 and 305 parasites per 20 mm³ respectively. The patients showing least reactions were MID-1, EW-2, MUS-5 and SYA-8. There may be a tendency for more severe reactions to be present in patients with higher microfilarial counts although this is by no means absolute. A similar situation exist in dogs infected with *Dirofilaria immitis* (Boreham and Atwell, 1983) where it was suggested that the number of microfilariae in the blood is not the only factor which affects the severity of the reaction. A similar situation may occur here.

Fever was normally the first symptoms seen, occurring 5-10 hours after treatment. (Sasa *et al.*, 1963) reported that fever occurred in *W. bancrofti* patients who had blood microfilarial levels greater than 30 per 30 mm³ while for *B. timori* the same corresponding figure was also reported (Partono *et al.*, 1979).

In this study patient with more than 5 microfilariae per 20 mm³ of blood developed fever. There seemed to be no association between the time of fever onset and microfilarial density (Table 1), nevertheless a study on a larger population sample is needed to make any firm conclusion.

The abdominal pain which occurred in 5 patients following treatment, 4 of which were around the site of the spleen and one in the vicinity of the liver, also did not appear to be related to microfilarial density.

No evidence of blood pressure changes were found in any of the patients although the collapse of 2 patients on standing during DEC reactions does suggest that there was some effect on the vascular system.

Respiratory distress was not a common feature and was observed only in a patient with the highest microfilarial count. A similar distress has been reported in patients heavily infected with *O. volvulus* (Fuglsang and Anderson, 1974) and provocation of asthmatic attacks have been recorded in *B. timori* infected persons (Partono *et al.*, 1979).

Local reactions suggestive of adult worm destruction (Ottesen, 1984) were seen in 3 patients with 3, 16, and 40 microfilariae per 20 mm³. The fact that all the local reactions were in patients with low microfilaraemia is interesting but further studies are required before any conclusions can be drawn.

This study indicated that reactions commonly occur in *B. malayi* infections when DEC is used for chemotherapy. Every person with microfilariae in their blood must be considered to be at risk of adverse effects to treatment. It is important to identify the mechanisms involved in those reactions and to develop strategies for preventing them. Although the reactions seen were not life threatening they were sufficiently serious for the patient to spend approximately 48 hours

in bed and as such will affect village life and economy, especially in mass treatment campaigns.

SUMMARY

A study on the adverse reactions, occurring after treating microfilaremic patients infected with *B. malayi*, revealed that all reacted to a single oral dose of DEC (5 mg/kg). The major reactions were fever, headache, anorexia, abdominal pain, muscle and joint pains, nausea and vomiting. There seemed to be no association between the time of fever onset and microfilarial density, but the number of cases observed was too small to make any firm conclusion. There was a tendency for more severe reactions to occur in patients with higher microfilaria counts. Local reactions, probably due to destruction of adult worms, were seen in 3 patients. The reactions were serious enough to necessitate the patients spending approximately 48 hours in bed.

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