Effect of bendiocarbamate on selected blood parameters of rabbits

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Introduction

Carbamates have toxic symptoms and physiological changes in different animals (Mullie et al., 1991). Haematology is a valuable tool for assessing the injuries caused by carbamate (Zaahkouk et al., 2000). Changes in the biochemical blood profile indicate alterations in metabolism and biochemical processes of the organism, resulting from the effects of various pollutants, and they make it possible to study the mechanisms of the effects of these pollutants (Luskova et al., 2002).

Carbamates inhibit the enzyme acetylcholinesterase (AChE) which is present in erythrocyte in rat (Tyaniwara, 1991). The reduction in the blood parameters is attributed to internal haemorrhage, possibly as a consequence of the toxic effect of carbamate on bone-marrow, spleen and liver (Reena et al., 1989).

Significant changes in total serum lipids, glucose, protein levels, AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase) in mammals were reported (Fayez and Kilgore, 1992; Chevalier et al., 1993). Zaahkouk et al. (2000) found significant changes in haematological and serum biochemical parameters in rats after carbamate addition.

Liver is the primary site involved in the metabolism of carbamates (Pineiro-Carrero and Pineiro, 2004). Cholesterol and triglyceride levels were elevated in liver of rats after carbofuran exposure (Gupta et al., 1994). Lipophilic nature of carbamates may render them with the ability to interact with serum and tissue lipids (Rai et al., 2009).

The aim of this work was to determine the effect of bendiocarb on selected haematological and biochemical parameters of rabbits.

Materials and methods

Experimental design and animal management of experimental intervention with bendiocarb addition per os for rabbits

The experiment was conducted on adult rabbits (n=42) of breed Hyla–27. Animals were 54 days old with average weight 1250 g. The experiment was carried out in an accredited experimental laboratory at University of Veterinary Medicine in Košice. Animals were kept in cages (5 per a cage), at standard conditions (temperature 16–18°C, 12 hours light period) and fed with granular feed mixture (KK-O10).

Drinking water was available for all animals *ad libitum.* Animals were divided into 4 groups (control C and experimental groups E1, E2 and E3 according to days of administration: 10 Days, 15 Days and 25 Days). Animals from experimental groups received bendiocarbamate (96% Bendiocarb, Bayer) *per os* in a dose 5 mg/kg of body weight per day and after day 13 in the same dose per 48 hours (Table 1).

Tab. 1. Administration of bendiocarb *per os* for rabbits; C – control group, E1, E2, E3 – experimental groups, bw – body weight

	C	E1	E2	E3
Amount of bendiocarb in mg/kg of bw per day	0	5	5	5
The duration of administration (days)	0	10	15	25
Total amount received by animals (mg)	0	100	150	250

Animals from all experimental trials were healthy and their condition was judged as good at the commencement of the experiment. Conditions of animals care, manipulations and use corresponded with the instruction of ethical commission.

Blood sampling and analyses

Blood samples from *vena auricularis* from rabbits were taken from all animals by macromethod. For biochemical analyses blood samples were centrifuged for 30 min at 3000×g and blood serum was obtained. The following metabolites, electrolytes and enzymes in serum (calcium, phosphorus, magnesium, sodium, potassium, chlorides, urea, total proteins, glucose, aspartate aminotransferase

AST (EC 2.6.1.1), alanine aminotransferase ALT (EC 2.6.1.2), gamma glutamyl transferase GGT (EC 2.3.2.2), alkaline phosphatase ALP (EC 3.1.3.1), glutamate dehydrogenase GLUD (1.4.1.3), cholesterol, triglycerides and total creatinine) were determined using Ecoline kits and automatic analyzer Microlab 300 (Merck®, Germany), spectrophotometer Genesys 10 (Thermo Fisher Scientific Inc., USA) and microprocessor-controlled analyzer EasyLite (Medica, Bedford, USA) according to manufacturer conditions.

