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Research Article

EFFECTS ON ANTIOXIDANT SYSTEM OF CARDIAC TISSUE FOLLOWING REPEATED ORAL ADMINISTRATION OF ARSENIC, QUINALPHOS AND THEIR COMBINATION IN WISTAR RATS

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ABSTRACT: Prevalence of insecticides and toxic metals in nature is a potential threat to mammalian well being. Simultaneous exposure to co-existing environmental toxins can severely impair cardiovascular health possibly by compromising cardiac antioxidant system. The present study was conceptualized to determine the consequences of concurrent exposure to arsenic and quinalphos on antioxidant status of cardiac tissue in rats. Fifty-four adult Wistar rats of either sex were randomly allocated to nine groups of six rats each. Animals were subjected to either individual or simultaneous oral administration of quinalphos (1/100th or 1/10th of LD_{50}) and arsenic (50 or 100 ppb) incorporated in drinking water, for 28 days. Significantly ($p<0.05$) declined cardiac antioxidant biomarkers *viz.* total thiols, catalase, superoxide dismutase, glutathione peroxidase, glutathione-s-transferase, glutathione reductase along with increased ($p<0.05$) malondialdehyde levels indicated oxidative damage to heart following simultaneous administration of higher doses of quinalphos and arsenic when compared not only to control rats but also to rats exposed to either toxicant. Likewise, significant reduction in activity of cardiac acetylcholinesterase (AChE) was seen in rats co-exposed to higher doses of quinalphos and arsenic. These results show that simultaneous co-exposure to arsenic and quinalphos particularly at their higher doses imposed severe cardiac oxidative stress in rats as reflected by reduced antioxidant biomarkers, increased lipid peroxidation and reduced AChE activity.

Key words: Acetylcholinesterase, Quinalphos, Arsenic, Wistar rat, Cardiac toxicity.

INTRODUCTION

Quinalphos is an organophosphate compound commonly employed for pest control in agriculture and livestock sector. Less than 0.1% of pesticide reaches the target species and the remaining 99.9% is dissipated in the environment. Quinalphos and its metabolites can persist in water, soil or plants for varying periods of time thus posing a grave threat to exposed animals and humans (Gupta *et al.* 2011). Quinalphos inhibits the activity of acetylcholinesterase (AChE) leading to accumulation of acetylcholine at synaptic and neuromuscular junctions (Sarkar *et al*. 2000). Recent studies indicate that intoxication with quinalphos and its intermediate metabolites causes oxidative stress due to free radical generation and lipid peroxidation (Sarkar *et al.* 2000, Singh *et al.* 2020). Therefore, environmental pollution due to indiscriminate use of quinalphos is a cause of great concern.

Arsenic is a naturally occurring metalloid found in air, soil and water. Presence of high arsenic levels in drinking water predisposes humans and animals towards toxicosis all over the world (Chen and Karagas 2013). In India, high arsenic level in water has been found in sixteen states including Jammu and Kashmir (Chakraborti *et al.* 2002).

Also, drinking ground water contaminated with naturally occurring inorganic arsenic in Bangladesh is said to be the cause of mass poisoning affecting a large section of its population. Toxicity of arsenic is attributed to its binding with accessible thiol groups in key enzymes such as pyruvate dehydrogenase, as the latter uses dithiol lipoic acid as a cofactor.

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Cardiac dysfunction is a leading cause of morbidity and mortality around the world. Environmental pollution is being increasingly linked with development of cardiovascular disorders (Goodman and Hochstein 1977, Jennrich 2012). Arsenic exposure has been associated with cardiac ischemia, arrhythmia and failure. Possible mechanisms of arsenic cardiotoxicity include oxidative stress, DNA fragmentation, apoptosis, and altered functioning of ion channels. Evidence suggests that mitochondrial disruption, caspase activation, MAPK signaling and p^{53} are involved in arsenic induced apoptosis (Doroshow *et al.* 1980, Alamolhodaei *et al.* 2015). Moreover, exposure to organophosphates can also inflict cardiotoxicity (Anand *et al.* 2009, Akbel *et al.* 2018). Therefore, rampant use of organophosphorus compounds in areas with high levels of arsenic in ground water is a potential threat to cardiac health of both humans and animals. However, data on cardiac tissue injury resulting from such co-exposure in mammals is deficient. Particularly, no previous research has been carried out to assess the extent of oxidative damage occurring in cardiac tissue after simultaneous exposure to arsenic and quinalphos. Therefore, this study was undertaken to determine the severity of cardiac oxidative changes resulting from repeated simultaneous exposure to quinalphos and arsenic in Wistar rats.

