CARDIOTOXIC EFFECTS OF DICHLORVOS (DDVP) IN ALBINO RATS

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Summary : Dichlorvos (O, O-dimethyl O-(2, 2-dichlorovinyl phosphate: DDVP 76.6× EC) an organophosphate pesticide had a profound effect on cardiac activity of albino rats. Adult male rats anesthetized with pentobarbitone were administered 30,50,70 and 90 *mg/kg* body weight of dichlorvos. The heart rate and electrocardiogram were monitored and acetylcholinesterase activity was measured in heart and brain. Dichlorvos produced abnormalities in ECG, decrease in heart rate, cardiac arrest and inhibition of cholinesterase activity. It is suggested that cardiotoxic effect of DDVP may be mediated by the accumulated acetylcholine as a result of cholinesterase inhibition.

Key words : DDVP bradycardia heart rate acetylcholinesterase inhibition

INTRODUCTION

Dichlorvos (DDVP) an organophosphate pesticide (OP) produces effects different from those of chlorinated hydrocarbons (e.g. DDT, Endrin). The OP compounds are potent inhibitors or acetylcholinesterases. However, symtoms of OP poisoning in human are often associated with serious and fatal cardiac complications resulting in sudden deaths even after the patient appears to be recovering from initial nervous and respiratory symptoms (1,7). There are few reports in literature regarding the cardiovascular effects of insecticides. Decrease in cardiac contractility, blood pressure and blood flow have been reported in dogs intoxicated with acute doses of chlordemiform (10). Marked

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changes in heart rate have been observed in rats exposed to acute doses of organophosphate insecticides (6). The present report deals with changes in cardiac responses in DDVP treated animals.

MATERIAL AND METHODS

Animals : Adult albino rats of Wistar-CFT strain (*Rattus norvegicus albinicus)* of both sexes weighing 250-300 g were used, Animals were fed with Institute's stock diet and water *ad libitum.*

Determination of LD_{50} : Dichlorvos (DDVP, 76,6% EC supplied by NOCIL, Bombay) was carried in isotonic Tween-80 solution and administered intraperitoneally in adult male and female rats to determine median lethal dose of DDVP. The LD_{50} values (for active ingredient of DDVP) were obtained by probit analysis (3).

Recording of ECG: Twenty five adult male rats in groups of five each were anesthetized with pentobarbitone (55 *mg/kg*, b.w.) and their ECG were recorded; these served as untreated controls (Fig. 1). Recordings were obtained with needle electrodes inserted

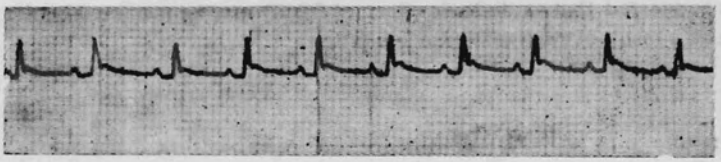

Fig. 1 : ECG of rat prior to treatment of DDVP. Heart rate : 315.8 BPM; chart speed: 50 *mm/sec.* Amplitude : 1 *cm/mv.*

under the skin of fore and hind limbs. These electrodes were connected to an ECG recorder (Cardiomin) and responses from limb leads : I, II and III were recorded. The same animals were immediately injected with 30,50,70 and 90 *mg/kg* body weight of DDVP and ECG recorded at 5, 10, 15 and 30 min postinjection. The heart rate was calculated from ECG recordings. The animals were sacrificed prior to death which ensued within 5-15 minutes at higher doses (70 and 90 *mg/kg*, b.w,) and after 30 min at lower doses. The acetylcholinesterase activity in brain and heart were estimated by the method of Ellman *et al.* (2). Acetylthiocholine was used as a substrate at a concentration of 1.5 μm. The acetylcholinesterase activity was expressed as μm of substrate hydrolysed/min/g. The data were analysed statistically by students 't' test method.

