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Deltamethrin exposure affects host resistance to *Plasmodium* infection in mice

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Abstract

Effects of exposure to deltamethrin on host resistance to malaria infection (*Plasmodium berghei*) were examined in Swiss albino male mice. Four doses of deltamethrin were initially tested with two non-lethal doses, 5 and 10 mg/kg, selected for more detailed study. Survival times of infected mice did not change when they were exposed to the compound for 14 days before the infection. However, survival times were shortened when they were exposed to the compound, particularly at the high-dose, after and during the initial infection. Percent parasitemia of these animals also elevated faster than that of the control. Deltamethrin exposure also caused alteration of white blood cell populations. Specifically, total white blood cell and lymphocyte counts significantly decreased in the high-dose treated mice. Granulocyte counts were comparatively lower in both treated groups than that in the control. Red blood cells, hemoglobin, and hematocrit were not affected. The obtained results suggest that deltamethrin exhibits an immunosuppressive effect and negatively impacts host resistance to malaria infection.

Keywords: Deltamethrin; Oral toxicity; *Plasmodium berghei*; Malaria infection; Parasitemia; White blood cells

1. Introduction

Synthetic pyrethroids have become a major class of active insecticides due to high insecticidal potency and low mammalian toxicity (Elliott, 1976). Deltamethrin, an alpha-cyano type-II synthetic pyrethroid, was first synthesized in 1974, and has been widely used in controlling insect pests of medical and agricultural importance (Elliott et al., 1974; IPCS, 1990). It is used as an active ingredient in many household insect-control products, and also in public health programs in several countries. Like other pyrethroids, the mode of action of deltamethrin is exerted mainly by interacting with neuronal sodium channels resulting in alteration of nerve activity (Narahashi, 1996).

Adverse effects by deltamethrin are reported in several epidemiological and experimental studies. Clinical manifestations of acute deltamethrin poisoning have been documented in occupationally and accidentally exposed cases (He et al., 1989; Zhang et al., 1991). Agarwal et al. (1994) showed that deltamethrin administered to adult female albino rats increased the frequency of chromosomal aberrations in the bone marrow at 24 h after exposure. Deltamethrin can elicit neurotoxicity by inducing neuronal apoptosis both in vivo and in vitro (Wu and Liu, 2000; Wu et al., 2003). The compound also has a potential of initiating tumors in mice (Shukla et al., 2001), and inducing DNA damage in the presence of metabolic activation in human peripheral blood leukocytes (Villarini et al., 1998). Data regarding the immunotoxic effects of deltamethrin are few and show both suppression and stimulation of the immune system in experimental animals (Kowalczyk-Bronisz et al., 1990; Lukowicz-Ratajczak and

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Krechniak, 1992; Madsen et al., 1996). Lukowicz-Ratajczak and Krechniak (1992) examined the influence of deltamethrin on the immune system in female Balb/c mice and demonstrated that agglutinin and hemagglutinin titers, and the number of plaque-forming cells were decreased in treated mice. Another study showed that the level of circulating IgM was not affected by deltamethrin, whereas the level of IgG was affected only at a very high-dose (Kowalczyk-Bronisz et al., 1990). Evidence on modulation of white blood cell and lymphocyte populations by deltamethrin is limited, and seems to be dependent on dosages, and sex and species of tested animals (Madsen et al., 1996; Toś-Luty et al., 2001). Supplemental data would be required.

Cellular and humoral immunity plays a crucial role in host defense against malaria, a parasitic disease caused by infection of the *Plasmodium* protozoans. Immunity to the pre-erythrocytic and erythrocytic stages is mainly mediated by $CD8^+$ T cells, $CD4^+$ T cells, γδ T cells, natural killer cells, antibody, interferon-γ, nitric oxide, and certain cytokines (Good and Doolan, 1999; Plebanski and Hill, 2000). The infection can be fatal if the patients do not receive immediate medical attention. In certain cases, residents in endemic areas are repeatedly exposed to the parasites via mosquito bites and consequently develop the physiological protection that reduces the severity of subsequent malaria infection. However, many environmental toxicants potentially impair immunity resulting in alteration of host resistance to infection, including malaria (Loose et al., 1978; Tucker et al., 1986; Silbergeld et al., 2000). Exposure of humans to such compounds could occur along with the infectious agents, which may modulate the performance of the immune system. Deltamethrin is currently used in the national programs for controlling mosquito vectors of malaria and dengue in Thailand through spraying and spacial fogging (S. Seangtharatip, personal communication). Pyrethroid-impregnated bednets have also been used for malaria prevention in affected regions of the world (WHO, 1995). Risk assessment and safety of bednets impregnated with pyrethroids, including deltamethrin, approved by the World Health Organization have been recently reviewed (Zaim et al., 2000; Barlow et al., 2001). Whether exposure to deltamethrin could impact host resistance to *Plasmodium* infection is not known.