MATERIALS AND METHODS

Experimental animals

Fifty-four adult Wistar rats (180-200g) of either sex were procured from Indian Institute of Integrative Medicine (IIIM), Jammu. The animals were provided standard pelleted ration and clean drinking water ad-libitum. All animals were maintained under standard managemental conditions (22 ± 3°C, 50-60% relative humidity and 12 h light-dark cycles). Prior to start of experiment, rats were acclimatized to the laboratory conditions for a period of 15 days. All the experimental animals were kept under constant observation during the entire period of study. The experimental protocol was duly approved by Institutional Animal Ethics Committee (IAEC) vide proposal no 7/IAEC-17/2017. The maximum contaminant level (MCL) of arsenic in drinking water is 50 ppb and in the present study, two dose levels *viz.*, 50 and 100 ppb in drinking water were used (Steinmaus *et al.* 2005). Two different doses of quinalphos $1/100^{th}$ and $1/10^{th}$ of median lethal dose (LD_{50} - 19.9 mg/kg) were given alone and also in-conjunction with two different levels of arsenic (Raizada *et al.* 1993). Quinalphos (25%) used in the present study was commercially available by Biostadt India Ltd. Mumbai-400018, Maharashtra, India.

Experimental design

Rats were randomly divided in nine groups of six rats each and subjected to different treatments for 28 days. Group I served as control receiving only distilled water (1ml/day), group II and III received orally quinalphos at $1/100^{th}$ and $1/10^{th}$ of LD_{50} (19.9 mg/kg), respectively, whereas group IV and V received arsenic @ 50 and 100 ppb, respectively, in drinking water. Group VI and VII received quinalphos @ $1/100^{th}$ and $1/10^{th}$ of LD_{50} through oral gavage along with arsenic in drinking water at the concentration of 50 ppb, respectively. The animals comprising group VIII and IX received quinalphos @ $1/100^{th}$ and $1/10^{th}$ of LD_{50} orally along with arsenic in drinking water at the concentration of 100 ppb, respectively. The animals received daily dosing of quinalphos orally at 9.00-10.00 AM for a period of 28 days. All animals were weighed weekly for calculating dose of quinalphos to be administered and monitored for any clinical signs during entire period of study.

Processing and estimation of parameters

At the end of experiment, animals were sacrificed by cervical dislocation and heart was collected for evaluation of various oxidative stress parameters and acetyl cholinesterase activity. Preparation of samples for estimation of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-s-transferase (GST), acetylcholinesterase (AChE), malondialdehyde (MDA) and total thiols (TTH) was done as per the standard method. Briefly, heart (1 g) was collected in 10 ml ice cold phosphate buffer solution (0.5M, pH-7.4). Tissue samples were homogenized using teflon coated homogenizer (1000 rpm for 5-7 min at 4°C) and 10% tissue homogenate was prepared. The estimation of above parameters in the prepared homogenate was done as per the methods previously described [CAT (Aebi 1974), SOD (Marklund and Marklund 1974), GPx (Hafeman *et al*. 1974), GR (Carlberg and Mannervik 1985), GST (Habig *et al.* 1974) and AChE (Voss and Sachsse 1970), TTH (Mochnik *et al*. 1994) and MDA (Shafiq-Ur-Rehman 1984)].

Statistical analysis

The antioxidant parameters were presented as mean ± standard error and analyzed by analysis of variance at 5% level of significance using the Duncan Multiple Range Test (SPSS 16.0).

RESULTS AND DISCUSSION

Effects on antioxidant system of cardiac tissue

Effects of repeated administration of quinalphos and arsenic alone and in combination on antioxidant biomarkers in cardiac tissue of rats of different groups are presented in Table 1 and Table 2.

SOD: Administration of toxicants reduced SOD levels in all the groups when compared to their respective levels in control group. But this decrease was significant ($p<0.05$) only in group IX rats.

