Filariasis Control with Diethylcarbamazine in Three Major Endemic Areas in Japan

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1 Diethylcarbamazine (DEC)

Hewitt et al. (1947) [1] reported that DEC acted as effective filaricide to *Litomosoides carinii* in rats. Later, Santiago-Stevenson et al. (1947) [2] showed that this compound was effective in the treatment of *Wuchereria bancrofti* infection in humans. Hawking et al. (1950) [3] proposed the action mechanism of DEC. Since the extensive studies by Kessel (1957) [4] and his colleagues, the drug’s strong filaricidal activity with few side reactions has been widely recognized and accepted. Studies were thus started by various parasitologists on different dosage regimens for DEC administration.

In Japan, immediately after the appearance of DEC, chemotherapeutic studies of filariasis using DEC were performed in the early 1950s in various endemic areas (Katamine, 1952; Kitamura 1951; Nogi et al., 1951; Hayashi et al. 1951; Sasa et al. 1951; Sato et al. 1952) [5-10]. The followings summarize the data reported by those workers and the characteristics of DEC. A more detailed contents of these findings will be seen in the review of Sato (1962) [11].

DEC was able to remarkably clear the microfilaremia of *W. bancrofti* and *Brugia malayi*. In the cases of nocturnally periodic filariasis, DEC administration rapidly caused microfilaremia and microfilaruria. Then the rapid reduction of microfilariae was seen in the peripheral blood.

DEC caused side reactions, particularly in the first 1-2 days of administration. The reactions included: i) specific allergic reactions such as high fever, swelling of lymph nodes, fatigue, etc., and ii) toxic reactions such as headache, lumbago, loss of appetite, nausea etc. The intensity of side reactions was dose-dependent, and it was found later that the microfilarial density in the blood was closely related to the degree of fever. The rise of fever was usually accompanied by leukocytosis.

A total dose of approximately 70 mg/kg of body weight, to be given in the certain period of days with divided doses, was necessary to obtain long-term clearance of microfilariae in the blood. Eventually a total DEC dose of 72 mg/kg divided in 12-14 days was administered to microfilaria carriers in Japan.

Within 24 hours, 60% of DEC was excreted in the urine.

2 Control campaigns in Japan

2.1 Control in Okinawa.

Okinawa or Ryukyu Archipelago had been the most densely infested area with lymphatic filariasis since the first blood survey on recruited soldiers performed by the Ministry of Army in 1912. Before World War II, various surveys indicated a high prevalence in the three island groups (Okinawa, Miyako and YaeYama). After the war, Okinawa was occupied by the U.S.A. and the United States Civil Administration of the Ryukyu Islands (USCAR) managed this region including the health sector. With the cooperation of the USCAR and the Japanese government, the Ryukyu government started a control project of lymphatic filariasis in 1965.

The main strategy for this program was the quantitative night blood survey and mass selective treatment of detected microfilaria positives with DEC based on the regimen established after many trials in Japan.

In Okinawa, DEC tablets (each tablet containing 50 mg) were administered to the microfilaria positives as follows: A total of 3.6 g (72 tablets, 72mg/kg) for adults aged 18 years and above, 1.8 g for children of 12 years or less, and 3.0 g for people between 13 and 17 years. For the first 6 consecutive days, 6 tablets (3 for 12-year-olds, and 5 for 13-17 years) were given each day after meals, and the second round with the same dosage started 2 months later. The total amount of DEC was 72 mg/kg each. It was considered important to examine 30 µl of blood taken from the earlobe at night by graduated pipette for the epidemiological assessment of the control.

Health education was carried out intensively in all the islands through school, radio, TV and newspaper in terms of advocacy. It should be mentioned that the public health...
nurse system played a very important role in the campaign in Okinawa. The nurses had been in charge of community health of people for decades and thus they persuaded inhabitants of the meaning and process of the filariasis control. As the side reactions frequently disturbed successful administration of DEC, public health nurses urged people to follow the regimen and raised compliance.

In Miyako Islands, 66,333 out of 67,020 inhabitants (99.0%) were screened by night blood examination, which resulted in 12,607 (19.0%) positives in 1965. After 4 courses of annual selective treatment with DEC, in 1969, 174 microfilaria positives were detected out of 12,691 people examined (1.4% positive rate) in the total registered population of 12,915. High participation rate (98.3%) and rapid reduction of microfilarial rate among the inhabitants were noted.

Likewise in Yaeyama Islands, the first examination was performed in 1967 on 46,595 subjects out of 49,432 inhabitants (94.2% participated) and 3,400 (7.3%) were found positive for microfilariae. Four years later 12,494 of 16,426 inhabitants (76.1%) were examined, and 160 (1.3%) were found positive. Rapid reduction during the short period was shown. In the remaining regions including the main Okinawa Islands, similar results were obtained in the control. Eventually all the microfilaria positives disappeared in 6-7 years after control activities started. In Okinawa, spraying operations of insecticide, diluted 50% malathion, were periodically implemented at houses against adult Culex fatigans and at breeding places for larvae. The total cost for the whole control activities was 336,000 thousand Japanese yen.