The present study was designed to examine effects of exposure to deltamethrin on host resistance to *Plasmodium* infection. The effects were demonstrated in terms of toxicity, hematologic profile, parasitemia, and survival time using mice as a model system.

2. Materials and methods

2.1. Chemicals

Deltamethrin (99% purity) was purchased from Chem-Service (West Chester, PA). Corn oil (pharmaceutical grade) was purchased from Sigma (St. Louis, MO). Other chemicals and solvents were of the highest quality commercially available.

2.2. Animal and parasite

Swiss albino male mice were obtained from the National Laboratory Animal Center, Mahidol University at Salaya. The animals were housed in stainless steel cages (six mice per cage) and provided with food and water ad libatum. They were acclimatized for 7 days before treatment. Mice with 25–30 g body weight were used for all experiments. The experimental infection was initially established using frozen stabilate of *Plasmodium berghei*-parasitized red blood cells (pRBCs). After continuous in vivo passages, the animal served as a pRBC donor. On the fifth day of infection, the infected mice were sacrificed, and blood samples were collected via cardiac puncture. The parasitemia percentages were determined by counting the infected red blood cells from a Giemsa-stained thin smear. The blood samples were mixed with 1% (w/v) sodium citrate in phosphate buffer saline (pH 7.2) as an anticoagulant in a 1:1 ratio. For experiments, mice were inoculated with 1×10^8 parasitized erythrocytes intraperitoneally.

2.3. Deltamethrin toxicity

Mice were randomly divided into groups, with approximately the same mean body weight (six mice per group). The animals were treated with deltamethrin orally at doses of 2.5, 5, 10, and 20 mg/kg body weight daily for 14 days. Corn oil was used as a vehicle, and a control group was treated with corn oil only. Mortality was recorded daily. Another set of mice was treated in the same fashion except that their rectal temperature and hematocrit were examined. The latter set was carried out to ascertain that mortality produced in the former set was solely due to the toxicity of the compound. For the following experiments, two doses of deltamethrin, 5 and 10 mg/kg, were used.

2.4. Hematologic profile

After treatment with deltamethrin daily for 14 days, mice were sacrificed and blood samples were collected via cardiac puncture. The hematologic parameters – hemoglobin amount, red blood cell count, total white blood cell and differential white blood cell counts – were determined by using the Coulter JT3 Automated Hematology Analyzer. All experiments were duplicated.

2.5. Organ weights

After treatment with deltamethrin daily for 14 days, the thymus and spleen were removed from each treated mouse and placed individually into pre-weighed small containers. Wet organ weights were immediately measured and recorded.

2.6. Survival time

Three modules of experiments were set-up. Each module consisted of three groups: control, 5 and 10 mg/kg treated groups (DM5 and DM10). For the first module, mice were infected with *P. berghei* after treatment with deltamethrin daily for 14 days, and administration of the compound was repeated daily until the mice died. For the second module, mice were treated with deltamethrin daily for 14 days, and treatment was terminated upon the infection. And for the last module, mice were treated with deltamethrin daily from the day of infection and thereafter until death. The control of each module was treated with corn oil. Mortality in each group was recorded daily.

2.7. Parasitemia

Blood samples were collected from the tail vein at a certain time of day at each sampling. Parasitemia percentages were evaluated by using the microscopic standard method.

2.8. Statistical analysis

All statistical analyses were performed by using the SPSS Software Version 9.0 (SPSS Inc.).

3. Results

When mice were treated with deltamethrin daily at doses of 2.5, 5, 10, and 20 mg/kg, only the highest dose caused mortality, which reached 100% during the 14-day period of treatment. Only mice in this group showed obvious signs of poisoning within a few hours, and most developed very intense symptoms, i.e. marked salivation, ataxia, stretching of hind limbs, jerking tremors, and choreoathetotic movements. None of the other doses caused mortality even up to 21 days of treatment (data not shown). The non-lethal doses of 5 and 10 mg/kg were used for further experiments.

