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Research Article

SUBLETHAL ETHION-INDUCED CHANGES IN THE CARDIAC BIOCHEMISTRY OF ALBINO RATS

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ABSTRACT

Ethion [(O, O, O′, O′-tetraethyl S, S′-methylene bis (phosphorodithioate))], an organophosphorus (OP) compound, has been widely used as an insecticide, acaricide, and ovicide for over seven decades in agricultural and veterinary practices. The present study aimed to assess the sublethal effects of ethion on protein metabolism in the cardiac tissue of adult male Wistar Albino rats. Rats were orally administered ethion at a sublethal dose (1/5th of the LD_{50}, i.e., 42 mg/kg body weight) over a 30-day period with a 48-hour interval between doses. The animals were randomly assigned to four groups: Group I served as the control; Group II received ethion treatment for 10 days; Group III for 20 days; and Group IV for 30 days. At the end of the respective exposure periods, animals were sacrificed, and heart tissues were collected for biochemical and histopathological analyses. The results demonstrated a reduction in total protein levels in the ethion-treated groups compared to controls. Other parameters associated with protein metabolism showed a progressive increase, with the most significant alterations observed in the 30-day exposure group. Histopathological examination of the cardiac tissues revealed dose-dependent damage, including slight infiltration (SI), blood vessel congestion (BVC), degeneration of muscle fibres (DMF), and severe necrosis of cardiac muscle fibers (SNCMF), particularly in the group exposed for 30 days. These findings indicate that ethion disrupts protein metabolism in cardiac tissues, leading to physiological impairments and structural damage in the hearts of Albino rats. The study highlights the potential cardiotoxic effects of prolonged sublethal ethion exposure.

Keywords: Albino rats, Ethion, Heart, Protein Metabolism, Biochemical Changes, Light microscopy, Histopathology.

INTRODUCTION

Organophosphates (OPs) are a group of synthetic organic chemicals that have played a significant role as insecticides for several decades, currently dominating the global pesticide market. These compounds are extensively utilized in agriculture to safeguard crops and control pests (Heudorf *et al*., 2006). Out of the thousands of OP compounds tested, more than a hundred have been commercialized for such purposes (Mogda *et al*., 2009). However, the widespread and often careless application of OP pesticides has led to harmful exposure in humans and various non-target organisms. According to the World Health Organization (WHO, 1990), pesticide poisoning causes over 200,000 deaths annually, with a majority occurring in Asia and approximately half linked to OP compounds (Eddleston, 2000). Exposure to these chemicals can severely damage critical organs, including the liver, kidneys, heart, nervous system, and reproductive organs (Ferah Sayim, 2007). Several cases of mass poisoning from OP pesticides have been documented in developing nations such as Pakistan and India. One of the earliest recorded incidents in India occurred in 1958 when parathion-contaminated wheat caused the deaths of over 100 individuals (Karunakaran, 1958; Baker *et al*., 1978; Chaudhary *et al*., 1998).

Ethion, chemically known as [(O, O, O′, O′-tetraethyl S, S′-methylene bis (phosphorodithioate)], is an organophosphate (OP) compound that was first introduced in 1956 for agricultural and veterinary applications. It serves as an insecticide, acaricide, and ovicide. Classified as a moderately hazardous pesticide (Class II), Ethion is widely used in India, with an estimated annual consumption of 3,000 to 4,000 metric tons. This compound

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is a small, lipid-soluble molecule with a molecular weight of 384, and it can enter the body through passive diffusion via the skin, lungs, or digestive system. Ethion is primarily applied to citrus crops for pest management, but it is also used on cotton, nut and fruit trees, and various vegetables. Despite its effectiveness, Ethion is recognized as a significant environmental pollutant in numerous regions worldwide, raising serious environmental and health concerns. It is available in multiple formulations, including oil-based solutions and chemical mixtures, which leads to a wide range of acute toxicity levels.