High community spirit also played on important role in the control program, which was enhanced by the health education. In order to expel the scourge that had been agonizing their ancestors for several hundreds years, community people participated eagerly to the control activities. Further more, mind of competition rose among people in a community not to be inferior to other communities in terms of blood examination rate, DEC administration rate, insecticidal operations, etc. This spirit was called “Araragama” in Miyako Islands. Nowadays we see a memorial stone standing in the garden of Miyako Health Center in which this spirit was described as an important element to successfully combat with the filariasis there (see Chapter 3, 2.4, Fig. 4).

2.2 Control in Kagoshima prefecture

In Kagoshima, the following regimens were adopted in the oral DEC administration: For adults, 100 mg daily for the first three days, 300 mg daily for the next three days and then 300 mg once a week for 8 weeks. For the children below 12 years old half the above dosage was administered in the same schedule.

The prevalence of microfilaria positives was particularly high in Amami Islands in comparison with other areas in this prefecture. In 1962, the overall prevalence of Kagoshima was 6.6% (8,968 positives out of 135,557 examined). The positive rate was gradually reduced to 3.9% (1963), 3.2% (1966) and 0.8% (1971). The last three microfilaria positives were found in Amami Islands, and no more positives were found thereafter anywhere in Kagoshima. Escapees from the night blood surveys and those who refused to take DEC were the main problem in the filariasis control. Insecticide spraying was also performed in this prefecture by using DDT, malathion, etc.

2.3 Control in Nagasaki prefecture

In Nagasaki, DEC was administered to microfilaria positives as follows: Two tablets (100 mg) daily for the first 3 days, 6 tablets (300 mg) daily for consecutive 3 days and then 6 tablets once a week for 8 weeks. This strategy was applied in order to avoid strong side reactions. In Nagasaki prefecture a total 202,941 out of 340,822 registered people were examined in 1962. The participation rate of 60.0% was rather low and the survey revealed 2,660 (1.3%) microfilaria positives. After 4 annual examination and drug administration courses in 1966, only 255 (0.6%) remained positive. Insecticide spraying was included in the control activity. The total cost between 1962 and 1967 was 53.9 million yen.

3 Single dose administration of DEC and DEC salt

In Japan, only selective treatment of microfilaria positives with DEC was adopted for the national control campaign. However this campaign experienced some important inconveniences; nocturnal examination of community people, incompliance for a big dose of DEC, necessity of a high participation rate, skill of health staff; difficulty in transportation for the campaign, etc. In order to conquer these problems, effects of single dose administration of DEC for use in mass treatment were examined by various workers. Actually the present global elimination program of lymphatic filariasis supported by WHO adopted an annual single dose regimen using DEC (or ivermectin) and albendazole. The effect of this combination was previously confirmed (see Ismail et al., 2001 [12]). Before the start of the global program, various trials were made in many endemic areas. One of these pioneer works was done by Kimura and his colleagues in Samoa (1992) [13]. They administered a single-dose of DEC at 6 mg/kg body weight annually in three mass treatment campaigns to over 80% of the esti-
mated total Samoan population (160,000) in 1982, 1983, and 1986. The drug reduced the prevalence of *W. bancrofti* microfilaremia from 5.6% to 2.5% (a 55% reduction), while the transmission potential (the estimated mosquito infection rate if everyone is supposed to be equally exposed to mosquito bites) dropped from 2.18 to 0.67 (a 70% reduction).

In China DEC medicated salt (4-10 g per person) was supplied to endemic communities for several months for filariasis control in the 1980s. This type of mass treatment markedly reduced prevalence within years as reported by Liu *et al.* (1992) [14]. In the South Pacific endemic islands, this regimen was sporadically tested for efficacy. However, this strategy was not applied in Japan.

4 Evaluation of control program using skin test

Evaluation of the effect of filariasis control is very important to judge whether the transmission will no longer continue. From this point of view, Tada *et al.* (1982) [15] monitored the microfilaria prevalence and skin test reactivity of a population in an endemic island for 13 years (1967 to 1980) since the start of control activity. The initial microfilarial rate of 13.2% was successfully reduced to almost 0% by 1970, by the selective administration of DEC to microfilaria positives. The age distribution of skin-test positivity changed year by year, especially in the younger age groups. Children were considered a useful sentinel population to assess the state of transmission.

Acknowledgement

This paper is revised from Asian Parasitology Vol.3 Filariasis in Asia and Western Pacific Islands, 101-104 by The Federation of Asian Parasitologists in 2004.

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