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Toxico-Pathological Studies of the Insecticide Metasystox-R (Oxydemeton-Methyl) in Rabbits

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الدراسات الباثولوجية النسيجية على المبيد الحشري ميتاسيستوكس-أر (أوكسيديميتون ميثايل) على الأرانب

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ABSTRACT

One of the widely used insecticides in agriculture and urban pest control is oxydemeton-methyl, which is an organothiophosphate compound. It has a high bioaccumulation effect due to its increased solubility and mobility. This study was carried out to investigate the effect of oxydemeton-methyl toxicity on the environment, and female New Zealand rabbits were used as a model. The rabbits were given oxydemeton-methyl orally in drinking water at a concentration of 34 ppm for six weeks. The clinical signs were diarrhoea, emesis, salivation, lacrimation, fasciculation, muscle tremors and weakness. The haematological parameters, such as the RBCs count, the Hb concentration and the PCV % were significantly decreased. On the contrary, the WBCs count were significantly increased. In addition, an acetylcholinesterase enzyme was inhibited, and a histopathological examination on the liver showed small areas of oval and bridge necrosis infiltrated with mononuclear cells. In the kidneys, there was a variable degree of nephrosis, and the heart showed foci of myocardial degeneration infiltrated with mononuclear cells. Therefore, it is concluded that oxydemeton-methyl is highly toxic to the environment.

الملخص

أوكسيديميتون ميثايل هو أحد المُبيدات الحشريّة الشائعة والذي ينتمي إلى مُركّبات الفوسفات العُضوي ويُستخدمُ على نِطاقٍ واسع في الزراعة ومكافحة الآفات. ونَتيجة إلى سرعةِ ذوبانه وسرعةِ انتقاله في المصادرِ البيئية، يُعتبر الأوكسيديميتون- ميثايل من المُركّبات التي لها تأثيرات تراكميّة بيولوجيّة عالية. ولذلك تمَّ تخطيطُ و إجراءُ هذه الدراسة لمعرفة مدى تأثير هذا المُركّب على البيئة وذلك من خلال استخدام إناثِ الأرانبِ النيوزيلنديّة كنموذجٍ حيواني. حيث تمَّ إعطاءُ الأوكسيديميتون- ميثايل عن طريقِ الفم بإضافته إلى مياهِ الشربِ للأرانبِ بتركيز مقداره 34 جزء في المليون لمدة 6 أسابيع. وكانت الأعراضُ الإكلينيكية المسجلة على الحيوانات هي الإسهال والتقيؤ وسيلان اللعاب والإدماع والرّجفان وضَعف في العضلات. كما لوحظ انخفاض شديد في عدد كرات الدم الحمراء وتركيز الهيموغلوبين ونسبة خلايا الدم الحمراء . وفي المقابل، زاد عدد كرات الدم البيضاء بشكل كبير. بالإضافة إلى ذلك، تم تثبيط إنزيم أساتيل استريز. وأظهر الفَحصُ الباثولوجي للكَبِد وجودَ مناطق صغيرة من النُّخر المُصاحبة لخلايا وحيدةِ النواةِ الالتهابية. وفي الكُلى، كانت هناك درجاتٌ متفاوتةٌ من الالتهاب وأظهرت عضلاتُ القلبِ وجود بُؤر تَنكُّس مع انتشار لخلايا وحيدةِ النواةِ الالتهابية. وعليه، يُستَنتجُ من هذه الدراسةِ أن أوكسيديميتون- ميثايل شديدُ السُمِّية على البيئة.

KEYWORDS
الكلمات المفتاحية
Environments, insecticide, oxydemeton, pathology, pesticides, toxicity
أوكسيديميتون، باثولوجيا، البيئة، تسمم، مبيد، نسيج مرض

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1. Introduction

Although oxydemeton-methyl is restricted or banned in many countries due its high toxicity, it is still widely used in some parts of the world (Fan and Jackson, 1989; Kumar et al., 2016; Moses, 1989). It is an organothiophosphate (OP) insecticide, which is broadly used in agricultural and urban pest control. It has a large bioaccumulation and strong water solubility and mobility, which has led to its long-lasting nature in the environment and wildlife. Due to this bioaccumulation, many studies have focused on its potential harm to humans and animals. Nonetheless, only a few studies have focused on oxydemeton-methyl contamination toxicity in the environment.