Ethion poisoning has been documented among agricultural workers involved in harvesting grapes and peaches. In humans, exposure to Ethion has been associated with diaphragmatic breathing characterized by shallow respiratory movements and intercostal muscle retraction (Comstock *et al*., 1967). Additional clinical manifestations include respiratory arrest, tachycardia, weight loss, diarrhea, vomiting, decreased food intake, and inhibition of acetylcholinesterase activity (Lewis *et al*., 2016), along with a spectrum of histopathological changes ranging from mild to severe in vital organs. The heart is notably one of the critical organs adversely affected by organophosphate compounds. Reports of accidental Ethion ingestion in humans have indicated occurrences of cerebral anoxia and cardiorespiratory arrest (Dewan *et al*., 2008).

In view of these findings, the present study aims to evaluate the cardiotoxic effects of Ethion under organophosphate-induced stress. Organ-specific toxicity due to OP exposure is typically assessed through clinical biochemical assays and histopathological examinations. Accordingly, this investigation focused on analyzing various components and enzymes involved in protein metabolism within the cardiac tissue of Ethion-exposed Albino rats. Previous research by Bhatti *et al*. (2011) has demonstrated that in vivo Ethion administration causes oxidative damage to erythrocyte membranes in rats. While numerous clinical reports describe cardiac impairment following acute organophosphorus poisoning, there remains limited experimental data specifically addressing Ethion's toxic impact on rat cardiac tissue. Therefore, the current study assessed multiple biochemical and histopathological parameters in the hearts of Albino rats exposed to Ethion. The results clearly demonstrate that Ethion exposure significantly disrupts protein metabolism in cardiac tissue.

MATERIALS AND METHODS

Test Chemical

Crystalline Ethion with a purity of 92.5% was procured from Hyderabad Chemical Limited, Hyderabad, Andhra Pradesh, India.

Animal and Experimental Design

The experimental protocol received approval from the Institutional Animal Ethics Committee of S.V. University (Registration No. 438/01c/CPCSEA). Male adult Albino rats, aged 7 weeks and weighing approximately 200 ± 20 g, were procured from the Indian Institute of Science (I.I.Sc.), Bengaluru. The animals were maintained under controlled conditions at 28 ± 2°C with a 12-hour light/dark cycle and a minimum relative humidity of 40%. They were provided unrestricted access to a commercial pellet diet (Sai Durga Feeds and Foods, Bengaluru, India) and water ad libitum.

The healthy rats were randomly assigned into four groups, each containing six animals. The first group served as the control. The second group received Ethion orally via gavage at a dose of 42 mg/kg body weight (equivalent to one-fifth of the LD50) daily for 10 days. The third and fourth groups were similarly treated for 20 and 30 days, respectively, with dosing intervals of 48 hours. Animals were euthanized by cervical dislocation on days 11, 21, and 31 post-treatments, followed by immediate excision of the heart for subsequent biochemical and histological analyses.

Biochemical analyses

Total protein concentration in cardiac tissue was determined using the method developed by Lowry *et al*. (1951). Free amino acid levels were measured following the protocol outlined by Colowick and Kaplan (1957). Protease activity was assessed based on the release of free amino acids from protein substrates, following the method of Moore and Stein (1954), which serves as an indicator of proteolytic function. The enzymatic activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALAT) were evaluated according to the procedures described by Bergmeyer and Bernt (1965). Glutamate dehydrogenase (GDH) activity was measured using the technique established by Lee and Lardy (1965). Ammonia concentration was determined following Bergmeyer's method (1965), while urea levels were quantified using the diacetyl monoxime method described by Natelson (1971).

Histopathological Examination

For microscopic evaluation, heart tissues were harvested from both control and Ethion-treated rats. Samples were gently rinsed with 0.9% saline solution to remove residual blood and debris. Subsequently, tissues were fixed in 5% formalin for 24 hours. After fixation, the samples were thoroughly washed under running tap water overnight to eliminate any remaining fixative.The tissues were then dehydrated through a graded ethanol series, cleared with methyl benzoate, and embedded in paraffin wax. Thin sections of 6 µm thickness were prepared using a microtome. These sections were stained with Harris hematoxylin (Harris, 1900) and counterstained with eosin in 95% ethanol. Following dehydration and clearing, the stained sections were mounted in Canada balsam and examined under a light microscope for histological analysis.

