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Original article

Glutathione and glutathione-related enzymes in rats exposed to dimethoate and/or pyrantel

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Abstract

The study was undertaken to examine the effect of single and combined administration of dimethoate (an OP insecticide) and pyrantel embonate (an anthelmintic agent) on the concentration of reduced glutathione (GSH) and the activity of glutathione peroxidase (GPx) and glutathione reductase (GR) in rats. Dimethoate (Group I) was administered to rats at a dose of 1/10 LD_{50} for 5 consecutive days and pyrantel embonate (Group II) at a dose of 1/5 LD_{50} for 3 consecutive days. The animals of group III were given both of the mentioned above compounds in the same manner as group I and II, but pyrantel embonate was applied on day 3, 4, and 5 from the beginning of dimethoate intoxication. Material from 6 rats randomly selected from each group was obtained after 3, 6 and 12 hours and 2, 7 and 14 days following the last applied dose of the compounds under study. It was found that application of pyrantel embonate caused only slight changes in the analysed parameters i.e. GSH, GPx and GR. Dimethoate administration caused disturbances in the antioxidative system manifested as a decrease in GSH concentration in the liver (max. – 37.7% after 6 hours) and an increase of GPx and GR activities in erythrocytes (max. – 21.7% and 29.6% after 3 hours, respectively), compared to the control group. The profile of changes after combined intoxication was similar, but their intensity was higher compared to the group of animals exposed to dimethoate only. Based on current studies, it was concluded that both dimethoate and pyrantel embonate at the applied doses showed a pro-oxidative activity.

Key words: dimethoate, pyrantel, glutathione, glutathione peroxidase, glutathione reductase, rats

Introduction

Among numerous chemical compounds posing a health hazard to animals and humans, the substances with high biological activity such as pesticides and drugs are particularly important. Organophosphate insecticides are one of the most important and widely-used pesticides because they do not show a tendency for accumulation in the environment and the food chain, have relatively low acute toxicity and are rapidly degraded. These compounds affect not only the target organisms (pests), but also other living organisms and all components of the environment (Uygun et al. 2005, Hundekari et al. 2011). They may also non-specifically influence a number of metabolic processes in mammals, including generation of free radicals and, particularly, reactive oxygen species (Costa 2006, Yarsan and Cakir 2006).

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Dimethoate (O,O-dimethyl-S-methyl-carbamoylmethyl phosphorodithioate) is a broad spectrum organophosphate insecticide and acaricide. Its mechanism of toxic activity (similarly to other OP) on humans and animals results mainly from the inhibition of acetylcholinesterase (AChE) at the synapses and neuromuscular junctions of skeleton muscles. Dimethoate as the parent compound is a weak AChE inhibitor, but under *in vivo* conditions it is activated to an oxidative analog (oxon) i.e. omethoate, which is a 75-100 times stronger AChE inhibitor. It has also been shown that the toxicity of dimethoate may be associated with the induction of oxidative stress and excessive generation of reactive oxygen species (ROS) as well as with alterations in the antioxidative system (Abdallah et al. 2011, Al-Awthan et al. 2012).

Infections with intestinal helminths are thought to be one of the most serious health issues in the world which significantly affect human and animal health. Pyrantel embonate (1,4,5,6-tetrahydro-1-methyl-2-[2(2-thienyl)ethenyl] pyrimidine) is an effective compound with good anthelmintic activity against the most common gastro-intestinal nematodes in humans and animals (Catton and Van Schalkwyk 2003). It affects the parasites in the gastrointestinal tract by blocking their neuromuscular transmission and inhibiting the activity of cholinesterase; this results in the contraction and spastic paralysis of parasites and enables their expulsion (Rayes et al. 2001). Despite being on the list of drugs recommended by WHO (WHO 1996) for many years, there have been no detailed publications on its impact on the variety of processes that occur in mammals, including oxidative processes.

Apart from the benefits associated with the use of dimethoate and pyrantel, these compounds may also cause different disturbances in the organism such as the generation of free radicals and induction of oxidative stress (Albonico et al. 2002, Ben Amara et al. 2012). Possible interactions between the compounds present an additional problem as they may sometimes unexpectedly change the effects of an individual preparation and unfavourably affect the health and productivity of animals.

