Original article

Activity of selected antioxidative enzymes in rats exposed to dimethoate and pyrantel tartrate

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Abstract

This study presents the results of research concerning the effect of single and combined application of pyrantel tartrate and dimethoate on selected antioxidative enzymes: catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx), in rat erythrocytes. Pyrantel tartrate was applied twice, at a dose of 85 mg/kg bw at a two week interval, i.e. on day 14 and 28 of the experiment, orally, in a water solution with a stomach tube. Dimethoate was administered with drinking water for 28 days at a dose of 25 mg/kg bw/day. It was found that pyrantel tartrate caused only small changes in the activity of the antioxidative enzymes under analysis. Subchronic exposure of rats to dimethoate caused a significant increase in the activity of CAT, SOD and GPx in erythrocytes, indicating the existence of strong oxidative stress. In combined intoxication, no significant effects of administering pyrantel tartrate on the activity of CAT, SOD and GPx was found in animals poisoned with dimethoate. The profile of changes was similar to that observed in rats exposed only to the organophosphorus insecticide. This may indicate a lack of interaction between the compounds used in the experiment.

Key words: dimethoate, pyrantel tartrate, rats, CAT, SOD, GPx

Introduction

Among the many chemical compounds posing a potential threat to human and animal health, substances of high biological activity, such as pesticides and medicines, are of particular importance. Organophosphorus insecticides make up one of the quite well and comprehensively examined pesticide groups. They form a numerous group of products used for plant protection and sanitary hygiene purposes (Uygun et al. 2005, Bhanti and Taneja 2007, Bisdorff

and Wall 2008). Organophosphorus insecticides dissolve well in fats and do not dissolve easily or do not dissolve at all in water. They are easily absorbed from the alimentary tract, as well as through the respiratory tract and skin. These compounds reveal a multidirectional effect on the organism. The mechanism of their neurotoxic effect consists in inhibiting the activity of acetylcholinesterase, the accumulation of acetylcholine and excessive stimulation of the nervous system (Vale 1998, Bajgar 2004, Jintana et al. 2009).

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Dimethoate is a classic representative of this group of compounds. This is a systemic and contact insecticide which is metabolized relatively quickly and remains in the body for a short time (Barski and Zasadowski 2006). The main mechanism of the toxic effect of dimethoate, as with other organophosphorus insecticides, consists in inhibiting the activity of cholinesterases (Hoffmann and Papendorf 2006). This effect is attributed to its oxygen analogue – omethoate, which is created in the body as a result of the biotransformation process with the participation of the monooxygenase system particularly cytochrome P-450 (Buratti and Testai 2007).

Pyrantel tartrate is an anthelmintic medicine belonging to the group of tetrahydropyrimidines. It is characterized by a broad scope of effects against gastrointestinal parasites in various species of animals (Chartier et al. 1995, Valdez et al. 1995, Slocombe and Lake 2007). It is efficient against both young and mature forms. It is easily dissolved in water and absorbed from the alimentary tract, particularly in monogastric animals, reaching the maximum concentration in blood after 2-3 hours (Faulkner et al. 1972). It demonstrates an acetylcholine-like effect on cholinergic receptors and an associated effect on parasympathetically innervated internal organs, vegetative ganglia and a neuromuscular junction. At higher concentrations, it can act as an acetylcholinesterase inhibitor and evokes a direct cholinergic effect (Köhler 2001).

The compounds used in the experiment, i.e. dimethoate and pyrantel tartrate, are typical examples of substances widely used in agriculture and veterinary medicine. This research demonstrates that these compounds cause various types of disorder in biochemical parameters, including the antioxidative system, which are manifested through changes in the activity and the content of individual elements of the antioxidative barrier of the organism (Spodniewska and Zasadowski 2008). The frequent occurrence of bacterial infections in animals and the common application of organophosphorus pesticides poses a risk of undesirable and unexpected interactions between these compounds. Due to the limited amount of data concerning the combined effect of dimethoate and pyrantel tartrate in the organism on oxidative processes, a study on their effect on the activity of selected antioxidative enzymes was undertaken.

The aim of the research was to determine the effect of dimethoate and pyrantel tartrate administered individually and in combination on the activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) in rat erythrocytes.