Oxydemeton-methyl has been primarily used to control pests (Ghadamyari et al., 2008; Schuphan and Casida 1983; Anitha et al., 2004). Yet, it is one of the most frequently used OP insecticides. Therefore, due to its high-water solubility and mobility, its leaves potentially harmful residues in the environment.

While studies on toxicity are generally performed on animal models, such as rodents and rabbits (Bondarenko et al., 2013; Guilhermino et al, 2000), such studies on oxydemeton-methyl are lacking in literature. Nonetheless, similar studies have been conducted on other pesticides and can be used as a guide in this investigation. Kemabonta and Akinhanmi (2013) investigated the toxicological effects of three pesticides, chlorpyrifos, dichlorvos and alphacypermethrin, on the haematological parameters of adult mice. The results showed a significant decrease in the red blood count (RBC), the haemoglobin and the packed cell volume (PCV) and a significant increase in the white blood cells' (WBCs) volume.

The objective of this study is to simulate oxydemeton-methyl environmental water toxicity and study its effect of on organs, blood pictures and the cholinesterase enzyme.

2. Materials and Methods

2.1. Animals:

Ten adult New Zealand rabbits weighing 2.8–3 kg were used. They were kept under hygienic conditions and were fed freshly prepared

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commercial pellets. Water was offered ad-libitum.

2.2. Insecticide:

Metasystox-R (oxydemeton-methyl, S-2-(ethyl-sulfinyl) ethyl O,O-Dimethyl phosphorothioate) (Bayer AG, Germany). It is a systemic and contact miticide and insecticide with a fairly long residual life. It is used mainly as a plant spray or for soil drenching to kill insects.

2.3. Assessment of the Experiment:

The rabbits were divided into two groups of five. The first group received drinking water containing 34 ppm (1/10 LD50) of Metasystox-R for six weeks. The second group was kept as the control group and was offered insecticide-free drinking water. The animals were kept under observation throughout the experiment. They were then sacrificed at the end of the experiment (six weeks), and blood and tissue samples were collected for haematological and histopathological investigation.

2.4. Haematological Study:

The haematological study of the effect of the oral administration of Metasystox-R included RBC and WBC counts, the haemoglobin (Hb) concentration and the PCV. Blood samples were taken from each rabbit in tubes containing Ethylenediaminetetraacetic acid (EDTA) (Analar, BDH). The estimation of the preceding values was measured using a VET Scan Hm5 (Abaxis, Germany).

Furthermore, acetylcholinesterase (ACHE) was estimated by an Ellman chemical test (Ellman et al., 1961). In this method, a reaction between chromogenic 5,50-dithiobis-2-nitrobenzoic acid and acetylthiocholine results in the formation of yellow ions of 5-thio-2-nitrobenzoic acid. The rate of the increased formation of the yellow ions is measured at 412nm using a spectrophotometer.

2.5. Pathological and Histopathological Studies:

At the end of the experiment, the animals were sacrificed, and a post-mortem examination was performed. Samples were taken from the following organs: the liver, the lungs, the kidneys, the heart and the spleen, which were fixed in 10% formalin, and then paraffin embedded. The samples were then sectioned at 4–6 microns and stained with haematoxylin and eosin to be examined microscopically (Suvarna, 2012).

2.6. Statistical Analysis:

The results were analysed by a student's-T test using an SPSS statistical analysis package. The results with a p value of P>0.05 were considered statistically significant.

3. Results

3.1. Symptoms of Oxydemeton-methyl Toxicity:

The rabbit group that received 34 ppm (1/10 LD50) of Metasystox-R for six weeks showed clinical signs, such as diarrhoea, emesis, salivation, lacrimation, muscle tremors and weakness, which suggested possible toxicity.