Because of the role that oxidative stress plays in the toxicity of many pesticides and other chemical compounds, including drugs (Altuntas et al. 2004, Kalender et al. 2004), the aim of this study was to determine the effect of single and combined intoxication with dimethoate and pyrantel embonate on the concentration of reduced glutathione (GSH) in the liver and the activity of selected glutathione-related enzymes, i.e. glutathione peroxidase (GPx) and glutathione reductase (GR) in erythrocytes in the rat.

Materials and Methods

Dimethoate ($C_5H_{12}NO_3PS_2$) obtained from Cheminova Inc. (Denmark) containing 99.1% of pure O,O-dimethyl S-N-methyl carbamoyl methyl phosphodithioate and pyrantel embonate obtained from POLPHARMA S.A. (Poland) containing 99.3% of pyrantel embonate were used in the experiment.

The studies were conducted on 144 male Wistar rats (from the certificated Laboratory Animal House, Brwinów, Poland) of initial body weight 170-180 g. The animals were kept under standard laboratory conditions (12h light/dark cycle, temperature 22 ± 1°C, humidity 70 ± 10%) and had free access to drinking water and a standard pellet diet. One week after acclimatization to laboratory conditions, the rats were randomly divided into three experimental (I-III) and one control (C) groups, 30 animals per group. The control group (C) received olive oil via a gastric tube (0.1 ml/100 g). Dimethoate (Group I) was administered to rats in olive oil solution at a dose of 1/10 LD_{50} (37.8 mg/kg b.w.) for 5 consecutive days and pyrantel embonate in aqueous suspension (Group II) at a dose of 1/5 LD_{50} (400 mg/kg b.w.) for 3 consecutive days. The animals of group III were given both of these compounds in the same manner as groups I and II, but pyrantel embonate was applied on day 3, 4, and 5 from the beginning of dimethoate intoxication. Dimethoate and pyrantel embonate were administered intragastrically via a gastric tube. All animals had free access to drinking water and a standard pellet diet.

The study was approved by the Local Ethics Committee for Animal Experiments at the University of Warmia and Mazury in Olsztyn.

Experimental material from 6 rats randomly selected from each group was obtained after 3, 6 and 12 hours and 2, 7 and 14 days following the last applied dose of the compounds under study. Under halothane anaesthesia, blood samples were collected by cardiac puncture (into heparinized tubes) and the animals were then sacrificed and their livers were quickly excised. The livers were immediately washed in ice-cold 0.9% NaCl, weighed and frozen at -85°C for further analysis.

The concentration of reduced glutatione (GSH) in the liver homogenates was measured according to the method of Ellman (1959), modified by Sedlak and Lindsay (1968). The determination of glutathione peroxidase (GPx) and glutathione reductase (GR) activity in erythrocytes was performed using a Ransel and GR 2368 diagnostic kit (Randox Lab. Ltd., UK).

The data were analysed statistically by a one-way analysis of variance (ANOVA) followed by the Newman-Keuls test. The probability of $p<0.05$ was considered significant.