Body weight gain, thymus and spleen weights, rectal temperature, and hematocrit were examined. No significant differences were observed among the control and treated groups in any of these parameters (one-way ANOVA, $P > 0.05$) (Tables 1 and 2). The numbers of monocytes, red blood cells, and hemoglobin levels were also in the same ranges in all groups (Table 3). In contrast, total white blood cell counts significantly decreased in DM10-treated mice in comparison with the control (Tukey's test, $P < 0.05$). The numbers of lymphocytes also decreased in the same manner. Although the difference in the numbers of granulocytes among the control and treated groups was not statistically significant (one-way ANOVA, $P > 0.05$), it was comparatively lower in both treated groups.

Survival times of DM10-treated mice were significantly reduced when they were exposed to deltamethrin repeatedly before and after the infection (Tukey's test, $P < 0.05$) (Fig. 1A). In order to indicate which period of exposure would cause reduction of the survival times, further experiments were carried out. Groups of mice were either treated with deltamethrin daily for 14 days before the infection or after the antigenic challenge. In Fig. 1B, survival times were not affected in the case of animals exposed to deltamethrin prior to the infection. In contrast, the survival times were significantly shortened when the animals were exposed to deltamethrin, particularly at the high-dose, during the infection period (Tukey's test, $P < 0.05$) (Fig. 1C). In the latter groups, blood samples of the mice were collected, and percent parasitemia was evaluated. Parasitemia percentages of both DM5- and DM10-treated groups clearly increased faster and reached peak sooner than those of the control (Fig. 2).

Table 1
Body weight gain and organ weights (mean ± S.E.) of mice treated with deltamethrin daily for 14 days ($N = 6$)

Treatment	Body weight gain (g)	Thymus (g/100 g body weight)	Spleen (g/100 g body weight)
Control	4.94 ± 0.69	0.12 ± 0.01	0.32 ± 0.01
DM5	4.87 ± 0.25	0.13 ± 0.01	0.33 ± 0.02
DM10	4.84 ± 0.28	0.12 ± 0.02	0.32 ± 0.01

Table 2
Hematocrit and rectal temperature (mean ± S.E.) of mice treated with deltamethrin daily for 14 days ($N = 6$)

Treatment	Hematocrit (%)		Rectal temperature (°C)	
	Day 0	Day 14	Day 0	Day 14
Control	51.67 ± 0.92	50.17 ± 0.48	36.63 ± 0.15	35.96 ± 0.34
DM5	51.50 ± 0.50	52.00 ± 0.52	36.88 ± 0.18	36.17 ± 0.18
DM10	50.08 ± 0.92	52.83 ± 0.48	36.67 ± 0.17	36.33 ± 0.21

Table 3
Hematologic parameters (mean ± S.E.) of mice treated with deltamethrin daily for 14 days ($N = 12$)

Treatment	Total white blood cells ($\times 10^6$/ml)	Differential white blood cells			Red blood cells ($\times 10^9$/ml)	Hemoglobin (g/dl)
		Lymphocytes ($\times 10^6$/ml)	Monocytes ($\times 10^6$/ml)	Granulocytes ($\times 10^6$/ml)		
Control	4.68 ± 0.45	4.09 ± 0.44	0.32 ± 0.04	0.27 ± 0.06	7.96 ± 0.29	12.51 ± 0.41
DM5	4.20 ± 0.34	3.74 ± 0.37	0.31 ± 0.06	0.16 ± 0.04	7.91 ± 0.23	12.46 ± 0.37
DM10	3.29 ± 0.21*	2.79 ± 0.21*	0.33 ± 0.02	0.17 ± 0.02	8.32 ± 0.16	13.07 ± 0.24

* Significant difference from the control at the 0.05 level.