Statistical Analysis

Data was analyzed using one-way analysis of variance (ANOVA), followed by post hoc comparisons employing the student–Newman–Keuls (S-N-K) test. Statistical

analyses were performed using SPSS software, version 21. A p-value of less than 0.01 was considered statistically significant.

RESULTS AND DISCUSSION

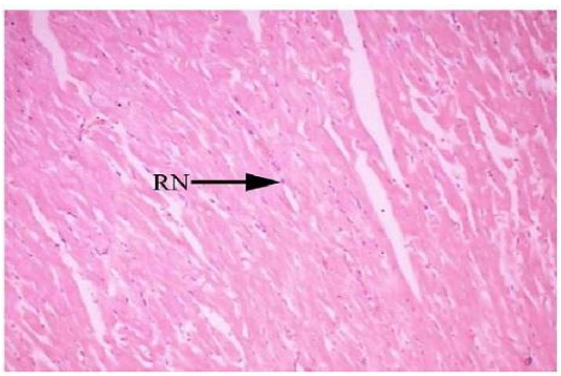
The biochemical findings are summarized in Table 1. A notable reduction in total protein content was observed in the hearts of Ethion-treated Albino rats compared to the control group. In contrast, the levels of all assessed enzymes, as well as ammonia and urea concentrations, showed a marked increase in the treated groups. These elevations were progressive, with the most pronounced changes observed in rats exposed to Ethion for 30 days, followed by the 20-day and 10-day exposure groups, respectively (Plate 1).

Table 1. Biochemical and Enzymatic Alterations in the Cardiac Tissue of Ethion-Exposed Albino Rats.

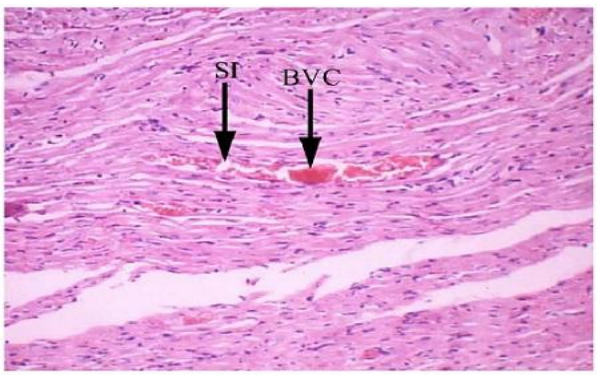
Heart	Control	10 days	20 days	30 days	F value
Total Proteins	130.911	110.927	95.148	76.061	30.358*
(mg/g. wet wt. of tissue)	13.009	11.626	9.153	7.382	
		(-15.26)	(-27.32)	(-41.90)	
Free amino acids	51.589[a]	53.358[a]	65.748	74.504	15.826*
(µmoles of tyrosine/g. wet wt. of tissue)	6.107	3.792	7.686	1.799	
		(3.42)	(27.44)	(44.42)	
Protease	0.772	0.900	0.926	1.008	13.801*
(µmoles of tyrosine/mg protein/h)	0.039	0.052	0.062	0.103	
		(16.58)	(19.95)	(30.57)	
Aspartate Amino transferase	0.743	0.885	0.905	0.965	11.262*
(µmoles of pyruvate/mg protein/h)	0.071	0.051	0.077	.063	
		(19.11)	(21.80)	(29.88)	
Alanine Amino transferase	5.367	6.396	7.365	8.571	21.314*
(µmoles of pyruvate/mg protein/h)	0.137	0.203	1.149	0.504	
		(19.17)	(37.23)	(60.00)	
Glutamate dehydrogenase	0.392	0.454	0.499	0.547	51.335*
(µmoles of formazan/mg protein/h)	0.018	0.023	0.026	0.010	
		(15.82)	(27.29)	(39.54)	
Ammonia	5.597	6.198	6.876	7.457	7.135*
(µmoles of ammonia/g. wet weight of	0.578	0.437	0.802	0.601	
tissue)		(10.74)	(22.85)	(33.23)	
Urea	0.392[a]	0.409 [a]	0.493	0.562	22.512*
(µmoles of urea/g. wet weight of tissue)	0.043	0.022	0.057	0.026	
		(4.34)	(25.76)	(43.37)	

Values are expressed in Mean ± SD of six individual observations. Values in parenthesis indicate % change cover control.
Mean values with the same superscript do not significantly differ among themselves through S-N-K test. *P < 0.01.