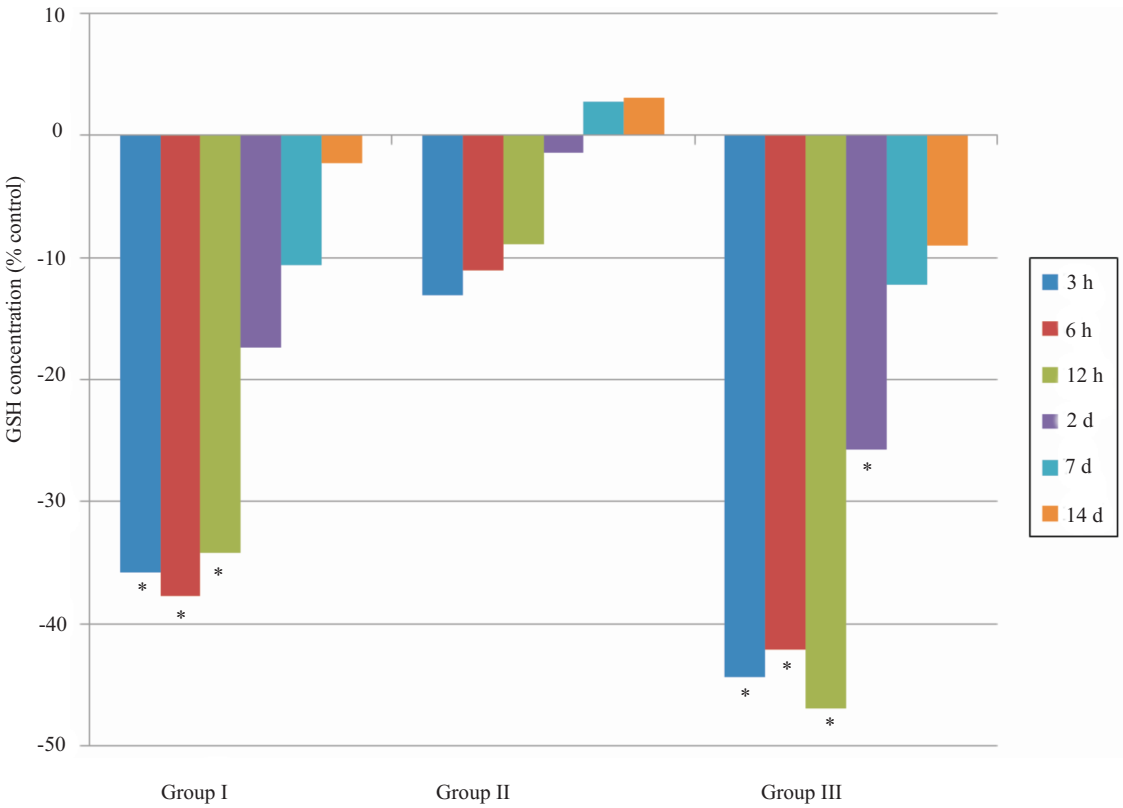

Fig. 1. Glutathione (GSH) concentration in hepatic tissues of rats exposed to dimethoate (Group I), pyrantel embonate (Group II), dimethoate and pyrantel embonate (Group III). Data expressed in % of the unexposed control.
* Significantly different from control group at $p<0.05$.