Materials and Methods

The studies involved the application of dimethoate ($C_5H_{12}NO_3PS_2$) – CHEMINOVA (Denmark) which, according to the manufacturer's declaration, contained 99.1% pure O, O-dimethyl S-(N-methylcarbomoyl methyl) phosphorodithioate and pyrantel tartrate ($C_{11}H_{16}N_2S \cdot C_4H_4O_6$) obtained from the Biowet-Gorzów Pharmaceutical Company (Poland), containing 100% 1,4,5,6-tetrahydro-1--methyl-2-(2-(2-thienyl)vinyl)-pyrimidin(e)-pyrimidin-tartrate.

The studies were carried out on 120 male rats of the Wistar strain, with initial body weights of 170-190 g. The animals originated from the Animal Breeding Centre in Brwinów near Warsaw, and during acclimatization and the experiment they were kept in standard environmental conditions (12-hour daily cycle in artificial light conditions, ambient temperature 22 ± 1°C, air humidity 70 ± 10%, gravitational – mechanical ventilation). The rats were fed balanced, granulated "Murigran" feed and were divided into three experimental groups (I-III) and a control group (C), 30 animals per group. Group I was given pyrantel tartrate twice, at a dose of 85 mg/kg bw at a two-week interval (i.e. on day 14 and 28 of the experiment), orally, in a water solution with stomach tube. Dimethoate was administered to group II with drinking water for 28 days, at a dose of 25 mg/kg bw/day. Rats of group III received dimethoate as in group II and pyrantel tartrate as in group I. The control animals were given only feed and water *ad libitum*.

The studies were carried out pursuant to the guidelines of the Act on Animal Protection and recommendations of the Local Ethical Committee for Animal Experiments at the University of Warmia and Mazury in Olsztyn.

In selected periods after intoxication, i.e. after 6, 24 h and on day 3, 7 and 14, samples of heart-blood were taken for examination from animals under halothane anaesthesia. The following parameters were determined in erythrocytes: catalase (CAT) using the Aebi kinetic method (1984), superoxide dismutase (SOD) applying the kinetic method with the use of the RANSOD analytical kit (RANDOX Lab. Ltd. UK), and glutathione peroxidase (GPx) applying a kinetic method with the use of a RANSEL analytical kit (RANDOX Lab. Ltd. UK).

The data obtained were statistically analysed using a one-way analysis of variance (ANOVA) followed by the Newman-Keuls test. The results were presented as arithmetic means and standard error of the mean (± SEM). Differences between the means at the level of $P \leq 0.05$ were assumed to be statistically significant.

Results

The results of examinations concerning the activity of CAT, SOD and GPx in rat erythrocytes after the application of pyrantel tartrate, dimethoate and dimethoate and pyrantel tartrate are presented in Tables 1-3.

The application of pyrantel tartrate (Group I) in the administered dose resulted only in small changes in the observed activity of the enzymes under analysis in relation to the control group. The changes and their intensity depended on the type of enzyme and the period during which its activity was examined. A decrease of a few percent was observed in the activ-

Table 1. Catalase (CAT) activity in rat erythrocytes exposed to pyrantel tartrate and/or dimethoate (U/g Hb).

Time after intoxication	Group of animals			
	Control (C) (n = 6)	Pyrantel tartrate (I) (n = 6)	Dimethoate (II) (n = 6)	Dimethoate and Pyrantel tartrate (III) (n = 6)
6 h	509.45 / ± 7.64/	535.37 / ± 18.68/	562.76 / ± 24.91/	567.01 / ± 17.97/
24 h	566.46 / ± 13.97/	540.96 / ± 17.55/cd	657.16 / ± 32.11/ab	678.91 / ± 27.68/ab
3 d	502.70 / ± 11.79/	475.89 / ± 15.98/cd	594.60 / ± 23.30/ab	584.38 / ± 34.83/ab
7 d	523.22 / ± 14.97/	499.57 / ± 21.36/cd	635.04 / ± 26.20/ab	637.05 / ± 38.83/ab
14 d	586.41 / ± 22.48/	545.68 / ± 18.89/	622.55 / ± 21.49/	620.28 / ± 22.57/

Values expressed as means ± SEM
n – number of rats in the group, p – statistically significant in comparison with: a – control, b – pyrantel tartrate, c – dimethoate, d – dimethoate and pyrantel tartrate

Table 2. Superoxide dismutase (SOD) activity in rat erythrocytes exposed to pyrantel tartrate and/or dimethoate (U/g Hb).