Control rat heart showing cardiac muscle fibres with rounded nucleus (RN).



10 days of Ethion administered rat heart showing Slight Infiltration (SI) and Blood Vessel Congestion (C).



20 days of Ethion administered rat heart showing Rounded Nucleus (RN), Denatured Nucleus (DN) and Nucleus (N).

30 days of Ethion administered rat heart showing Degenerated Muscle Fibre (DMF), Severe Necrosis in Cardiac Muscle Fiber (SNCMF) and Rounded Nucleus (RN).

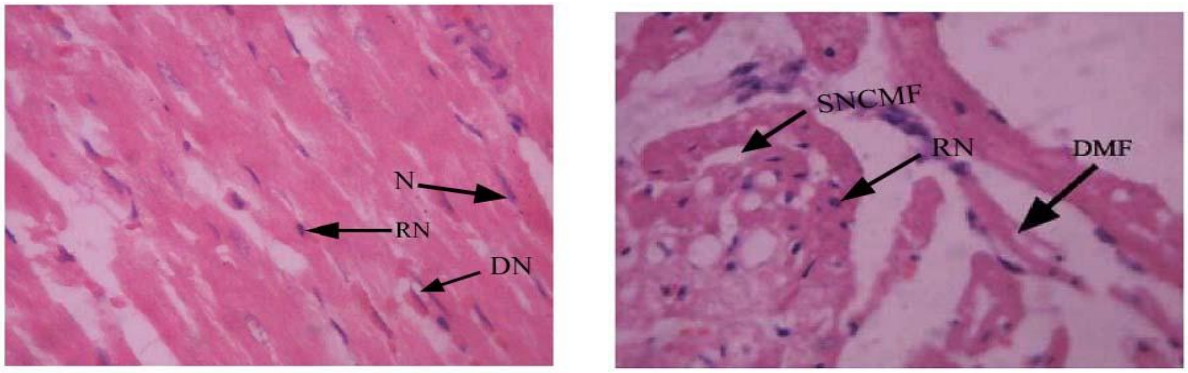


Plate 1. Ethion exposure induced distinct histopathological changes.

In this study, Ethion exposure induced distinct histopathological changes in the cardiac tissue. Observed pathological features included vascular congestion and mild cellular infiltration, which may contribute to the disturbances in protein metabolism enzymes identified in this investigation. Additional notable alterations comprised nuclear condensation (denatured nuclei) and severe necrosis of cardiac muscle fibres. Exposure to sublethal doses of Ethion elicited characteristic signs of organophosphate (OP) toxicity. All biochemical parameters examined in this study were significantly affected by OP-induced stress. The impact of Ethion was found to be time-dependent, with rats exposed for 30 days exhibiting more pronounced alterations compared to those treated for 20 and 10 days. Over the past three decades, the widespread use of OP pesticides in agriculture has resulted in severe adverse effects on non-target organisms. Many of these chemicals lack high specificity, leading to considerable toxicity in humans and other beneficial species sharing the environment. Improper application of such pesticides poses significant health risks, including illness and mortality. Damage to cellular membranes of various organs results in the release of enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALAT), and alkaline phosphatase into the bloodstream (Ncibi *et al*., 2008). These serum enzymes serve as reliable biomarkers of organ injury (Eraslan *et al*., 2009). Previous studies by Safi *et al*. (2010) and Ben Amara *et al*. (2011) demonstrated elevated ALT and AST levels following OP exposure in rats, corroborating the findings of the present investigation. Furthermore, Yahya *et al*. (2012) reported structural damage to multiple organs under OP toxicity. Proteins serve as an energy source during prolonged stress. Under such conditions, the organism's energy demand increases to facilitate detoxification and counteract stress effects. In this study, elevated free amino acid levels were observed, indicating enhanced protein catabolism and impaired amino acid synthesis (Singh *et al*., 1996). It is well established that stress induces activation of the transamination pathway. Disruptions in amino acid metabolism lead to the accumulation of catabolic products such as ammonia and urea, causing significant metabolic disturbances. Pesticides and their metabolites exert significant toxic effects on cardiac tissue. In this study, a pronounced increase in free amino acid levels was observed in the hearts of Ethion-exposed Albino rats. This elevation may result from enhanced proteolysis or increased synthesis of free amino acids via transaminase activity. The expanded pool of free amino acids could also serve as an adaptive response, helping the animals cope with Ethion-induced stress.

