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THE EFFECT OF SUBACUTE POISONING WITH DELTAMETHRIN ON THE LEVELS OF INTERLEUKIN 1B AND TUMOUR NECROSIS FACTOR A IN THE LIVERS AND KIDNEYS OF MICE

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ABSTRACT

Deltamethrin is a type II pyrethroid. Deltamethrin's action is characterised by nephrotoxicity, hepatotoxicity and immunotoxicity.
The aim of the study was to evaluate the effect of poisoning with deltamethrin on the levels of interleukin1ß and TNFα in the livers and kidneys of mice.
A total of 24 female mice were divided into 3 groups of 8:
- controls,
- receiving deltamethrin i.p. at the dose of 41.5 mg/kg for 28 days
- receiving deltamethrin i.p. at the dose of 8.3 mg/kg for 28 days.

On day 29 the animals were euthanised, livers and kidneys were obtained, homogenised and centrifuged. The supernatant was used for measuring IL-1ß and TNFα concentration with ELISA tests. The results were analysed with Statsoft Statistica.
The interleukin 1ß concentrations were significantly higher in the kidneys (18.30±16.85) of mice exposed to the higher dose of deltamethrin than in the controls (8.15±4.66) ($p<0.05$). In the livers of mice receiving 41.5mg/kg deltamethrin it was 203±71.63 vs 46.77±34.79 ($p<0.05$). In the livers of animals receiving the lower dose it was higher than in the control group (96.51±24.73) ($p<0.05$). The TNF α was elevated in the kidneys of mice exposed to the higher dose of deltamethrin (6.56±3.26 vs 2.89±1.57)($p<0.05$).
Conclusion: Deltamethrin produces a significant increase of interleukin 1ß in the livers and kidneys of mice and so the cytokine seems to be a good marker of hepatotoxicity and nephrotoxicity in the course of subacute poisoning.
Keywords: deltamethrin; interleukin 1ß; tumour necrosis factor α.

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INTRODUCTION

Deltamethrin is a type II pyrethroid. Pyrethroids are used indoors and outdoors worldwide. They are recommended for agricultural, public, residential, and veterinary usages [1]. This group of insecticides is widely used in malaria control [2]. In temperate climate zones it is used in agriculture to protect potatoes, cabbages, wheat and barley from insect pests. Therefore, there is a risk of animal and human exposure to deltamethrin by ingestion of contaminated water or feed.

Pyrethroids act on insects as target organisms *via* voltage-gated sodium channels in neurons and in the same way on non-target organisms like humans. Therefore, they are classified as neurotoxins. Pyrethroids used in agriculture for pest control contain an α-cyano group, like deltamethrin. They accumulate in sediments, which cause pyrethroid contamination in aquatic products [3]. Among pyrethroids found in urban dust ones without an α-cyano group predominate.

Pyrethroids are metabolised in the liver and their metabolites are passed with urine. The 3-phenoxybenzoic acid (3-PBA) is the most commonly detected urinary metabolite of several pyrethroids [4]. The pyrethroid metabolites are frequently detected in the urine of children and adults from rural and urban areas, confirming widespread exposure of the human population to these compounds. Non-occupational exposure occurs *via* ingestion with food and water or contact with contaminated house dust after the use of bednets, burning coils, pyrethroid-soaked mats, electrovaporises and aerosols [1,5]. Acute poisoning with pyrethroids produces paraesthesia, and respiratory, eye and skin irritation in humans [1]. There is data that nephrotoxicity, hepatotoxicity [6] and immunotoxicity signs develop due to subacute or chronic poisoning with pyrethroids [7].

Interleukin 1ß and tumour necrosis factor α are proinflammatory cytokines produced by numerous cells in response to infection, oxidative stress and intoxication [8,9].

The aim of the study was to evaluate the effect of subacute poisoning with deltamethrin on the levels of interleukin1ß and tumour necrosis factor α in the livers and kidneys of mice.

MATERIALS AND METHODS

The study project was approved by The Local Ethical Committee in Lublin, Poland. The experiment was conducted according to European law regulations at the Centre for Experimental Medicine at The Medical University of Lublin.

Deltamethrin was purchased from the Organic Chemistry Institute (Annopol 6, 03-236 Warsaw, Poland). Saline was purchased from Glenmark Pharmaceuticals (Warsaw, Poland) in 5ml ampules. At the Centre for Experimental Medicine (CEM) at The Medical University of Lublin, Poland where the experiment was conducted there were standard laboratory conditions with 12h light/dark cycles, temperature 21-22°C and relative humidity of 55-60%. All the animals had free access to sterile water (sterilised with UV) and feed for rodents purchased from Altromin International (Lage, Germany). A total of 24 young adult non-gravid female Albino Swiss mice was used. The animals were approximately 6 weeks old at the beginning of the experiment. The animals were bred at CEM and the original source of the colony was Charles River Laboratories (Cologne, Germany).

