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Research Article

Effect of Oral Sub-Lethal Dose of Abamectin in the Rat: Serum ALT, AST, Urea, Creatinine and Histopathological Changes

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Abstract

In this study, the effect of ABA on serum ALT, AST, urea and creatinine were studied as well as histological changes in the liver and kidneys. Group 1 animals were given with abamectin at a dose of 30mg/kg B. Wt. (1/10 LD50), double oral doses \week for 15 days and one month. Group 2 animals were given with abamectin at a dose of 30mg/kg B. Wt. (1/10 LD50), double oral doses \week for 15 days and one month.

The results of the current study showed that in the administration of abamectin in 1/10 LD50, for 15 days and one-month (group 1 and 2) significantly increased plasma levels of ALT, AST, urea and creatinine in male rats treated, compared with control group. Changes in ALT and AST levels vary depending on exposure time, where an increase in enzyme activity was observed in animals of group 2 compared with that group 1.

The results also showed that the abamectin tended to cause a significant change in the liver and kidney rat. The permeability of the leukocyte pockets, congested blood vessels in the portal tract, destruction of some liver cells and vacuolation of liver cells. Significant necrosis of tubular cells, glomerular atrophy, and interstitial infiltration areas of round cells were found.

Keywords: Abamectin; Oral sub-lethal dose; ALT; AST; Urea; Creatinine; Histopathological changes

Introduction

Abamectin (ABA) is a powerful endo - and parasite agent with a wide range of activity in many animal species. It is a fermentation product produced by actinomycete *Streptomycetesavermitilis* [1]. Abamectin (ABA) is composed of about 80% of avermectin B1a and ≤ 20% avermectin B1b. ABA's mechanism of action is concerned with the gamma-aminobutyric acid (GABA) system and Cl channels. GABA receptors are performed for regulating the neural basal tone of the brain [2] and are in all nerve cells in the central nervous system (NES). Symptoms of toxicity of Abamectin in experimental animals are; pupil spasms, vomiting, convulsions and/or tremors and coma.

Abamectin, is an analog of Ivermectin, is made up of a mixture of avermectins. It is a macrocyclic lactone disaccharide, a member of the avermectins group which is extensively used as an anti-parasitic drug in agricultural and domestic animals. Abamectin has been extensively used to control insects for a wide range of agricultural products such as fruits, vegetables and ornamental crops [3]. They are also developed in commercial baits to control ants and cockroaches [4]. Abamectin acts as an insecticide by interfering with the nervous system of insects causing paralysis. It activates its function by stimulating the fused glutamate chloride channel in the invertebrate nervous system [5].

The Avermectin deactivate electrical activity in nerve and muscle preparations by increasing membrane behavior of conductance to chloride ions [6]. The action of abamectin involves G-aminobutyric receptors (GABA) in the periph¬eral nervous system. It appears that the channel glutamate gate (GWC), together with G-aminobutyric acid (GABA) spin-channel chloride (GAB) and the his¬tamine-gated chloride channel (HisCl), is the target site of avermectin and ivermectin in insects and nematodes [7]. The aim of this research was to study the effect of ABA on serum ALT, AST, urea, and creatinine as well as histological changes in the liver and kidneys in rats.

Materials and Methods

Adult male albino rats (Rattus norvegicus), with body weights of 125-130g. The animals were housed in small groups (6 each),

inside propylene cages. The temperature in the ex¬perimental animal room was maintained at 24.5±1.5 °C with 12h dark: light cycle, and 72% humidity. The animals were provided with commercial pelleted rodent food and drinking water ad libitum. The animals could acclimatize to the laboratory conditions for one week prior to the start of the study. The experimental animals were divided into two groups of six adult males each. Animals of group-1 were administered with abamectin at a dose of 30mg/kg B. Wt. (1/10 LD50), two times a week, for a period of 15 days. Animals of group-2 were administered with abamectin at a dose of 30mg/kg B. Wt. (1/10, LD50), two times a week, for one month.