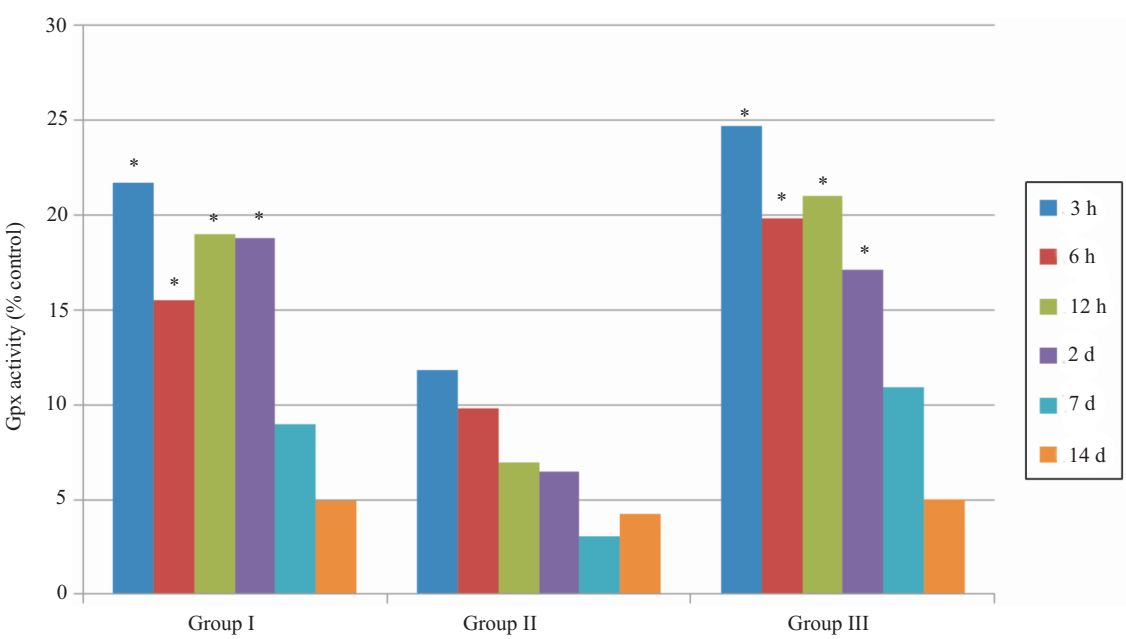

Fig. 2. Glutathione peroxidase (GPx) activity in erythrocytes of rats exposed to dimethoate (Group I), pyrantel embonate (Group II), dimethoate and pyrantel embonate (Group III). Data expressed in % of the unexposed control.
* Significantly different from control group at $p<0.05$.

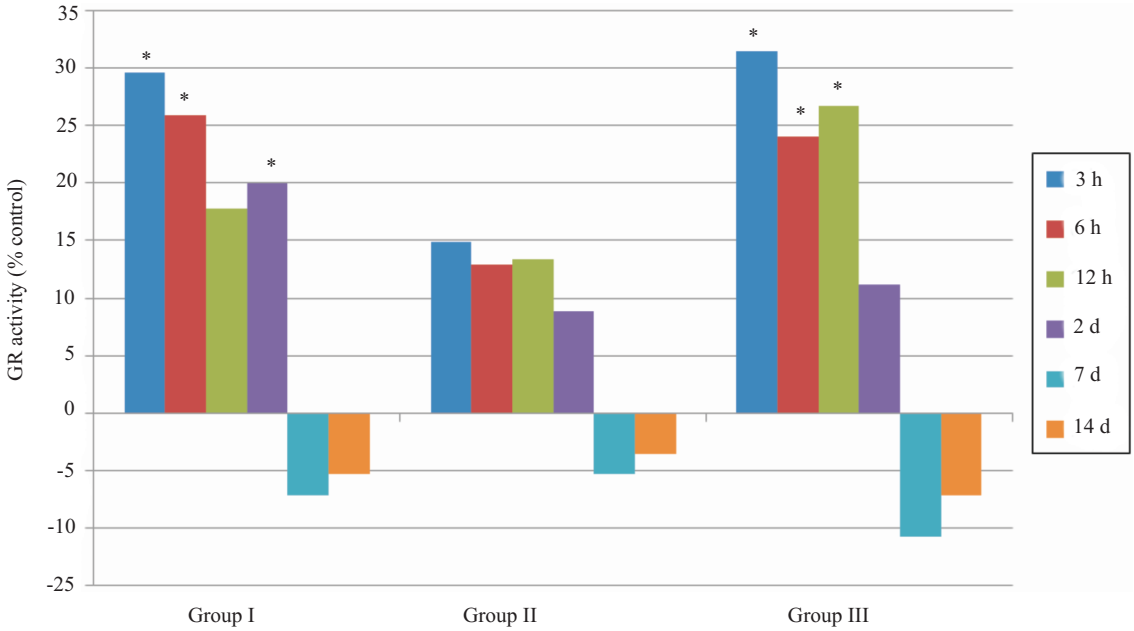

Fig. 3. Glutathione reductase (GR) in erythrocytes of rats exposed to dimethoate (Group I), pyrantel embonate (Group II), dimethoate and pyrantel embonate (Group III). Data expressed in % of the unexposed control.
* Significantly different from control group at $p<0.05$.

Results

The results of reduced glutathione concentrations in the liver homogenates and activities of glutathione peroxidase (GPx) and glutathione reductase (GR) in erythrocytes are shown in Figs. 1-3.

The concentration of GSH in the liver decreased in comparison with the control in all experimental groups throughout the experiment. The highest and statistical significant ($p\leq0.05$) decrease was detected following dimethoate intoxication (Group I) in the initial period of the experiment, i.e. within 12 hours, and ranged from 34.2 to 37.7%. Pyrantel embonate (Group II) did not significantly influence the concentration of GSH. The co-administration of dimethoate and pyrantel embonate (Group III) slightly reduced the GSH level in comparison with the dimethoate-only group. A statistically significant decrease of GSH content relative to the control was recorded until day 2 (Fig. 1).