The animals were randomly divided into 3 groups of 8:

- Group 1-controls (receiving saline daily *i.p.* for 28 days),
- Group 2-animals receiving deltamethrin *i.p.* at the dose of 41.5 mg/kg for 28 days ($0.5LD_{50}$)[6]
- Group 3- animals receiving deltamethrin *i.p.* at the dose of 8.3 mg/kg for 28 days ($0.1LD_{50}$).

On day 29 the animals were euthanised, and their livers and kidneys were harvested.

The intraperitoneal route of administration was chosen as it guarantees absorption of the xenobiotis. It is unlikely however for animals to get intoxicated intraperitoneally in the real world. Learning from our previous experiments conducted at the Hygiene Department we knew the intraperitoneal LD_{50} for deltamethrin = 83mg/kg.

The kidneys and livers were homogenised with a mechanical blender MPW-120(MPW Med. Instruments, Warsaw, Poland) in 0.1 mol buffer of Tris-HCl, of pH 7.4. For further analyses 0.5g of tissue was blended in 5ml of buffer. The homogenates were centrifuged for 15min (5000xg) twice (Sigma1-6P centrifuge, Polygen, Engelwood, NY, USA). The supernatant was used for measuring interleukin 1ß and tumour necrosis factor α concentration with the ELISA test. The interleukin 1ß and tumour necrosis factorα kits were purchased from the manufacturer (Cloud-Clone Corp. Katy, TX, USA).

The results were analysed with Statsoft Statistica (Statsoft Sp.zo.o.,Cracow, Poland) using the U-Mann-Whitney test. The results were expressed as mean± SD. The $p<0.05$ was considered statistically significant.

RESULTS

The interleukin 1ß concentrations were significantly higher in the kidneys (18.30±16.85) of mice exposed to the higher dose of deltamethrin than in controls (8.15±4.66) ($p<0.05$). In the livers of mice receiving $0.5LD_{50}$ deltamethrin it was 203±71.63 *vs* 46.77±34.79 in controls ($p<0.05$). In the livers of animals receiving the lower dose of deltamethrin it was also significantly higher than in the control group (96.51±24.73) ($p<0.05$). Tumour necrosis factor α level was significantly elevated in the kidneys of mice exposed to the higher dose of deltamethrin (6.56±3.26 *vs* 2.89 ±1.57 in controls)($p<0.05$) (Tab.1.).

Tab. 1

The concentrations of interleukin1ß and tumour necrosis factor α (TNFα) in mice kidneys and livers after intoxication with deltamethrin.

Group	Interleukin 1ß in the kidneys [pg/mL] mean±SD	TNF α in the kidneys [pg/mL] mean±SD	Interleukin 1ß in the livers [pg/mL] mean±SD	TNF α in the livers [pg/mL] mean±SD
Group 1 (controls), n=8	8.15±4.66	2.89±1.57	46.77±34.79	4.41±1.17
Group 2 (41.5mg /kg b.w. deltamethrin for 28 days i.p.), n=8	18.30±16.85*	6.56±3.26*	203.17±71.63*	5.78±2.49
Group 3 (8.3mg/kg b.w. deltamethrin for 28 days i.p.), n=8	8.30±12.25	2.24±1.20	96.51±24.73*	4.64±4.83

*p<0.05 *vs* controls

DISCUSSION

Burns analysed 61 articles about health outcomes of exposure to pyrethroids. Many of them were based on a single assessment of pyrethroid urinary metabolites [10].

In a study conducted in France, in which 245 families, each having 6-year old children, participated, permethrin, cypermethrin, cyfluthrin, deltamethrin, and tetramethrin pyrethroids were detected in 100, 56, 9, 15, and 26% of the dust samples, respectively [11].

Al-Omar et al. detected necrosis, hyperaemia, and fatty changes in the liver after exposure of male Albino Swiss mice *via* inhalation for 21 days to pyrethroids [5]. In the kidneys Al-Omar et al. visualised glomerular necrosis, cytoplasmic degeneration of renal tubular cells, necrosis of tubules and dilatation of kidney blood vessels [5].

Amin et al. conducted a study on catfish exposed to deltamethrin for 4 days. After exposure to deltamethrin at the dose of 0.75 µg/l of water in the tank an increased level of lipid peroxidation in the liver and kidney was noted. Catalase activity was decreased in the tissues. Serum alanine transaminase, urea, and creatinine were increased. The authors concluded that deltamethrin is highly toxic to catfish. The effect is best visible in the liver [8]. Abdel-Daim et al. confirmed high deltamethrin toxicity to fish: in their experiment on tilapia subacute intoxication, with deltamethrin administered at the dose of 1.46 µg/L for 28 days, it was observed that serum alanine transaminase, total cholesterol, urea, uric acid, creatinine and malonaldehyde all increased. In the same animals' glutathione peroxidase, superoxide dismutase and catalase were reduced confirming oxidative stress [12]. Dubey also confirmed that deltamethrin's toxicity in mammals demonstrates itself as hepatotoxicity [13].