In blood selected haematological parameters (WBC – total white blood cell count, LYM – lymphocytes count, MID – medium size cells count, GRA – granulocytes count, LYM% – lymphocyte percentage, MID% – medium size cells percentage, GRA% – granulocytes percentage, RBC – red blood cell count, HGB – haemoglobin, HCT– hematocrit, MCV – mean corpuscular volume, MCH – mean corpuscular haemoglobin, MCHC – mean corpuscular haemoglobin concentration, RDWc – red cell distribution width, PLT – platelet count, PCT – platelet percentage, MPV – mean platelet volume, PDWc – platelet distribution width) were measured using haematology analyzer Abacus junior VET (Diatron®, Austria).

Statistical analyses

To calculate basic statistic characteristics, determine significance of differences, and compare the results the analysis of variance, one-way ANOVA test and Duncan's test were performed at p level less than 0.05. The SAS and Sigma Plot 11.0 (Jandel, Corte Madera, USA) statistical software were used. Data presented were given as mean and standard deviation (SD).

Results

Serum mineral parameters and electrolytes content of rabbits

The results of serum mineral parameters and electrolytes parameters are shown in Table 2. Significant differences ($p<0.05$) in sodium (Na) content between E1 (the lowest amount of bendiocarb) and E3 group (the highest amount of bendiocarb) were found. In E3 group the level of Na was higher in comparison with the control group but without significant confirmation ($p>0.05$). In other experimental groups (E1 and E2) the values of Na were insignificantly lower ($p<0.05$) when compared with the control group. In the case of other minerals (calcium – Ca, phosphorus – P, magnesium – Mg, potassium – K, chlorides – Cl), values in the control group did not differ from those in experimental groups ($p>0.05$).

Tab. 2. Mineral parameters of control group and experimental groups of rabbits after bendiocarbamate addition; C – control group, E1 (100 mg), E2 (150 mg), E3 (250 mg) – experimental groups (total bendiocarb addition), values shown are the mean±SD, significant difference among the groups ($p<0.05$) presented as equal letters [a-a]

Mineral parameters				
	C	E1	E2	E3
Calcium (mmol/l)	4.57±0.61	4.23±0.83	3.95±0.31	4.00±0.32
Phosphorus (mmol/l)	2.44±0.68	1.92±0.23	1.77±0.15	1.78±0.11
Magnesium (mmol/l)	1.38±0.40	1.54±0.45	1.38±0.02	1.92±0.58
Sodium (mmol/l)	142.84±3.64	137.20±2.16[a]	142.73±1.69	147.40±4.35[a]
Potassium (mmol/l)	5.26±0.71	6.44±0.59	6.33±0.64	6.13±0.38
Chlorides (mmol/l)	107.89±2.65	108.97±1.87	107.10±1.06	110.20±3.46

Serum biochemical parameters of rabbit's blood

The results are shown in Table 3. In E1 group the highest level of serum glucose was observed versus other groups (control, E2 and E3). Significant difference ($p<0.05$) was noted between E1 and E3 group. Serum creatinine values were gradually rising with increasing dose of bendiocarb. The lowest value was found in the control group and significantly ($p<0.05$) highest in E3 group. Rabbits exposed to bendiocarb and those from the control group showed no significant differences ($p>0.05$) in the content of total proteins, cholesterol, triglycerides, urea and bilirubin.

Parameters of enzymatic profile of rabbit's blood

The results are shown in Table 4. Serum AST activity was found increased in the experimental groups when compared with the control group. The highest AST activity was observed in the experimental group with the highest dose of bendiocarb (E3 group) and this group significantly ($p<0.05$) differ from the control and E1 group.

Also in the case of GGT the highest activity was found in E3 group. Statistical evaluation confirmed significant difference ($p<0.05$) between E3 and the control group. Other differences among the groups remained insignificant ($p>0.05$).

The activity of GLUD decreased in all experimental groups in comparison with the control group. Significant difference ($p<0.05$) was found between the control and E3 group.

No significant differences ($p>0.05$) were observed among the groups in activity of ALT and ALP.