Animals

Adult male albino rats (Rattus norvegicus) of body weights of 125-130g, were used for the study. The animals were housed in groups (6 each), inside the stander cages. The temperature in the laboratory chamber was maintained at 24.5±1.5 °C with 12 hours dark: light cycle, and 75% humidity. The animals were supplied with commercial rodent food and drinking water ad libitum. Animals could adapt to laboratory conditions for one week before the start of the study. A gastric tube was used to administer the abamectin (5ml/kg B. Wt.) suspended in a car corn oil. Control groups were used to parallel study, only received oil corn twice a week for 15 and for one-month.

Blood Samples

Blood samples collected in a sterile tube then into a centrifuge tube. The samples allowed to coagulate at room temperature, then the serum was separated by centrifugation at 3000rpm for 20 minutes.

Methods

Determination of serum creatinine

The assay is based on creatinine reaction with sodium picrate [8] forming a red compound. The density of the colour formed was proportional to the creatinine concentration in the sample [9].

Determination of serum urea

Chromatography was used to detect serum urea with the Urea Assay Kit. The concentration of urea is determined by a combined enzyme assay, resulting in a chromatic (570nm) product, proportional to the present urea. The linear range for detecting this assay is between 1.0-5.0nmol.

Determination of Aspartate amino transferase (AST) and Alanine amino transferase (ALT) as liver marker

AST and ALT catalyse the amino group of glutamic acid to oxalacetic acid and pyruvic acid in reversible reaction. There is a substance known 2,4 dinitro-phenyl hydrazine reacts with pyruvate and oxaloacetate to form the corresponding 2,4-dinitrophenylhydrazine derivative of pyruvate 2,4-dinitrophenylhydrazine derivative of pyruvate in case the product is pyruvate and 2,4-dinitrophenylhydrazine derivative of oxaloacetate in case the product is oxaloacetate which can be measured spectrophotometrically at 546nm.

Histological Examination

The kidney and liver samples were excised, flushed with saline and then fixed in 10% buffered formalin PH 7.0 phosphate puffer. In brief, the fixed specimens were dehydrated, cleared in xylene and embedded in paraffin wax. Blocks were made, and 2-4µm-thick sections were cut using a sledge microtome. The tissue sections were deparaffinized, rehydrated and stained with haematoxylin and eosin (H&E). The stained slides were examined using bright field light microscopy to determine the histoarchitecture and the changes in kidney and liver.

Statistical Analysis

The analysis was carried out in triplicates for all determinations and results of the triplicates were expressed as mean±SE. The SPSS program (version 22 SPSS Inc., Chicago, IL, USA) [10] was used for the analysis of variance followed by the Minitab 17 for multiple comparisons of the means, $P<0.05$ between mean values were considered statistically significant.

Result

Table 1: Effects of abamectin on ALT, AST, urea and creatinine parameters in the blood plasma of male rats after repeated double oral doses \week for 15 days and one monthof abamectin.

Parameter	15-Days Repeated Dose	One- Month Repeated Dose	C1	Control C2
ALT [IU\L]	36.26±2.6^{b}	47.26±3.23^{a}	27.26± 2.19^{c}	28.28± 2.55^{c}
AST [IU\L]	62.44‡4.32^{b}	64.24‡3.42^{a}	53.54‡2.53^{c}	56.34‡3.2
Urea [mg\dL]	38.66±22^{c}	35.76±44^{c}	37.54±38^{c}	39.56±24^{c}
Creatinine [mg\dL]	0.029±007^{b}	0.032±005^{a}	0.025±008^{c}	0.026±004^{c}

Values are means ±SEM. Means followed by the same letter(s) within each horizontal row are not significantly different at $p < 0.05$; ALT- alanine aminotransferase; AST- aspartate aminotransferase.

*Histopathological findings were normal except minimal congestion in two individuals of the control group (Table 1,2) ((Figure 1a & 1b).

Liver Histopathology

Light microscopy of the findings was revealed leucocytic sinusoidal permeation, congested blood vessels in the portal tract, degeneration of some hepatocytes and vacuolation of hepatocytes (Figure 2a).

Table 2: Histopathologic findings in liver and kidney.