CAT: When compared with their respective values in control group, only a non-significant fall in CAT activities was observed in groups II, III, IV, V and VI, however, this fall in CAT activity was significant ($p<0.05$) in groups VII, VIII and IX.

GR: A non-significant fall in activity of GR was observed in groups II and IV but significant ($p<0.05$) decrease was observed in groups III, group V and all the combination groups (VI, VII, VIII and IX) as compared to control group. Notably, depreciation in GR activity in group IX was also significantly lower than the corresponding values of all other combination groups.

GST: A non-significant decrease was observed in all experimental groups when compared with the respective values in control rats except in groups III and IX where GST values were found to be significantly ($p<0.05$) decreased.

GPx: Glutathione peroxidase activity reductions were seen in all treatment groups when compared with control animals and these depreciations were non-significant in groups II, IV and V. However, a significant ($p<0.05$) decrease was observed in group treated with higher dose of quinalphos as well as all the combined treatment groups (groups III, VI, VII, VIII and IX) when compared to control group values.

TTH: When compared with control group values, a significant decrease in mean TTH level was observed only in group III and combination groups VII, VIII and IX. On the other hand, this decrease was non-significant ($p<0.05$) in groups II, IV, V and VI.

MDA: MDA levels were non-significantly raised in groups treated with arsenic alone (group II and III), whereas in groups treated with quinalphos alone and all combination groups, the increase in MDA values was significant ($p<0.05$) when compared with control group rats. Strikingly, values of MDA in group IX animals were

Table 1. Effects of repeated oral administration of quinalphos alone and in-conjunction with arsenic on various antioxidant biomarkers and AChE in cardiac tissue of rats.

Groups	AChE	SOD	CAT	MDA
I - Control	$14950.00^{d} \pm 824.18$	$283.0^{a} \pm 29.78$	$4008.5^{a} \pm 480.3$	$35.74^{a} \pm 2.74$
II - Quinalphos (0.199 mg/kg)	$12428.75^{cd} \pm 882.84$	$269.83^{a} \pm 17.76$	$3506.7^{a} \pm 443.8$	$47.78^{bc} \pm 0.96$
III - Quinalphos (1.99 mg/kg)	$11452.50^{bc} \pm 701.10$	$263.0^{a} \pm 27.22$	$3295.1^{a} \pm 337.3$	$55.90^{bc} \pm 4.00$
IV - Arsenic (50 ppb)	$14608.75^{cd} \pm 1903.48$	$278.16^{a} \pm 23.33$	$3776.8^{a} \pm 479.7$	$38.92^{ab} \pm 1.81$
V - Arsenic (100 ppb)	$12575.00^{cd} \pm 1164.70$	$274.69^{a} \pm 22.91$	$3559.7^{a} \pm 448.9$	$42.09^{ab} \pm 3.02$
VI - Quinalphos (0.199 mg/kg) + As (50 ppb)	$13075.00^{cd} \pm 1294.90$	$253.47^{a} \pm 21.68$	$3207.8^{a} \pm 308.9$	$47.38^{bc} \pm 3.20$
VII - Quinalphos (1.99 mg/kg) + As (50 ppb)	$11803.75^{cd} \pm 1081.31$	$245.3^{a} \pm 23.29$	$3053.7^{b} \pm 343.4$	$59.66^{c} \pm 4.57$
VIII - Quinalphos (0.199 mg/kg) + As (100 ppb)	$8511.25^{a} \pm 442.94$	$245.83^{a} \pm 25.04$	$3105.6^{b} \pm 253.4$	$68.22^{bc} \pm 3.66$
XI - Quinalphos (1.99 mg/kg) + As (100 ppb)	$7305.00^{a} \pm 285.16$	$210.2^{b} \pm 27.54$	$2999.6^{b} \pm 343.0$	$95.19^{d} \pm 4.10$

Values are given as Mean ± SE of 6 animals unless otherwise stated.
Values having different superscripts (a, b, c) in a column are statistically different from one another at 5% level of significance.
Activities of acetylcholinesterase (AChE) are expressed in nmole of thiol group produced /min/mg of tissue.
Values of SOD (Superoxide dismutase) expressed in Unit/ g of tissue.
Values of CAT (Catalase) are expressed in µmol H_2O_2 decomposed/ min/ g of tissue.
Values of MDA (malondialdehyde) are expressed in nmol MDA produced/g of tissue/hr.