Time after intoxication	Group of animals			
	Control (C) (n = 6)	Pyrantel tartrate (I) (n = 6)	Dimethoate (II) (n = 6)	Dimethoate and Pyrantel tartrate (III) (n = 6)
6 h	1532.38 / ± 20.76/	1414.19 / ± 39.05/cd	1902.10 / ± 75.01/ab	1846.11 / ± 74.97/ab
24 h	1462.13 / ± 31.01/	1367.76 / ± 53.48/cd	1754.81 / ± 62.88/ab	1782.47 / ± 69.20/ab
3 d	1391.88 / ± 35.85/	1473.78 / ± 24.04/	1627.91 / ± 51.34/a	1609.20 / ± 53.83/a
7 d	1323.38 / ± 38.54/	1418.50 / ± 34.98/	1525.05 / ± 72.18/	1478.33 / ± 65.52/
14 d	1296.38 / ± 32.11/	1400.64 / ± 36.93/	1361.54 / ± 45.54/	1375.96 / ± 22.45/

Values expressed as means ± SEM
n – number of rats in the group, p – statistically significant in comparison with: a – control, b – pyrantel tartrate, c – dimethoate, d – dimethoate and pyrantel tartrate

Table 3. Glutathione peroxidase (GPx) activity in rat erythrocytes exposed to pyrantel tartrate and/or dimethoate (U/g Hb).

Time after intoxication	Group of animals			
	Control (C) (n = 6)	Pyrantel tartrate (I) (n = 6)	Dimethoate (II) (n = 6)	Dimethoate and Pyrantel tartrate (III) (n = 6)
6 h	508.72 / ± 14.90/	528.22 / ± 44.05/	565.57 / ± 21.37/	584.73 / ± 22.34/
24 h	519.61 / ± 14.94/	545.65 / ± 19.96/	595.01 / ± 11.01/a	584.22 / ± 17.53/
3 d	530.63 / ± 11.94/	561.85 / ± 17.12/cd	628.63 / ± 15.86/ab	612.10 / ± 24.98/ab
7 d	508.53 / ± 16.38/	525.82 / ± 16.38/	570.80 / ± 17.98/	591.96 / ± 26.38/a
14 d	501.73 / ± 21.05/	530.71 / ± 11.96/	525.75 / ± 21.97/	519.51 / ± 17.34/

Values expressed as means ± SEM
n – number of rats in the group, p – statistically significant in comparison with: a – control, b – pyrantel tartrate, c – dimethoate, d – dimethoate and pyrantel tartrate

ity of CAT in relation to the control group between 24 h and day 14 of the experiment, and in the initial period of the study, i.e. up to 24 h after exposure in the case of SOD (Tables 1 and 2). In other time brackets, the activity of CAT, SOD and GPx was slightly increased in relation to the control group.

After application of dimethoate (Group II), an increase in the activity of CAT, SOD and GPx was observed in comparison to the control group, and this was maintained for the whole period of the experiment. After 6 h the activity of CAT was increased by 10.5%, and then a gradual intensification of this process was recorded. An increase in the activity of CAT was statistically significant in relation to the control group after 24 h, and after day 3 and 7 (Table 1). The activity of SOD revealed a quite different course. Its activity was maximally increased (24.1%) already after 6 h and, in subsequent analytical periods, its gradual decrease was observed, while after day 14 of the experiment, the activity of SOD was still increased by 5.0% in comparison to the control group (Table 2). Throughout the experimental period the activity of GPx was increased in relation to the control group, but this rise was statistically significant only after 24 h and day 3 (Table 3). The most intense increase of GPx occurred after day 3 of the experiment and amounted to 18.5% compared to the control group.

In the group of rats which received dimethoate and pyrantel tartrate (Group III), the profile of changes in the activity of the analysed enzymes in rat erythrocytes was similar to that observed in the group of animals exposed only to dimethoate, but those changes were slightly less intense. An increase in the activity of the examined enzymes was observed in relation to the control group; this persisted until the end of the experiment. As regards the activity of CAT, this increase was statistically significant after 24 h and day 3 and 7, SOD – after 6 and 24 h and after day 3, and GPx – after day 3 and 7 (Tables 1-3).