ABM	15-days	One month	Control*
Liver			
Hydropicdegeneration &disorganization	03/12	02/12	
Hemorrhages	04/12	04/12	
Congestion	02/12	11/12	
Sinusoidaldilatation	04/12	04/12	
Hepatocytesvacuolation	3/12	04/12	
Kidney			
Tubular epithelial vacuolization	04/12	03/12	
Interstitial mononuclear cell infiltration	04/12	04/12	
Focal necrosis and hemorrhage	03/12	02/12	
Atrophy of the glomeruli	03/12	02/12	

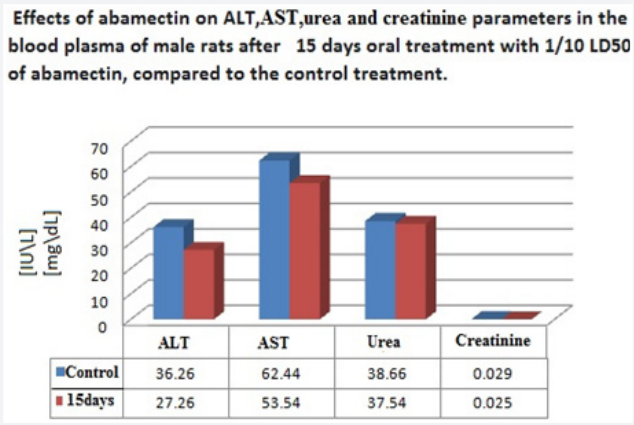

Figure 1a: Effects of abamectin on ALT, AST, urea and creatinine parameters in the blood plasma of male rats after repeated double oral doses \week for 15 days of abamectin.

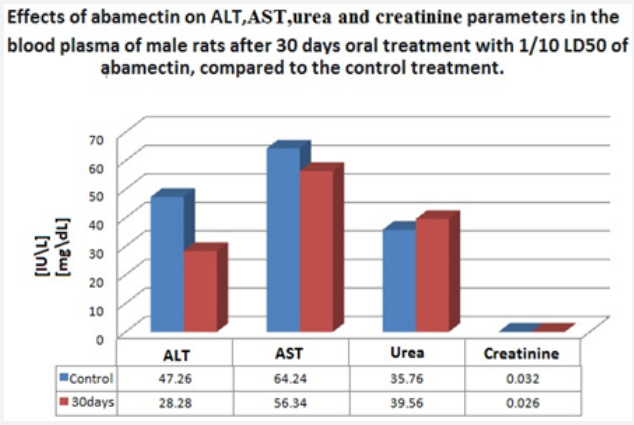

Figure 1b: Effects of abamectin on ALT, AST, urea and creatinine parameters in the blood plasma of male rats after repeated double oral doses \week for one-month. of abamectin.

Kidney Histopathology

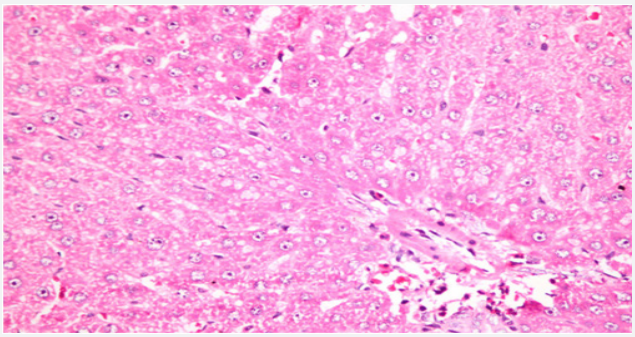

Figure 2a: Liver showing vacuolated hepatocytes (arrows) (H&E X 400).

Sections of the control rats' kidneys demonstrated normal renal histo-architecture of the kidney glomerular, and surrounding tubules (Figure 2b). Even the kidneys showed marked necrobiotic changes in abamectin-treated animals as compared to the normal histological examination of re¬nal tissue in the control rats. A marked necrosis of tubular cells, atrophy of the glomeruli, and areas of interstitial infiltration of round cells were found (Figure 2c & 2d).