3.2. Results of Haematological Examination and Cholinesterase Investigation:

The haematological findings of the RBC count, the haemoglobin and the PCV of the rabbits intoxicated by oxydemeton-methyl showed a severe decline from the normal parameters (table 1). They reached approximately (3.84 ± 0.35x10^6/mm^3, 46.80 ± 0.31g/dl and 23.19 ± 1.30 %), respectively, at the end of the experiment. The control group showed normal parameters of (7.14 ± 0.30x 10^6/mm^3, 110.90 ± 14g/dl and 42.8 ± 0.83%), respectively. The total leukocytic count showed a substantial increase and reached approximately (14.40 ± 0.43 X10^3/mm^3) at the end of experiment. In addition, the cholinesterase of the treated rabbits was drastically inhibited at the end of the experiment. This might explain the effect on the neurotransmitting function on treated animals (table 2).

Table 1: Shows a timeline effect on the haematological changes of the blood pictures between the control and treated groups after the oral administration of oxydemeton-methyl (Metasystox) (1/10 LD50). Different superscripts designate significant differences between means within the rows; upper-case letters.

Parameters	Means ± SE			
	Control	2 weeks	4 weeks	6 weeks
RBCs 10^6/mm^3	7.08^A/ ± 0.53	6.47^B/ ± 0.20	5.02^C/ ± 0.13	3.98^D/ ± 0.62
Hb g/dl	135.90^A/ ± 14	104.80^B/ ± 21	75.70^C/ ± 17	46.80^D/±0.31
PCV %	42.62^A/ ± 0.26	36.03^B/ ± 0.12	25.99^C/±0.19	23.19^D/±0.18
WBCs 10^3/mm^3	8.25^A/ ± 0.16	10.86^B/ ± 0.14	12.12^C/±0.11	15.34^D/±0.59

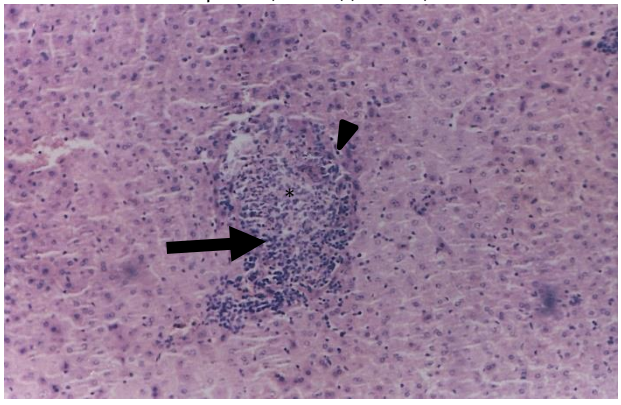
Table 2: Effect of oxydemeton-methyl (Metasystox) (1/10 LD50, 1.2 mg/kg body weight) on serum cholinesterase activity (U/L) in New Zealand rabbits at the end of the experiment. Different superscripts designate significant differences between means within the rows; upper-case letters.

Experimental period/week	Control U/l	Metasystox U/l	Inhibition %
2	4556.20^A/ ± 81.48	3201.20^B/ ± 59.12	29.74
4	4465.60^A/ ± 71.42	3170.00^B/ ± 17.96	29.02
6	4478.40^A/ ± 56.69	2303.40^C/ ± 9.6	48.57

3.3. Pathological and Histopathological Changes:

In the liver, clear hepatitis was observed among all the treated animals. This manifested as multiple areas of mononuclear cell aggregation in the parenchyma and portal areas. In addition, there were small areas of zonal and bridge necrosis infiltrated with mononuclear cells, hyperplastic Kupffer cells and/or biliary epithelial cells (Fig. 1).

Figure 1: Note area of necrosis (Asterix) infiltrated with mononuclear cell (arrow) in addition to Kupffer cells (arrowhead) (H & E X 200).



In the kidneys, there was a negative impact on their function, as demonstrated by the variable degrees of nephrosis, which was characterised by cortical tubular cell degeneration lined with flattened epithelium (Fig. 2). Furthermore, there were multiple areas of dilated cortical tubules and areas of atrophied cortical tubule associated with interstitial fibrosis (Fig. 3).

Figure 2: Note atrophied renal tubule (arrow) on cortical area with interstitial fibrosis (arrowhead) (H & E X 100).