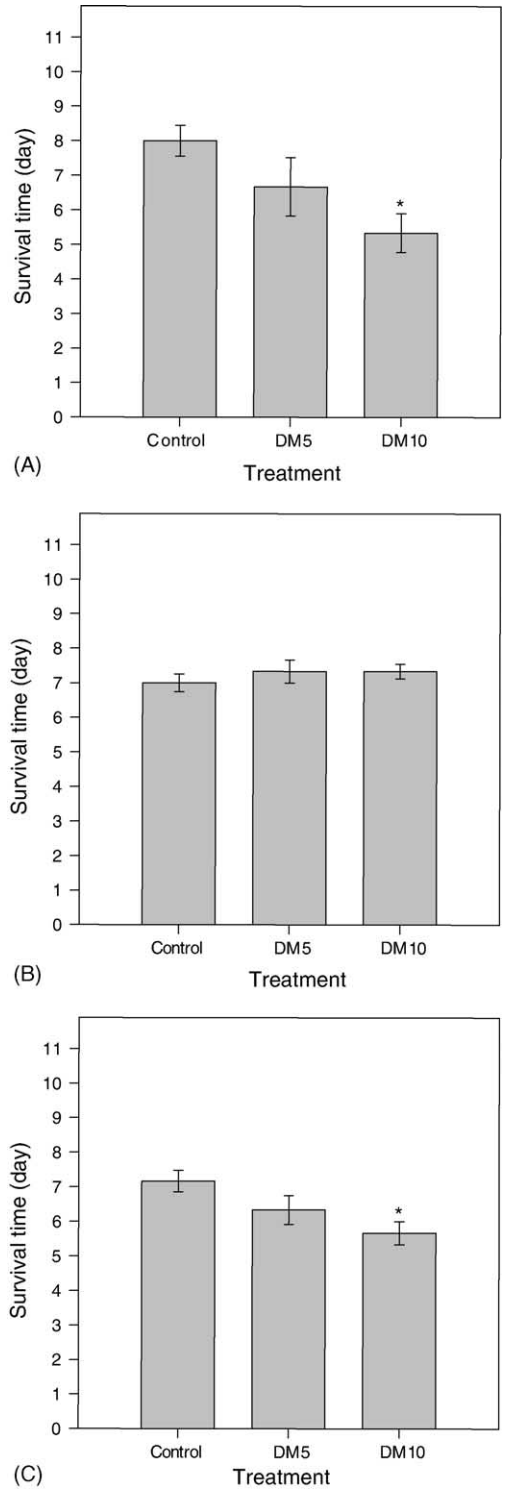

Fig. 1. Effects of exposure to deltamethrin on the survival times of mice infected with *P. berghei*. (A) Mice were treated with deltamethrin daily for 14 days before the infection and the treatment was repeated daily until the animals died. (B) Mice were treated with deltamethrin daily only before the infection. (C) Mice were treated with deltamethrin daily only after the infection (*: significant difference from the control at the 0.05 level; $N = 6$).

4. Discussion

Deltamethrin can be highly toxic, particularly at high doses of exposure. In this study, Swiss albino male mice were orally administered deltamethrin for 14 days. The dose of 20 mg/kg, the highest dose tested, caused mortality during the exposure period. Characteristic symptoms of deltamethrin poisoning were also observed, which were similar to those observed in toxicological studies previously reported (Pham et al., 1984; Dayal et al., 2003). These included salivation, stretching of hind limbs, ataxia, jerking tremors, and choreoathetotic movements with rolling convulsions.

Administration of deltamethrin daily for 14 consecutive days did not affect body weight gain, hematocrit, and rectal temperature of the treated animals. Deltamethrin treatment at the dose of 15 mg/kg also had no negative effects on the body weight in female Balb/c mice (Lukowicz-Ratajczak and Krechniak, 1992). However, decrease in body weights has been documented in male Swiss albino mice (Haratym-Maj, 2002) and male F344 rats (Madsen et al., 1996) that were treated with deltamethrin daily for 28 days at a dose of 5 mg/kg (Arabic gum–olive oil–water emulsion as vehicle) and 10 mg/kg (soybean oil as vehicle), respectively. In our study, exposure to deltamethrin did not change thymus and spleen weights. Madsen et al. (1996) previously found that deltamethrin could produce reduction in the thymus weights in male F344 rats immunized with sheep red blood cells. These rats received deltamethrin in soybean oil by gavage at doses of 5 and 10 mg/kg. Additionally, deltamethrin can cause thymus atrophy by interfering with the cell signaling cascades in male Balb/c mice injected intraperitoneally with a single dose of 25 mg/kg (Enan et al., 1996). The difference in experimental findings obtained from these toxicological studies might be due to the difference in animal strains, routes of chemical administration, tested doses, the chemical purity, or solvents as vehicles (IPCS, 1990).

When mice were treated with deltamethrin before and after the antigenic challenge by infection of *P. berghei*, the significantly shortened survival times correlated directly with the higher dose. The reduction of survival times was not caused by direct toxicity of deltamethrin because no mortality was produced at the doses tested even up to 21 days of exposure. In order to define which period (before antigenic challenge or during infection) would specifically affect the survival times, further results were obtained. Mice that were treated with deltamethrin daily for 14 days before infection had the same levels of survival times as the control. In contrast, the survival times were decreased when the infected animals were also treated with deltamethrin during the infection period. Percent parasitemia in the latter groups rose faster and peaked sooner than that in the control in a time-dependent manner. In this study, red blood cell and hemoglobin parameters were not altered by deltamethrin exposure; however, the number of total white blood cells decreased, particularly in high-dose treated mice. Reduction of lymphocyte populations significantly contributed to the reduction of total white blood cells.