Tab. 3. Serum biochemical parameters of control group and experimental groups of rabbits after bendiocarbamate addition; C – control group, E1 (100 mg), E2 (150 mg), E3 (250 mg) – experimental groups (total bendiocarb addition), values shown are the mean±SD, significant difference among the groups ($p<0.05$) presented as equal letters [a-a]

Blood parameters				
	C	E1	E2	E3
Urea (mmol/l)	6.93±1.09	13.77±9.11	6.73±1.62	5.90±0.85
Total proteins (g/l)	67.09±6.68	68.20±6.11	57.10±6.93	64.42±7.86
Glucose (mmol/l)	8.67±0.49	10.10±0.73 [a]	7.00±1.51	6.00±1.83 [a]
Cholesterol (mmol/l)	1.58±1.30	2.08±1.36	1.07±0.17	2.00±0.04
Bilirubin (mmol/l)	17.97±3.76	12.73±3.91	12.50±5.26	33.50±32.04
Triglycerides (mmol/l)	1.68±1.19	1.47±0.97	1.06±0.28	0.70±0.14
Creatinine (mmol/l)	11.90±5.69 [a]	14.71±7.59	17.63±2.98	36.16±15.73 [a]

Tab. 4. Parameters of enzymatic profile of control group and experimental groups of rabbits after bendiocarbamate addition; C – control group, E1 (100 mg), E2 (150 mg), E3 (250 mg) – experimental groups (total bendiocarb addition), AST – aspartate aminotransferase, ALT – alanine aminotransferase, GGT – gamma glutamyl transferase, ALP – alkaline phosphatase, GLDH – glutamatdehydrogenase, values shown are the mean±SD, significant difference among the groups ($p<0.05$) presented as equal letters [a-a, b-b]

Parameter				
	C	E1	E2	E3
AST (μkat/l)	0.28±0.05 [a]	0.59±0.36 [b]	0.46±0.11	1.05±0.37 [ab]
ALT (μkat/l)	0.35±0.07	0.78±0.08	0.93±0.18	0.79±0.09
GGT (μkat/l)	0.07±0.02 [a]	0.05±0.04	0.10±0.02	0.16±0.03 [a]
ALP (μkat/l)	1.42±0.65	3.27±1.03	3.24±1.14	3.09±2.07
GLDH (μkat/l)	0.26±0.06 [a]	0.10±0.04 [a]	0.13±0.06	0.21±0.05

Haematological parameters of rabbits

The results of haematological parameters are presented in Table 5. WBC and RBC counts decreased insignificantly ($p>0.05$) below the control group as a consequence to the increase in dose of bendiocarb administered to the rabbits. Consequently, haemoglobin content exhibited a decrease gradually with increasing dose of bendiocarb. Significant difference ($p<0.05$) was found between the control group and group with the highest dose of bendiocarb (E3 group). Bendiocarb caused decrease of MCH and MCHC as the statistically lowest value

($p<0.05$) was found in the control group in comparison with the experimental groups (E1, E2 and E3). PLT count decreased gradually from the highest value in the control group till the lowest value in E3 group what was also confirmed statistically ($p<0.05$).

The values of other haematological parameters (LYM, MID, GRA, LYM%, MID%, GRA%, HCT, MCV, RDWc, PLT, PCT and MPV) were not influenced after bendiocarb consumption by rabbits ($p>0.05$).

Tab. 5. Haematological parameters of control group and experimental groups of rabbits after bendiocarbamate addition; C – control group, E1 (100 mg), E2 (150 mg), E3 (250 mg) – experimental groups (total bendiocarb addition); WBC – total white blood cells count (10^9/l), LYM – lymphocytes count (10^9/l), MID – medium size cells count, GRA – granulocytes count (10^9/l), LYM% – lymphocyte percentage, MID% – medium size cells percentage, GRA% – granulocytes percentage, RBC – red blood cells count (10^{12}/l), HGB – haemoglobin (g/l), HCT – haematocrit (%), MCV – mean corpuscular volume (fl), MCH – mean corpuscular haemoglobin (pg), MCHC – mean corpuscular haemoglobin concentration (g/l), RDWc – red cell distribution width (%), PLT – platelet count (10^9/l), PCT – platelet percentage, MPV – mean platelet volume (fl), PDWc – platelet distribution width (%), values shown are the mean±SD, significant difference among the groups ($p<0.05$) presented as equal letters [a-a, b-b, c-c, d-d]