GPx activity in the erythrocytes increased in comparison with the control in all experimental groups and time intervals. In the rats intoxicated with dimethoate (Group I), a significant ($p<0.05$) increase in GPx activity remained until day 2 with the highest activity recorded as early as after 3 hours (21.7%). In the animals exposed to pyrantel embonate (Group II), the activity of GPx was slightly elevated compared to the control, with the increase ranging from 3 to 11.9% in given time intervals. In group III, in which the rats were administered dimethoate and pyrantel embonate, the profile of changes in the activity of GPx was similar to that recorded in group II, yet with a higher intensity. The highest increase was detected after 3 hours and was 24.7% in comparison with the control (Fig. 2).

The increase in GR activity in the erythrocytes in the rats intoxicated with dimethoate (Group I) was recorded until day 2, with the increase being statistically significant compared to the control between 3 hours (29.6%) and 6 hours (25.9%). The administration of pyrantel embonate (Group II) resulted in a slight rise in GR activity. The combined intoxication with dimethoate and pyrantel embonate (Group III) induced an increase in GR activity up to 12 hours in comparison with the animals in group I which were administered dimethoate exclusively (Fig. 3).

Discussion

Free radicals and other reactive forms are produced in physiological metabolic processes. They also originate from external sources, for instance, following exposure to different xenobiotics. The result is an increase in ROS, impairment of the antioxidative system and insufficient capability to repair oxidative damage (mainly including changes in cellular macromolecules such as membrane lipids, proteins and DNA). The exposure to ROS and RNS leads to activation of compounds with antioxidative properties, including glutathione and related enzymes, i.e.

glutathione peroxidase (GPx) and glutathione reductase (GR) (Hayes and McLellan 1999).

The results of the studies indicate that organophosphate insecticides (OP), apart from their typical activity as AChE inhibitors, also demonstrate the ability to generate free radicals responsible for oxidative stress. The available data suggests that these compounds can modify several parameters of antioxidant defence both under *in vivo* and *in vitro* conditions (Ranjbar et al. 2005, Durak et al. 2009). The results of the present study show that 5-day intoxication of the rats with dimethoate resulted in a significant decrease of GSH concentration and a considerable increase in GPx and GR activity which persisted throughout the experiment. These changes were most evident in the initial stage of the experiment, i.e. until day 2. The system dependent on glutathione and related enzymes (GPx and GR) is the most important component of the cellular antioxidant defence. GSH is involved in numerous processes that are essential to the normal functioning of the cell, for instance, the synthesis of proteins and DNA. It is also thought to protect the cells against the harmful influence of toxic compounds by conjugation. This leads to the formation of less toxic products and thus reduces the extent of cellular damage (Sies 1999). It is particularly evident in the disturbances of redox balance caused by excessive consumption of GSH for protection against the toxic impact of different xenobiotics (Pastore et al. 2003). GSH, as the antioxidant, acts as a non-enzymatic scavenger of free radicals and as a co-substrate for enzymatic degradation of toxic substances catalyzed by GPx. This enzyme is found in different tissues, mainly in the liver, erythrocytes and plasma, and plays a significant role in the elimination of hydrogen peroxide. GPx detoxifies peroxides with GSH acting in the reduction reaction, producing glutathione disulphide (GSSG) as an end product (Flohe 1988). GSSG is harmful to the cell due to its capability of forming combined disulphides with proteins and oxidation of thiol groups of proteins resulting in their inactivation. In order to prevent the accumulation of GSSG in the cell, GPx remains closely linked to GR, i.e. the enzyme capable of regenerating the reduced form of GSH at the expense of NADPH oxidation. GR is also involved in the process of oxygen detoxification (Abou Ghalia and Fouad 2000).