The studies of Abdou et al. show that deltamethrin is hepatotoxic [14]. Lu et al. in an excellent review summarised that oxidative stress and metabolism in the liver are highly correlated with deltamethrin's toxicity [15]. In other words, the mechanism of liver damage is the oxidative stress occurring in hepatocytes after intoxication with the pyrethroid.

Zhong confirmed a significant role of interleukin 1 in deltamethrin's neurotoxicity [16]. Before it was believed that only interaction with voltage gated sodium channels was responsible for the neurotoxic effects if pyrethroids.

Han et al. explained how hepatic fibrosis develops due to intoxication with deltamethrin *via* proinflammatory molecules. In their experiment quails were treated by intragastric administration with deltamethrin at the dose of 0 or 15, 30 or 45mg/kg bw. They also conducted experiments on chicken liver treated with deltamethrin. The authors confirmed that oxidative stress and activation of transforming growth factor-β1 led to liver fibrosis in a dose-dependent manner [17].

Feriania et al. studied the effect of bifenthrin (a pyrethroid type I: missing the α-cyano group) on cytokines in experimental animals. The authors recorded an increase in serum tumour necrosis factor α, interleukin 2, and inerleukin-6 [18].

Aouey et al. studied the effect of 60-day intoxication of rats with lambdacyhalothrin on liver function. Lambdacyhalothrin, like deltamethrin, is an α-cyano pyretroid insecticide. Intoxication produced a significant increase in hepatic oxidative stress markers in a time-dependent and dose-dependent manner [19]. Accumulation of 3-PBA in the livers, and significantly increased expression of tumour necrosis factor α and interleukin-1β genes was noted [18]. In our study tumour necrosis factor α was measured in kidneys and livers. Contrary to Feriani and Aouey, we did not see an increase in tumour necrosis factor α concentration, but there was a significant increase in the level of interleukin-1ß in a dose- proportionate manner in both organs: kidneys and livers in our experiment.

Possible explanation of the difference could be the difference in the time of exposure: in our study it was 28 days, while in Aouey's it was up to 60 days. It is possible that after subacute poisoning with low doses of deltamethrin the oxidative stress produces internal organ damage, thus inducing reactive oxygen species (ROS) production. ROS stimulate expression of gene coding proinflammatory cytokines. Both interleukin-1β and tumour necrosis factor α are produced in macrophages and monocytes. As they are secreted into the blood, they have a systemic proinflammatory effect. Tumour necrosis factor α is one of the first cytokines to appear during inflammatory reaction [20]. It stimulates production of

interleukin-1ß during prolonged oxidative stress [21]. This explains why in the course of our experiment tumour necrosis factor α was elevated only in the kidneys of mice exposed to the higher dose of deltamethrin, while interleukin-1ß differed significantly among the groups exposed to the pyrethroid and controls. Our results are in agreement with results of the study with lambdacyhalothrin administered to mice, which increases of interleukin-1ß in the kidneys and livers of mice [22].

In the study of Abdel-Daim et al. deltamethrin, administered orally at the dose of 2 mg/kg for four weeks to rats, significantly increased tumour necrosis factor α concentrations in the sera and kidneys, while ceftriaxone and ascorbic acid produced nephroprotective and antioxidant effects [23]. This may be the new perspective in treatment of pyrethroid poisoning.

The significance of pyrethroid poisoning markers was clerly shown in numerous publications [24-28]. All of them confirm widespread exposure of the human population to pyrethroids without significant age nor sex differences. Klimowska and Wilegomas described a new method for pyrethroid metabolites detection in the urine [29]. Interestingly, it was shown that the levels of pyrethroid metabolites were higher in city dwellers than in people living in rural areas [30]. Rodzaj et al. suggest that the widespread exposure of the Polish population to pyrethroids is from non-dietary sources [31]. Jurewicz et al. provided evidence that widespread use of pyrethroids affects male fertility [32]. All these publications indicate that there is a need for good markers of pyrethroid toxicity in mammals. In our experiments animals were intended to be the models in the search for such a marker in humans.

CONCLUSIONS

Deltamethrin produces a significant increase of interleukin-1ß in the livers and kidneys of mice, and so the cytokine seems to be a good marker of hepatotoxicity and nephrotoxicity in the course of subacute poisoning. Tumour necrosis factor α is a less sensitive marker of deltamethrin's toxicity, as it was elevated only in the kidneys of animals exposed to $0.5LD_{50}$ of deltamethrin.

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