Discussion

In mammals, one of the elements of the complex defence mechanism against the formation and unfavourable effects of reactive oxygen species is the system of cooperating antioxidative enzymes (Kulikowska-Karpińska and Moniuszko-Jakoniuk 2004). A key enzyme participating in the body's defence against oxidative stress is superoxide dismutase (SOD). This enzyme catalyses reactions in which superoxide anion radical is removed and molecular oxygen and hydrogen peroxide are created (Yim et al. 1993). The second important antioxidative enzyme is catalase (CAT). This is a hemoprotein of peroxidase properties, catalysing reactions of hydrogen peroxide reduction (Ścibor and Czeczot 2006). This effect is supported by glutathione peroxidase (GPx), which is a metalloenzyme which also participates in the reduction of hydrogen peroxide with simultaneous transformation of reduced glutathione in its oxidized form (Malmezat et al. 2000). At low concentrations of H_2O_2, GPx is primarily responsible for its elimination, but when the intracellular concentration of hydrogen peroxide is high, this process is carried out by CAT, the saturation of which does not occur even at very high concentrations of H_2O_2 (Lledias et al. 1998). Due to the fact that GPx also reacts with other hydrogen peroxides, it is believed that this enzyme plays a crucial role in the antioxidative defence system, particularly in cases of oxidative stress of low intensity (Mates et al. 1999).

The results of research carried out in recent years indicate that anthelmintic drugs cause oxidative stress (Karatas et al. 2008, Pinlaor et al. 2008, Dewa et al. 2009). Ince et al. (2010) demonstrated in research on rats that levamisole administered at a dose of 20 mg/kg bw for 7 days caused oxidative stress and peroxidase activity. The authors found a significant increase in the activity of SOD and CAT and the level of GSH and MDA in erythrocytes as well as in liver and kidney homogenates.

In our own studies, the application of pyrantel tartrate twice to rats at a dose of 85 mg/kg bw did not cause any significant changes in the activity of SOD, CAT and GPx, although during the experiment the activity of the analysed enzymes in erythrocytes was subject to slight fluctuations of a few percent. In a similar study, but concerning exposure of rats to pyrantel embonate applied twice at a dose of 1/2 LD_{50}, i.e. on day 14 and 28 (Barski and Zasadowski 2008) as well as at a dose of 1/5 LD_{50} for 3 subsequent days (Barski et al. 2007), the authors found similar changes in the activity of CAT and SOD to those in the present research concerning pyrantel tartrate. On the basis of those studies, it can be assumed that pyrantel in the doses applied does not demonstrate an antioxidative effect, regardless of the form of the compound (embonate, tartrate), dosage or the period of exposure.

The results of studies indicate that organophosphorus insecticides, besides having a neurotoxic effect, reveal the ability to generate free radicals, which results in the occurrence of oxidative stress (Akhgari et al. 2003, Abdollahi et al. 2004, Ranjbar et al. 2005, Karademir Catalgol et al. 2007). In research on rats, it was shown that both a single application of chlorfenvinphos at a dose of 0.3 mg/kg bw (0.02 LD_{50}) (Łukaszewicz-Hussain and Moniuszko-Jakoniuk 2005) and subchronic exposure, i.e. for 14 and 28 days

(Lukaszewicz-Hussain 2008) resulted in an increase in the activity of antioxidative enzymes in the examined tissues, i.e. erythrocytes, the liver and the brain. According to the authors, an increase in the activity of SOD and CAT in the examined tissues was the consequence of intensified production of reactive oxygen species (ROS) after exposure to chlorfenvinphos. ROS mainly attack biomolecules, including lipids, which are the most sensitive to their effects. In addition, the results of the research carried out by other authors showed that subchronic exposure of rats to malathion applied intraperitoneally at doses of 25, 50, 100 and 150 mg/kg bw caused oxidative damage in most tissues under analysis (Possamai et al. 2007). According to the authors, tissues that are most susceptible to oxidative changes after 28 days of exposure to this insecticide include the liver, quadriceps and serum. Similar observations were made by other authors examining the effect of dimethoate on oxidative stress. Sharma et al. (2005), orally applying to rats various doses of dimethoate (0.6, 6.0 and 30 mg/kg /day) for 30 days, found an increase in the activity of SOD, CAT and GPx in both the liver and the brain, and that this increase was most visible after the two highest doses. Kamath and Rajini (2007), giving rats dimethoate at doses of 1/10 and 1/20 LD_{50} for 30 days, recorded oxidative stress expressed e.g. by an increase in the activity of SOD and CAT and peroxidation of lipids in the pancreas. The highest increase of the analysed enzymes was found by the authors after applying the higher dose of the insecticide, i.e. 40 mg/kg bw.