Glutamate dehydrogenase (GDH) activity was significantly elevated in Ethion-treated rats, indicating increased glutamate oxidation. GDH catalyzes critical reactions supplying substrates for both protein synthesis and carbohydrate metabolism. The enhanced GDH activity observed here likely reflects increased glutamate oxidation, leading to elevated ammonia production, which is further supported by concurrent changes in transaminase activities. Additionally, increased GDH activity might be associated with mitochondrial membrane permeability alterations or lysosomal damage, as GDH is a mitochondrial enzyme sensitive to mitochondrial structural changes. Activities of aspartate aminotransferase (AAT) and alanine aminotransferase (ALAT) were also significantly increased following Ethion exposure. Elevated transaminase activity is commonly associated with pathological conditions affecting tissue integrity. Ammonia and urea, metabolic waste products of protein catabolism, showed marked increases, indicating possible renal dysfunction and potential progression toward cardiac failure. Similar elevations in urea and creatinine levels have been documented in animals exposed to organophosphates (Garba *et al*., 2007). Previous studies have reported that Ethion exposure induces hepatotoxicity in rats, characterized by increased activities of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase in cardiac tissue (Bhatti *et al*., 2010). These findings support the cardiotoxic effects of Ethion. Additionally, decreased

glutathione reductase activity was observed in Ethion-treated rats compared to controls. Recent investigations by Elizabeth *et al*. (2024) on maternal and foetal toxicity associated with Ethion exposure revealed elevated malondialdehyde levels and altered antioxidant enzyme activities (reduced glutathione, superoxide dismutase, and catalase) in maternal serum and tissues. They also reported increased serum levels of AST, ALT, total bilirubin, urea, uric acid, and creatinine, further confirming liver and kidney toxicity induced by Ethion.

Evaluating tissue histology is crucial for understanding the toxicological impact of pesticides. In the current study, significant histological alterations were observed in the cardiac tissue following Ethion exposure. The degree of tissue damage appeared to be both dose-dependent and time-dependent, reflecting the toxic potential and accumulation of the pesticide in the heart. As the central organ responsible for circulation, the heart is particularly vulnerable to toxic insults. Light microscopic analysis revealed notable histopathological changes in the hearts of Ethion-treated Albino rats. After 10 days of exposure, the heart tissue exhibited mild cellular infiltration and vascular congestion. At 20 days, more pronounced alterations including rounded and denatured nuclei were evident. Prolonged exposure for 30 days resulted in severe cardiac damage characterized by degeneration of muscle fibres, extensive necrosis of cardiac muscle, and prominent nuclear abnormalities.

CONCLUSION

The findings of this study demonstrate that Ethion exposure leads to significant disruption of cardiac function, indicating physiological impairment in Albino rats. Ethion toxicity appears to be mediated through alterations in key parameters associated with protein metabolism in cardiac tissue. The observed biochemical and histopathological changes may result from the bioaccumulation of Ethion or its toxic metabolites. As environmental contaminants, pesticides such as Ethion are known to provoke a wide array of biochemical and toxicological disturbances, posing substantial risks to both non-target organisms and human health. These results underscore the potential dangers associated with indiscriminate pesticide use and highlight the need for stricter regulation and safer alternatives.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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