Haematological parameters	Group of animals			
	C	E1	E2	E3
WBC	12.73±2.22	5.55±5.86	7.26±1.55	6.18±6.25
LYM	9.84±3.29	2.62±1.67	3.66±1.99	3.57±4.38
MID	0.38±0.07	0.19±0.14	0.29±0.21	0.36±0.28
GRA	2.52±1.50	2.63±4.15	3.31±1.29	2.24±1.73
LYM%	75.83±14.19	59.92±22.66	48.93±23.52	46.17±17.43
MID%	3.06±0.74	4.17±0.97	3.97±2.57	6.93±2.17
GRA%	21.20±13.78	35.95±23.34	47.07±21.22	46.90±15.71
RBC	5.99±0.41	5.89±0.80	5.05±0.62	4.81±1.43
HGB	129.14±9.65 [a]	110.00±14.05	88.00±12.00	82.00±34.83 [a]
HCT	38.99±2.20	37.02±4.55	32.49±4.11	30.40±10.61
MCV	65.14±1.95	63.00±3.16	64.33±1.15	62.67±3.06
MCH	21.60±0.67 [abc]	18.73±0.53 [a]	17.43±0.32 [b]	16.60±2.07 [c]
MCHC	331.43±7.28 [abc]	297.50±7.94 [ad]	271.67±3.21 [b]	264.67±22.03 [cd]
RDWC	14.86±0.47	15.75±0.57	15.73±1.19	15.73±0.51
PLT	401.29±110.41 [a]	157.00±113.94 [a]	194.00±29.37 [a]	165.00±26.61 [a]
PCT	0.27±0.08	0.13±0.09	0.61±0.20	0.11±0.19
MPV	6.86±0.69	8.03±1.26	7.80±0.44	6.63±0.32
PDWC	31.13±1.66	33.52±2.56	33.43±1.04	29.33±2.51

Discussion

The bendiocarb can affect some biochemical and immunological parameters of mammals (Bustnes et al., 2004; Eraslan et al., 2007). Within two days after feeding doses of up to10 mg/kg of bendiocarb to rats, 89 to 90% of the dose was eliminated in the urine, 2 to 6% was exhaled, and another 2 to 6% was eliminated in the faeces (Danko et al., 2005).

Serum parameters of energetic and mineral profile and activity of serum enzymes

In this experiment the highest value of Na was found in the group with the highest addition of bendiocarb (E3). Significantly lower value ($p<0.05$) was measured in E1 group (the lowest amount of bendiocarb) versus E3 group. Control group did not differ significantly ($p>0.05$) from other groups. Na content remained at similar level in control group, E1 and E2 group. Any other differences ($p>0.05$) were found in the case of other serum minerals (Ca, P, Mg, K, Cl). In experiment with guinea pigs the N-aryl carbamates were shown to be Ca ion antagonists (Ivanov, 1995). A progressive dose-dependent decline in serum Ca level and progressive hypocalcemia was observed in the rats treated with sublethal administration of pesticide Mipcin (Rangoonwala et al., 2007), of pesticide diazinon (Rangoonwala et al., 2005) or of insecticide heptachlor (Rangoonwala et al., 2004). Hypocalcemic response of the pesticide was dose- as well as time-dependent. In our experiment the decrease of Ca was noted after bendiocarb treatment, however, without significant differences ($p>0.05$). In dogs decreased level of blood Ca was observed after bendiocarb treatment (Baron, 1991). To our knowledge there is lack of data in literature concerning the bendiocarb and its effect on serum mineral parameters of rabbits.