Complicated relations between individual components of the antioxidative barrier and a limited number of publications concerning the influence of dimethoate on their concentration and activity, as well as its interactions with different xenobiotics, make interpretation of the results difficult. Studies by different authors indicate that both acute and subchronic intoxication with dimethoate induces oxidative damage by generating reactive oxygen species and alterations in the antioxidant system. Saafi et al. (2011) reported an increase in GPx activity in the liver following 2-month exposure of rats to dimethoate. Ben Amara et al. (2012) found an increase in GPx activity and a significant decrease in the concentration of GSH in the liver after 30-day intoxication with this insecticide. These results confirm the previous studies by Sharma et al. (2005a, b) which showed that oxidative stress caused by acute and subchronic intoxication with dimethoate contributes to the generation of LPO and changes the antioxidant status of different tissues in rats. Similarly to the current studies, dimethoate induced oxidative damage by producing ROS, which resulted in a change of biological concentration of GSH and activity of GPx and GR in rats. The decrease of GSH in the liver may be associated with direct binding of dimethoate or its metabolites, or with active scavenging of ROS. In the course of their neutralization, GSH is oxidized to GSSG which is rapidly transformed into a reduced form in the reaction catalyzed by GR. A reduced level of GSH was also caused by its use as a substrate for GPx which transforms H_2O_2 or other lipid peroxides into water or hydroxyl lipids. In our studies, the application of dimethoate to rats at a dose of 1/10 LD_{50} caused an increase in the activity of GPx and GR in erythrocytes. Red blood cells are very sensitive to oxidative injury (Bernabucci et al. 2002). The proteins in the erythrocyte membrane are susceptible to covalent damage caused by free radicals, for instance peroxides originating from autooxidation of haemoglobin. Thus, the reactions of haemoglobin with different compounds are a source of free radicals and lead to peroxidation of cellular membranes and haemolysis (Clemens et al. 1984). To defend against oxidative stress, erythrocytes are equipped with an effective, complete antioxidative system that contains, among others, SOD, CAT and GPx. Despite the efficacy of this system, the capability of RBC to repair oxidative damage is limited. The current studies showed an elevated GPx activity in the erythrocytes, which suggests an increased reduction of hydrogen peroxide to water due to the enhancement of free radical generation influenced by dimethoate. This increase may also result from its ability to reduce lipid peroxides to hydroxy acids and their elimination as well as inhibition of peroxidation processes. The increase in GR activity in the erythrocytes reported in the present study is also closely related to oxidative stress and may result from its activation in order to compensate for GSH losses. The elevated activity of GPx and GR in the erythrocytes may be regarded as a peripheral response of the organism to the increasing production of ROS. The results obtained in our studies are consistent with

the findings by other authors who, after the administration of various OP insecticides to animals, found similar changes in the analysed parameters (Lukaszewicz-Hussain 2008, El-Gendy et al. 2010, Mudaraddi and Kaliwal 2012). In the literature, there are also reports showing a different organism response to intoxication with different pesticides (including insecticides) than in our experiment (Karademir Catalgol et al. 2007, Ajiboye 2010). The differences in the findings of the studies may result from the fact that the cells exposed to toxic substances generate a specific antioxidative response which is dependent on the type of cell, exposure time, type and dose of pro-oxidants.

Anthelmintic drugs are widely used for treatment and eradication of mono- and polyparasitosis in human and veterinary medicine. Some of them act through the generation of ROS and RNS in parasites (Docampo 1990, Dayan 2003). Studies carried out in recent years have indicated that these compounds may also cause oxidative stress in a host (Pinlaor et al. 2008, Dewa et al. 2009). The majority of publications on pyrantel mainly focus on the efficacy of its therapeutic activity (Slocombe et al. 2007, Reinemeyer et al. 2010), and the data on its effect on the antioxidant status include only previous publications of authors (Spodniewska and Zasadowski 2006, Barski and Spodniewska 2012). In the present study, the exposure of rats to pyrantel embonate at a dose of 1/5 LD_{50} for three consecutive days caused only a slight decrease in GSH level and an increase in the activity of GPx and GR in comparison with the control group. Because of the scarcity of data on the effect of antiparasitic agents on the parameters of mammalian antioxidative system, it is difficult to compare the results with the findings reported by other authors. Similar results were found by Ince et al. (2010) who detected a decrease in the level of glutathione in the erythrocytes, liver and kidneys after 7-day treatment with levamisole. Karatas et al. (2010) reported an elevated activity of GPx in the erythrocytes following 30-day exposure to 3-(1H-pyrrol-2yl)-1H-indazole. However, Locatelli et al. (2004) showed different changes in GSH and GR in the hepatocytes after the administration of albendasole to rats. Spodniewska and Zasadowski (2008) administered pyrantel tartrate to rats twice at a dose of 85 mg/kg b.w. and observed an increase in GSH concentration in the liver. Based on the results of the present study, as well as studies by other authors, it is suspected that the changes in the antioxidative system related to glutathione after the administration of different antiparasitic agents show their pro-oxidative activity. The intensity of the changes reported in the current study (which was particularly evident at the beginning of the experiment) may be explained by the response of the organism to oxidative stress caused by the administration of pyrantel embonate, whereas a gradual decrease in the later periods was caused by the adaptation to the conditions created by the stress.