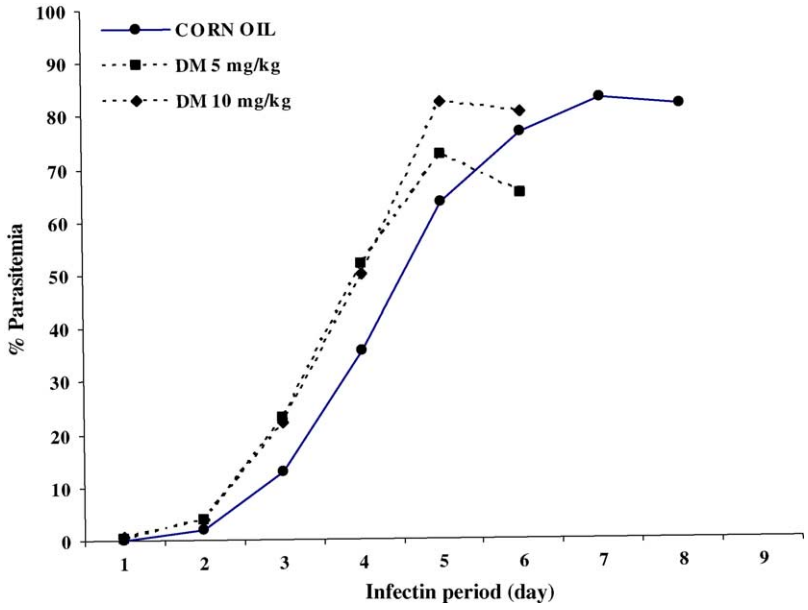

Fig. 2. Percent parasitemia of mice exposed to deltamethrin during the period of malaria infection (each point represents a mean of 3–6 mice per group).

Although the numbers of granulocytes among the control and treated groups were not significantly different in this study, they were comparatively lower in both treated groups. There was a much wider variation in the number of granulocytes in the control, with a few values being clearly greater than either treatment. This larger variation resulted in statistical insignificance. However, it is possible that the handful of clearly greater granulocyte values in the control represents a true biological or physiological difference between the control and both treatments.

Lymphocytes play a major role in immune defense against malaria infection (Good and Doolan, 1999; Plebanski and Hill, 2000). For instance, T_H1 cells and interferon-γ are required to control the primary peak parasitemia in mice infected with *Plasmodium chabaudi chabaudi* AS, and this mechanism is antibody-independent (Stevenson and Riley, 2004). $CD4^+$ T_H1 and T_H2 cells and antibody are required after the peak to eliminate the parasites. Depletion of natural killer cells can also cause a rapid increase in parasitemia (Mohan et al., 1997). Suppression of lymphocytes by deltamethrin might contribute to weakened host resistance and hence the reduction of survival times, particularly of mice exposed to the high-dose in this study. Although the survival times of low-dose treated mice were not significantly different from the control, they were apparently lower. Therefore, lymphocytes might not be the only cell types primarily involved in fighting the infection. Granulocytes are part of the immune system and have broad activities. This group of white blood cells includes neutrophils, eosinophils, and basophils. In particular, eosinophils are prevalent in parasitic infections, and their intracytoplasmic granules contain unique proteins that are toxic to certain parasites, including *P. falciparum* (Waters et al., 1987; Kurtzhals et al., 1998). In this study, the number of granulocytes decreased in both high- and low-dose treated groups. This suggests that, besides lymphocytes, alteration of the granulocyte population might also contribute to the reduction of survival times of treated mice.

Our study shows that deltamethrin has a potential to compromise the immunity and impair host resistance to malaria infection in mice. Realistically, the toxicological risk of people who live in the malaria endemic areas where deltamethrin is used might be low because the level of public exposure, e.g. air concentration of deltamethrin from spraying/fogging by health workers, household spraying, usage of deltamethrin-impregnated bednets, and consumption of deltamethrin-contaminated food products, is likely to be less than the doses tested in this study (Barlow et al., 2001; Zhang et al., 1991). The persons who could be exposed to deltamethrin at a high level are formulators, handlers, and spraymen. Nonetheless, the risk toward public health may increase if the users carelessly apply the insecticide at higher dosages than recommended. Although the typical level of exposure to deltamethrin in humans is lower than the dosages used in our study, adverse impact on humans at lower doses remains unknown. The aim of this study was to investigate if deltamethrin has the potential of immunosuppression and deleterious impact on host resistance to malaria infection as ascertained through a mouse model. The precise impact on humans will require further studies.

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