In this study the highest level of serum glucose was observed in E1 group versus other groups (control, E2 and E3). Significant difference was noted between group with the lowest amount of bendiocarb (E1) and group with the highest amount of bendiocarb (E3). Total intake of 100 mg caused increase of glucose level while the amount of 250 mg caused its decrease. Rodrigues et al. (1986) found increase in blood glucose level in rats treated with a single dose of 650 $mg.kg^{-1}$ of pesticide. On the contrary, Sadeghi-Hashjin et al. (2008) found decrease of glucose level in mice treated with organophosphate pesticides. The absorption of glucose was considerably reduced (35%) in other experiment with pesticide fed animals (Chowdhury et al., 1980). Administration of pesticide malathion at doses of 100, 200 and 400 ppm increased plasma glucose concentrations by 25, 17 and 14% of control, respectively (Abdollahi et al., 2004). The changes in carbohydrate metabolism induced by carbamate can be correlated with its effect on the activities of hepatic enzymes (Hassan et al., 1988).

Carbendazim (methyl–2-benzimidazole carbamate) caused increase in level of cholesterol in rats (Muthuviveganandavel et al., 2008). We found insignificant ($p>0.05$) increase of cholesterol level in E1 (the lowest dose of bendiocarb) and E3 group (the highest dose of bendiocarb). Similar results were obtained in the case of dogs (Baron, 1991). Significant increase of cholesterol level after carbamates administration in rats was observed (Zaahkouk et al., 2000; Rai et al., 2009). An increase in cholesterol level is a sign of liver damage (Igbedioh and Akinyele, 1992), blockage of liver bile ducts causing reduction or cessation of its secretion to the duodenum (Rai et al., 2009), or the consequence of stimulation of catecholamines which stimulate lipolysis, and due to the increase of fatty acid production (Dekundy et al., 2007).

In this study insignificant decrease of serum triglycerides in rabbits after bendiocarb treatment was observed. Our findings are in agreement with those found by Sawas (1998). On the contrary, an increase in plasma triglycerides, glucose and of cholesterol levels of male rabbits has been recorded after dithiocarbamate treatment for a period of 5 weeks (Mallem et al., 2006). Serum lipid concentration, particularly that of cholesterol and triglycerides, increased after 90 days of zinc ethylene-bis-dithiocarbamate (zineb) administration (Nebbia et al., 1995). Increased level of triglycerides in rats after carbamate administration for period of 1 week was found (Rai et al., 2009).

In this work the increase of AST and GGT activity was found in the experimental groups versus the control group. The activity of GLUD significantly decreased in all experimental groups against the control group. A highly significant increase in the activity of serum AST and ALT in carbamate-treated rats was reported (Zaahkouk et al., 2000). Authors explained that this increase may be due to the hepatic potency of carbamate resulting in destructive changes in the hepatic cells. The carbamate was administrated orally and, hence, it reached the liver first throughout the hepatic portal vein. Muthuviveganandavel et al. (2008) found significant changes in the serum AST and ALT activities of rats treated with carbendazim (methyl-2-benzimidazole carbamate). Serum ALT and serum AST showed irregular insignificant changes (mild decrease or increase) in rabbits after carbamate derivate treatment (Sawas, 1998).

Elevation in transaminases activity in blood has been considered as indicator of tissue damage, without any specific damage of one organ. Damaged cells release transaminases into blood stream, and factors such as alterations in permeability of cell membrane, increased synthesis or decreased enzyme degradation may be involved (Zaahkouk et al., 2000).

In this study serum creatinine values were gradually rising with increasing dose of bendiocarb. A significant rise in creatinine level was observed from the 4^{th} week of exposure until the end of the experiment. Similar results were observed in case of rats exposed to carbendazim (Muthuviveganandavel et al., 2008) what

suggests impairment of the glomerular function and tubular damage in the kidneys. These changes were confirmed by histopathological studies in the tubules (Mohssen, 2001).

No significant differences ($p>0.05$) were observed among the groups in levels of urea, total proteins, bilirubin, triglycerides, ALT and ALP. It was concluded that thyroid and liver are the main targets for zinc ethylene-bis-dithiocarbamate (zineb) toxicity in the rabbits (Nebbia et al., 1995). Alteration in activity of several liver enzymes after bendiocarb treatment may be due to liver failure and damage caused by insecticide.