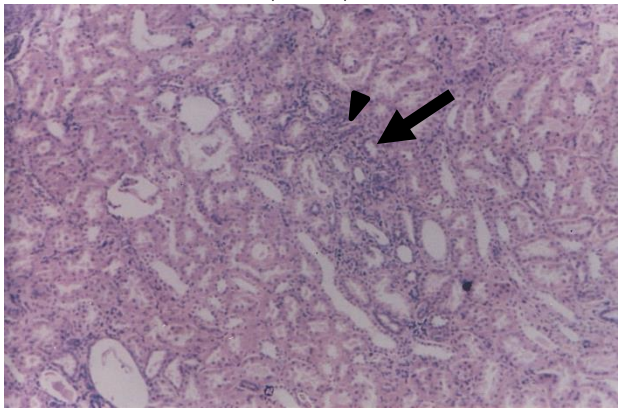
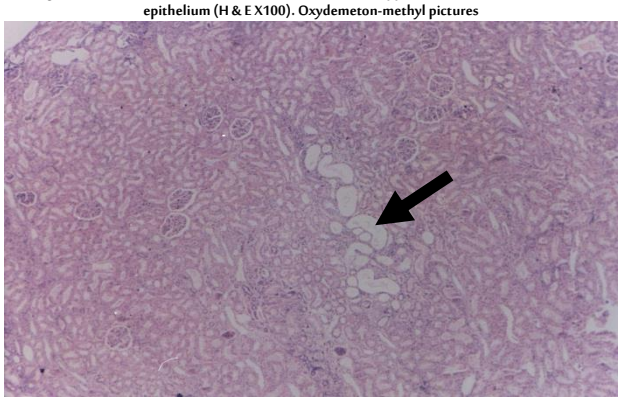


Figure 3: Note the dilated cortical tubule (arrow), which appears to be lined with flattened epithelium (H & E X100). Oxydemeton-methyl pictures



The spleen, on the other hand, showed extensive hemosiderosis, as seen in the red pulp of some animals whereby the counts are due to haemolysis and the inhibition of the RBC count in the treated animals (Fig. 4). In the lungs, the treated animals showed depletion of lymphoid tissue. The heart of the treated animals showed small foci of myocardial degeneration, which is associated with interstitial round cell aggregation (Fig. 5). These results suggest systemic and multi-organ toxicity on the treated animals.

Figure 4: Note extensive hemosiderosis in red pulp(arrow) (H & E X200).

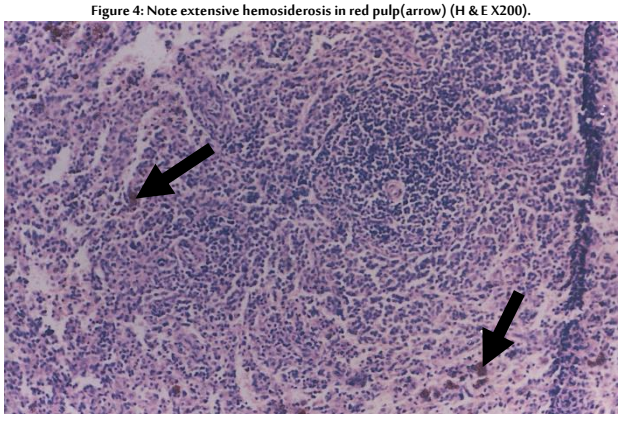
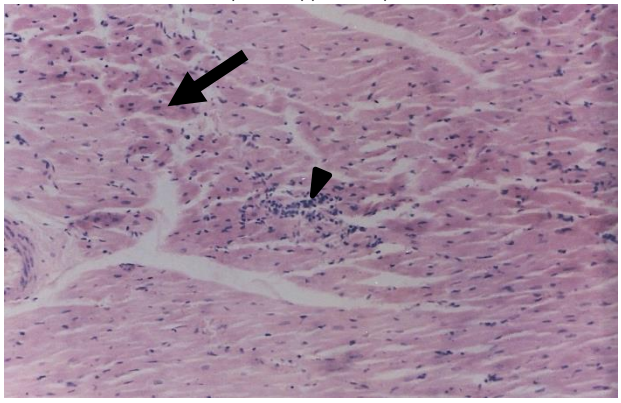


Figure 5: Note the foci of myocardial degeneration (arrow) infiltrated with mononuclear cells (arrowhead) (H & E X 200).