Table 2. Effects of repeated oral administration of quinalphos alone and in-conjunction with arsenic on glutathione homeostasis in cardiac tissue of Wistar rats.

Groups	TTH	GPx	GR	GST
I - Control	$3.96^{c} \pm 0.42$	$35.66^{b \pm} 2.48$	$21.28^{a} \pm 1.50$	$8.60^{b} \pm 0.77$
II - Quinalphos (0.199 mg/kg)	$3.52^{bc} \pm 0.23$	$32.19^{ab} \pm 2.54$	$16.56^{ab} \pm 1.47$	$6.42^{ab} \pm 0.53$
III - Quinalphos (1.99 mg/kg)	$3.04^{b \pm} 0.29$	$31.01^{a} \pm 3.56$	$15.84^{b} \pm 2.00$	$4.20^{a \pm} 0.59$
IV - Arsenic (50 ppb)	$3.59^{bc} \pm 0.17$	$34.77^{b} \pm 2.92$	$17.50^{a} \pm 1.31$	$5.32^{ab} \pm 0.69$
V - Arsenic (100 ppb)	$3.74^{c} \pm 0.28$	$33.24^{ab} \pm 3.19$	$15.80^{b} \pm 1.64$	$5.00^{ab} \pm 0.84$
VI - Quinalphos (0.199 mg/kg) + As (50 ppb)	$3.32^{abc} \pm 0.27$	$28.84^{a} \pm 2.00$	$14.88^{b} \pm 1.21$	$4.07^{ab} \pm 0.49$
VII - Quinalphos (1.99 mg/kg) + As (50 ppb)	$3.17^{ab} \pm 0.20$	$27.37^{a} \pm 2.67$	$13.92^{b} \pm 1.73$	$3.85^{ab} \pm 0.45$
VIII - Quinalphos (0.199 mg/kg + As (100 ppb)	$2.09^{ab} \pm 0.18$	$23.35^{a} \pm 2.11$	$14.16^{b} \pm 1.01$	$3.80^{ab} \pm 0.47$
XI - Quinalphos (1.99 mg/kg) + As (100 ppb)	$1.58^{a} \pm 0.19$	$21.59^{a} \pm 1.91$	$12.69^{c} \pm 2.68$	$3.50^{a} \pm 0.42$

Values are given as Mean ± SE of 6 animals unless otherwise stated.
Values having different superscripts (a, b, c) in a column are statistically different from one another at 5 % level of significance.
Values of TTH (total thiols) are expressed in µM.
Values of GPx (glutathione peroxidase) are expressed in Unit/ g of tissue.
Values of GR (glutathione reductase) are expressed nmol of NADPH/min.
Values of GST (glutathione S transferase) are expressed in µmol of CDNB conjugate formed/ min/ g of tissue.

significantly higher than the MDA levels in rest of the combination groups.

AChE: Even though the levels of AChE were reduced in all the treatment groups, significant reductions in AChE activities of heart tissues were only seen in groups III, VIII and IX when compared with the respective values in control animals. Moreover, the AChE values were significantly lower in group VIII and group IX in comparison to the AChE values in group III.

Exposure to environmental contaminants such as heavy metals and organophosphates is a risk factor for development of cardiovascular disease. Alterations in cardiac function directly impact the metabolic functioning of all other organ systems of the body and cardiac failure ultimately can lead to multi organ failure (Alamolhodaei *et al*. 2015). Chronic exposure to arsenic has been frequently associated with cardiac problems (Goldsmith and From 1980, Chen and Karagas 2013). Recent evidences have also reiterated association of arsenic exposure and occurrence of cardiac dysfunctions (Pichler *et al.* 2019). Adverse effects of arsenic exposure on the cardiovascular system have been documented by many other workers also (Moon *et al.* 2012, Chen and Karagas 2013). Likewise, organophosphorus poisoning can also result in life threatening cardiac complications in humans (Anand *et al.* 2009). In our study alterations occurred in biomarkers of oxidative stress and AChE in cardiac tissue of all treated rats but these were significantly altered in groups given combined treatments of arsenic and quinalphos.