In recent years, there has been an increasing amount of data concerning the interaction of organophosphate insecticides with different compounds and their impact on the oxidative processes. However, the majority of studies discuss the protective effect of vitamins or microelements following the exposure to organophosphate insecticides (Verma et al. 2007, Demir et al. 2011) or the influence of mixtures of pesticides (El-Demerdash 2011, Ojha and Srivastava 2012). In our study in the group with combined intoxication (i.e. the animals administered dimethoate and pyrantel embonate), a significant decrease in the concentration of GSH in the liver and an increase in the activity of GPx and GR in the erythrocytes was noted compared to the animals intoxicated with these compounds individually, and the changes in the parameters were more pronounced. These results are consistent with the findings reported by Ojha and Srivastava (2012), who administered chlorpyrifos, methyl parathion and malathion and their combination to rats and found a decrease in GSH and an increase in GR in the liver, brain, kidneys and spleen. The intensity of the changes depended on the type of pesticide and the tissue examined. A significant depletion of GSH was observed by El-Demerdash (2011) after the administration of different concentrations of fenitrothion and lambda cyhalothrin in the brain of rats in a time-dependent manner. Goel et al. (2005) reported an increase in the activity of GPx and GR and a decrease in GSH in the liver following exposure to chlorpyrifos and Zn. Slightly different results were reported by Sivapiriya et al. (2006), who administered dimethoate and ethanol to mice and found a decrease in GSH in the liver in the group exposed to combined intoxication (in comparison with the animals intoxicated with dimethoate only), although the activity of GPx was reduced. The reduced GSH level in the liver reported in our experiment and in studies by other authors suggests that a decrease in its stores may result from both excessive peroxidation due to synergic activity of administered compounds (dimethoate and pyrantel) and from its activity in conjugating reactions that lead to detoxification of these compounds. According to Lukaszewicz-Hussain (2008), a decrease in GSH which is accompanied by an increase in the activity of GPx and GR in the brain in rats exposed to chlorfenvinphos suggests that GSH is also used in non-enzymatic reactions with ROS. The excessive expression of GPx and GR in the erythrocytes observed in our study may be interpreted as

a protective response of red blood cells against oxidation by reactive oxygen species (ROS) as a result of oxidative stress caused by the administration of the analysed compounds as well as the adaptive mechanism in order to reduce the accumulation of toxic compounds.

Enzymatic processses resulting in the metabolization of xenobiotics with the involvement of cytochrome P450 may also have contributed to an increase in reactive oxygen species following the administration of the analysed compounds (Dostalek et al. 2008). Limited data in the literature suggests the possibility of modifying the system of cytochrome P450 by both pesticides and drugs (Bapiro et al. 2001, Jokanovic 2001). Previous studies by Wiaderkiewicz et al. (2006) showed that dimethoate and pyrantel (administered separately and in combination) affected the expression of CYP1A2, CYP2B1/2 and CYP3A1 which, in turn, could have generated ROS and, consequently, the disturbances in the analysed antioxidative parameters.

The present study indicates that both dimethoate and pyrantel embonate at the administered doses showed a pro-oxidative activity, which resulted in disturbances in the antioxidative system in rats. These disturbances were manifested as a decrease in GSH level in the liver and an increase in the activity of GPx and GR in the erythrocytes. These changes were particularly pronounced in the groups exposed only to dimethoate and the combination of dimethoate with pyrantel. The profile of the changes in these two groups was similar, yet the intensity was higher after mixed intoxication.

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