4. Discussion

Although the structures are diverse in nature, the mechanism by which the OP insecticides caused their toxicity is through matching, and it is related to the inhibition of the ACHE enzyme in the nervous tissue. This enzyme is responsible for the breakdown and termination of the physiological activity of acetylcholine's neurotransmitting function. The aforementioned results showed that the administration of Metasystox-R (oxydemeton methyl) at 34 ppm (1/10 LD_{50}) in drinking water for six weeks is capable of causing signs of toxicity. These clinical signs were diarrhoea, meiosis, emesis, salivation, lacrimation, fasciculation and muscle tremors and weakness. This indicates that the dose administered was enough to cause inhibition of the cholinesterase enzyme and that it creates clinical signs. The results were parallel, to some extent, with the clinical signs observed by Mehta et al. (2006) and Baba et al. (2017) were treated animals such as calves and rabbits showed similar response to chlorpyrifos treatment.

The haematological changes in this experiment, the RBCs, the Hb concentration and the PCV showed a significant decrease when compared with the control group. In addition, the WBCs showed a significant increase *($P \leq 0.05$)*. The results agree with those mentioned by Ali (1983) and Brown et al. (2015), who observed a decrease in the RBCs, Hb concentration and PCV in the buffalo calves, the sheep, the goats and the rats after exposure to toxic doses malathion, dimethoate, cyolane, methidathion and dichlorvos respectively. Kemabonta and Akinhanmi (2013) also observed similar results in mice after their exposure to chlorpyrifos, dichlorvos and alphacypermethrin.

Riaz and Yousafzai (2017) and Ali (1983) recorded an increase in the WBCs of rabbits, chickens and goats in the case of toxicity with malathion, malathion, cyolane and methidathion, respectively.

Therefore, one way to test the liver function is the ChE level in the serum, which is considered as a confirmatory indicator of organophosphorus insecticide poisoning. This conclusion is supported by the clinical signs of anticholinesterase action represented by diarrhoea, loss of appetite, drowsiness and mild tremors and muscle weakness, which were observed in organophosphorus poisoning in the treated rabbits (Kumar et al., 2010; Narang et al., 2015; Al malihi, 2016). These figures were parallel with Tutudaki et al. (2003) and Karanth et al. (2006), who reported the same effect with diazinon and chlorpyrifos on New Zealand rabbits.

The histopathological investigation revealed chronic toxic hepatitis as well as nephrosis in almost all the treated animals. These changes are attributed to the toxicity of organophosphorus on the liver and kidneys at a dose level of 34 ppm. Similar results were obtained by Lin and Hsueh (1993), Nishina et al. (1998), Owoeye et al. (2012) and Brown et al. (2015) on rat's livers.

In human beings, nephropathy after organophosphate toxicity appears mainly as a result of renal tubular damage (Peiris-John et al., 2005; Yurumez et al., 2007**;** Kaya et al., 2018). Similarly, we found renal tubular damage in our study, which suggests a similar cause of the neurological signs seen in the treated rabbits. The direct cause of the tissue damage observed in these animals is yet to be defined, but Pope (1999) stated that oxidative stress at the renal tubular level might lead to renal tubular damage.

Chronic interstitial pneumonitis is considered as more significant in relation to oxydemeton-methyl administration. A similar picture was observed by Tsao et al. (1990), Nishina et al. (1998) and Wang et al. (2010). Moreover, myocardial degeneration and the infiltration by inflammatory cells was observed in treated group similar to the result of Ali (1983) and Anand et al. (2009). The spleen showed only extensive hemosiderosis in some animals; this result matches the results obtained by Alakabi (2017) and Elshewey et al. (2013) under the effects of a low concentration of dimethoate in rabbits and rats, respectively. This may be due to an increase in the rate of the breakdown of erythrocytes after exposure to pesticides (van Banning, 1984). In addition, no gastrointestinal changes could be detected in the treated animals. However, Clarke and Clarke (1995) reported gastroenteritis in guinea pigs.

Biographies

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