Oxidative stress occurs when an imbalance between generation and scavenge of oxygen free radicals is created. The antioxidant defence system comprises of enzymes like SOD, GPx, CAT, GR, and GST. GR maintains the cytosolic concentration of reduced glutathione whereas GSH catalyzes the conjugation of reduced glutathione to a variety of xenobiotics for their ultimate detoxification. GR maintain glutathione in a reduced state. GPx, on the other hand is a free radical scavenger and checks lipid peroxidation. CAT and SOD also catalyze transformation of reactive oxygen radicals. So, any alteration in components of antioxidant machinery will result in accumulation of oxygen free radicals with resultant oxidative insult to cells.

Glutathione peroxide deficient mice were more susceptible to doxorubicin-induced cardiotoxicity (Gao *et al.* 2008). In the present study, a significant decline in key enzymes of glutathione antioxidant system in cardiac tissue of rats was seen after co-administration of toxicants. Likewise, a significant rise in lipid peroxidation, decline in reduced glutathione, decreased levels of glutathione dependent antioxidant enzymes, has been reported after arsenic administration in cardiac tissue of rats (Mathews *et al.* 2013). Subchronic exposure to malathion caused lipid peroxidation, reduced glutathione levels and decreased activities of SOD, AChE and CAT in rat heart (Akbel *et al.* 2018). Additionally, subacute exposure to arsenic and quinalphos severely reduced levels of glutathione dependent enzymes, CAT, SOD in rat kidneys (Singh *et al.* 2020).

Significantly raised MDA levels and reduced TTH levels in co-administered groups in the current study indicate increased peroxidation of membrane lipids and reduced potential of the cells to quench ROS in cardiac tissue, which can ultimately cause cellular damage. MDA levels were reported to be significantly elevated in heart of rats after exposure to diazinon, pointing to free radical formation and lipid peroxidation in heart tissue (Mohamed *et al.* 2000, Ogutcu *et al.* 2006). Similarly, various studies also observed an increase in MDA content with exposure of diazinon (Akturk *et al.* 2006) and imidacloprid (Mahajan *et al.* 2018) in rats. Consistent with our findings, administration of arsenic also caused significant increases in levels of MDA in heart of rats (Saad *et al.* 2006). Long term arsenic exposure was shown to cause significant decrease in heart glutathione level and CAT activity and a significant increase in MDA levels (Ahangarpour *et al.* 2018). The increase in MDA levels in cardiac tissues in response to organophosphorus or arsenic exposure have also been observed in many other studies (Hazarika and Sarkar 2001).

Acetylcholine is a key regulator of cholinergic signaling in cardiac tissue. Reduced AChE activities lead to accumulation of acetylcholine and this may disrupt cardiac physiology. Measurement of cholinesterase (ChE) activity can serve as a biomarker not only for detecting cardiovascular pathological conditions but also for ascertaining exposure to organophosphorus and arsenic (Patlolla and Tchounwou 2005, Lionetto *et al.* 2013, Waiskopf *et al.* 2016). In our study repeated oral administration of quinalphos and arsenic reduced AChE activity and this reduction was highly significant when higher doses of both the contaminants were given in combination highlighting implications of their combined exposure under natural conditions for cardiovascular system. Previous studies have shown that a significant fall in brain AChE activities can occur after chlorpyrifos administration in rats (Karanth and Pope 2000, Mehta *et al.* 2005). Similar significant reduction in AChE activities has also been reported upon combined administration of chlorpyriphos and fluoride in rats (Baba *et al.* 2014).

Thus, simultaneous administration of quinalphos and arsenic significantly affected not only the antioxidant machinery of cardiac tissue but also AChE activity in cardiac tissue of rats. The resultant diminished antioxidant potential leading to accumulation of reactive oxygen species and reduced AChE enzyme activity which causing accumulation of acetylcholine at neuromuscular junctions, can act as precursors for development of serious cardiac dysfunction.

CONCLUSION

Increased malondialdehyde levels along with decreased total thiol concentration, AChE activity and free radical scavenging enzymes in rat cardiac tissue after co-administration of quinalphos and arsenic indicated that repeated exposures to co-existing environmental toxins can cause significant cardiovascular damage in dwellers of such polluted regions.

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