Haematological parameters

WBC and RBC counts decreased insignificantly ($p>0.05$) below the control group values as a consequence of the increase in dose of bendiocarb administered to the rabbits. Consequently, haemoglobin content was decreasing with increasing dose of bendiocarb. Significant difference ($p<0.05$) was found between the control group and group with the highest dose of bendiocarb (E3 group). The decrease in the number of RBC may indicate a disruption of erythropoiesis or an increase in the destruction of red blood cells (Thibodeau and Patton, 1993). Zaahkouk et al. (2000) observed significant decrease of RBC, WBC, haemoglobin and hematocrit in rat blood after carbamate administration. Acute intoxication due to carbendazim generally decreased RBC and haemoglobin content, as also reduced reticulocyte and thrombocyte numbers in the blood of rats (Hayes, 1994). Red blood cells count significantly decreased in rats treated with 5 and 25 mM carbendazim (Muthuviveganandavel et al., 2008). A marked decline in hemoglobin concentration, hematocrit, and erythrocyte and leucocyte counts occurred at the highest zinc ethylene-bis-dithiocarbamate (zineb) dosage (0.6%) after 90 days of treatment was observed in rabbits (Nebbia et al., 1995). One of the molecular mechanisms of the toxicity of some pesticides seems to be lipid peroxidation; as a consequence these compounds can disturb the biochemical and physiological functions of the RBC (Akhgari et al., 2003). The susceptibility of RBC to oxidative damage is due to the presence of polyunsaturated fatty acid, haem iron and oxygen, which may produce oxidative changes in RBC (Kale et al., 1999).

White blood cells and lymphocyte counts decreased significantly at 10 mM dose of carbendazim what could suggest that this pesticide may posses an immune-suppressive potential in rats (Muthuviveganandavel et al., 2008). In our experiment bendiocarb caused decrease of MCH and MCHC as the statistically highest value ($p<0.05$) was found in the control group in comparison with the experimental groups (E1, E2 and E3). PLT count decreased gradually from the highest value in the control group till the lowest value in E3 group

what was confirmed also statistically ($p<0.05$). The values of other haematological parameters (LYM, MID, GRA, LYM%, MID%, GRA%, HCT, MCV, RDWc, PLT, PCT and MPV) were not under the influence after bendiocarb consumed by rabbits ($p>0.05$). Haematology is a valuable tool for assessing the injuries that are caused by carbamate. The reduction in the blood parameters may be attributed to internal haemorrhage, possibly as a consequence of the toxic effect of carbamate on bone-marrow, spleen and liver. Erythropenia in rats treated with carbamate may arise due to depression of erythropoiesis. Leucopenia in rats following carbamate may be due to depression of leukopoiesis, alteration of cell membrane or disintegration of white blood cells, because white blood cells combat against any carbamate introduced into the blood stream (Zaahkouk et al., 2000; Reena et al., 1989). The discrepancies in literature about carbamates effect on animals may be due to another chemical structure of carbamate and animal species. Chickens and human serum hydrolysed carbaryl at comparable rates, and rabbits have exhibited an activity about double as high (Sogorb and Vilanova, 2002).

In relation to blood biochemistry and haematological parameters there is a lack of data and information in literature about the effect of bendiocarbamate.

A further concern is that humans are very likely to be exposed to a number of pesticides and other neurotoxic compounds simultaneously. Because it is possible that some of these may have synergistic or additive effects, exposure to even very low doses during development may cause neurotoxic damage (Bjorling-Poulsen et al., 2008).

Conclusions

Bendiocarb addition caused imbalance in internal milieu of rabbits. Main changes were observed in serum creatinine content and activity of serum enzymes. Significant increase of creatinine content in E3 group (the longest administration of bendiocarb), increase of AST (E1 and E3 against control group) and GGT (E3 against control group) and decrease of GLUD (E1 against control group) inform about possible failure of liver and/or kidney caused by bendiocarb. Decrease of HGT (significantly in E3 group against control group), MCHC (in all experimental groups), PLT (in all experimental groups) can signify defection in haemoplastic system.

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