The results of the current study also demonstrate that subchronic (28 day) exposure of rats to dimethoate caused a significant increase in the activity of CAT, SOD and GPx in rat erythrocytes, as a response of the organism to an increasing concentration of reactive oxygen species. An increase in the activity of SOD accompanied by a simultaneous increase of CAT is a phenomenon advantageous for the organism, preventing an increase in the production of reactive oxygen species. SOD is an "incomplete antioxidant" which, by scavenging peroxide anions, participates in the overproduction of H_2O_2, and the accompanying simultaneous increase in CAT activity prevents excessive production of H_2O_2. Catalase is therefore the main enzyme responsible for removing H_2O_2 in erythrocytes, which are morphotic elements particularly exposed to attacks by ROS (Mueller et al. 1997). Additionally, decomposition of hydrogen peroxide by catalase does not bring about generation of other reactive oxygen species (Girotti 1998). In our own research, the authors also found an increase in the activity of GPx, i.e. the enzyme forming the enzymatic arrangement connected with glutathione and glutathione reductase (Burk 1990).

In recent years, an increasing number of studies have examined the interactions of organophosphorus insecticides with various types of xenobiotics, including their effect on oxidative stress and lipid peroxidation (Durak et al. 2008, Mansour and Mossa 2009). The results of such research depend on the type, the dose and the method of exposure to chemical compounds used in experiments. Hazarika et al. (2003) found that exposure of rats to malathion at a dose of 700 mg/kg bw 3 hours before applying anilophos does not essentially intensify the anticholinesterase effects of the herbicide, but can increase oxidative brain damage caused by it. John et al. (2001), intoxicating rats on a one-off basis with dimethoate and/or malathion administered per os at doses of 0.01% LD_{50}, found that the compounds applied separately result in the occurrence of oxidative stress and lipid peroxidation. In the case of combined exposure of animals to these insecticides, the authors recorded no effects on oxidative stress intensification. Increases in the activity of SOD, CAT and MDA concentration in erythrocytes of rats from the mixed intoxication group were only slightly lower than the values recorded in groups of animals to which these compounds were provided separately. The results of those studies correspond to the results of our own studies concerning the effect of dimethoate and pyrantel tartrate. Sivapiriya et al. (2006), in research on mice intoxicated for 14 days with dimethoate and ethanol, also observed antioxidative status disorders. According to the authors, such disorders result not only from the independent effects of applying dimethoate and/or ethanol, but also their mutual interaction. In our previous studies (Barski and Zasadowski 2008), in which the Bi 58 Nowy preparation and/or pyrantel embonate were applied to rats, an increase in the activity of SOD and CAT was recorded in both erythrocytes and in the MDA content in rat liver homogenates, which indicates the occurrence of oxidative stress. Changes in the analysed parameters were particularly intensive in rats intoxicated for 4 weeks with the Bi 58 Nowy preparation, as well as with Bi 58 Nowy and pyrantel embonate. The profile of these changes was similar, but their intensity was higher after combined intoxication, which we did not observe when applying dimethoate and pyrantel tartrate.

Conclusion

The present study found that the application of pyrantel tartrate in the applied dose did not cause any significant changes in the activity of the examined enzymes, which indicates a lack of its oxidative action. Twenty-eight-day intoxication of rats with dimethoate

caused a significant increase in the activity of CAT, SOD and GPx in rat erythrocytes. This indicates an oxidative action of the organophosphorus insecticide used in the study. In the group of animals which received both dimethoate and pyrantel tartrate, the profile of changes in the activity of the antioxidative enzymes analysed was similar to that found in the group of rats exposed only to the insecticide, but changes in the activity of these enzymes were slightly less intense than in the group intoxicated with dimethoate. This could indicate the lack of a synergistic oxidative effect of the chemical compounds used in the experiment, i.e. dimethoate and pyrantel tartrate.

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