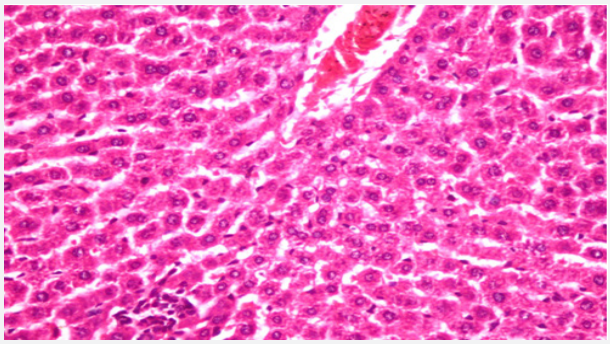

Figure 2b: Liver showing congested central vein (arrow head) and minute area of mononuclear cells infiltrations (arrow) (H&E X 400).

Discussion

Each drug was associated with liver toxicity almost because of the central role of the liver in the metabolism of the drug. Hepatic metabolism is, first and foremost, a mechanism to convert drugs and other compounds into products that are more easily excreted and usually have less drug activity than the carrier [11,12]. Metabolism may be higher activity and/or toxicity than the original drug.

In toxicological studies, a variety of biochemical parameters are measured to assess a wide range of physiological functions and metabolism that affect target organ identification and tissue injury assessment [13]. The combination of some common biochemical parameters provides better information than the recognition pattern, for example. enzymes such as ALT and AST, certain constituents (urea and creatinine) for glomerular function (Evans 1996) [14].

The results of the current study showed that in oral administration of abamectin, in 1/10 LD50, for 15 days and one-month (group 1 and 2) significantly increased (P< 0, 05) plasma levels of ALT, AST, urea and creatinine in male rats treated once a week, compared with control group.

Changes in ALT and AST levels varied depending on the time of exposure. An increase in enzyme activity was observed in group 2 compared to group 1. These results were consistent with the results obtained by [15]. ALT and AST levels activity was high as it is a dose-dependent pattern.

The activity of serum enzymes such as AST and ALT, representing the functional state of the liver [16]. Since some hepatic changes are irreversibly satisfactory [17], a higher AST may make the liver more susceptible to other pathological diseases [18,19]. Aspartate aminotransferase (AST) is an important indicator of liver damage in clinical studies. During liver injury, AST is secreted in the blood [20]. In deadly or damaged cells, these enzymes fall into the bloodstream [21].

The rise in liver enzyme activity may be due to liver weakness with a consequent reduction in the enzyme's biosynthesis and bio-change membrane permeability allowing enzyme leaks in the blood where the liver is vulnerable to direct exposure to toxic products. The liver plays a role in the detoxification of metabolic products and toxicants. In our study, increased AST and ALT levels could be due to liver toxicity that causing permeable changes and leakage of lysosomal enzymes promoting the release of enzymes [22,23]. Elevated ALT levels in this study suggest that hepatocellular tissue may be damaged by abamectin. Damage can be observed in pathogenic lesions in the liver of rats treated with abamectin. Abamectin was able to elevate levels of serum aspartate aminotransferase (AST) [24].

Effect on Kidney Function

Current results indicated that the oral administration of 1/10 LD50 ABM significantly (P< 0,05) increased the level of creatinine compared with control groups. Similar results were reported by [25,26]. Creatinine level is a useful indicator in the early deduction of renal toxicity induced by external compounds and agents. The current results have been explained that oral input of abamectin resulted in a marked increase in creatinine compared to controls. High serum creatinine concentration can be attributed to lower glomerular filtration in the kidneys and reflects a defect in kidney tubes.

Conclusion

Administration of abamectin in 1/10 LD50, for 15 days and one-month significantly increased plasma levels of ALT, AST, and creatinine in male rats. Changes in ALT and AST levels vary depending on exposure time. The results also showed that the abamectin tended to cause significant change to the liver and kidney of rats. The permeability of the leukocyte pockets, congested blood vessels in the portal tract, destruction of some liver cells and vacuolation of liver cells S and significant necrosis of tubular cells, glomerular atrophy, and interstitial infiltration areas of round cells.

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