RESULTS

Within five minutes of i.p. injection of acute doses of DDVP, rats developed the typical symptoms of organophosphate poisoning viz. tremors, convulsions, diarrhoea, exopthalmia, chromolachrymation, respiratory distress and cyanosis. Death occured within 5-15 minutes of DDVP treatment. The LD_{50} values determined were 23.3 *mg/kg* for females and 60.9 *mg/kg* for males respectively (Table I) The females were more susceptable to toxic effect than males.

TABLE I : Survival rate and morbidity in DDVP-treated rats.

Sex	*Dosage (mg/kg)*	*Mortality*	*Survival time (min)*	LD_{50} *(mg/kg, b.w.)*
Female	10	0/6	—	
	20	2/6	15	23.3
	30	4/6	15	(14.9-32.2)
	40	5/6	10	
	50	6/6	8	
Male	30	0/6	—	
	50	1/6	15	60.9
	60	2/6	15	(45.0-82.0)
	70	4/6	15	
	90	6/6	5-8	

95% confidence limits are presented in parenthesis.

ECG of DDVP treated male rats showed decrease in heart rate and abnormalities in ECG pattern. The decrease in heart rate was directly related to the dose of DDVP. Administration of 30 and 50 *mg/kg* DDVP caused abrupt decrease in heart rate in 5 and 10 min, but cardiac rhythm gradually recovered to initial pretreatment rate within 30 min (Table II). However, at 70 *mg/kg*, b. w., DDVP produced irreversible bradycardia leading to cardiac arrest within 15 min. At higher dose there was a maximal reduction in heart rate in 5 min resulting in instantaneous death of the animals. ECG pattern showed prolonged P-R intervals, increased R-wave potentials (Fig. 2), elevated S-T segment (Fig. 3), sinus bradycardia and first, second and third degree A-V block (Fig. 4).

TABLE II : Effect of DDVP on heart rate of albino rats.

Pre-treatment	*i.p. injection (mg/kg b.w.)*	*Mean heart rate (beats/min)* Post injection (min) 5	10	15	30	*Mortality (%)*
315 ±40	30	270[a] ±47	250[c] ±67	307 ±13	320[c] ±16	0
340 ±30	50	215[c] ±68	226[c] ±69	293[c] ±12	320[c] ±13	33.3
335 ±34	70	273[c] ±25	122[c] ±20	69[c] ±40	—	100
295 ±15	90	115[c] ±11	—	—		100

Values are mean and S.D. of five animals. Degree of significance; a = $P < 0.05$; c = $P < 0.001$.

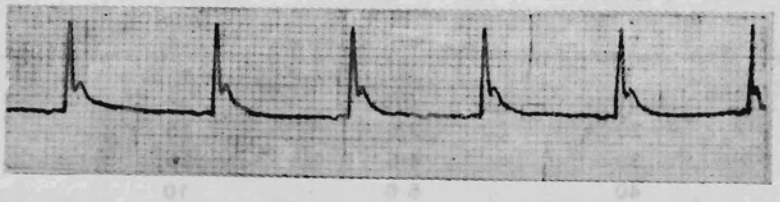

Fig. 2 : ECG of rat treated with 70 *mg/kg* of DDVP showing increased R-wave potentials. Heart rate : 167 BPM, chart speed : 50 *mm/sec.* Amplitude : 1 *cm/mv.*

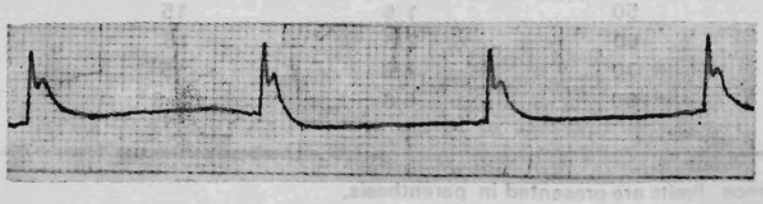

Fig. 3 : ECG of rat treated with 70 *mg/kg* of DDVP showing elevated S-T segment. Heart rate : 100 BPM; Amplitude : 1 *cm/mv* Chart Speed : 50 *mm/sec.*

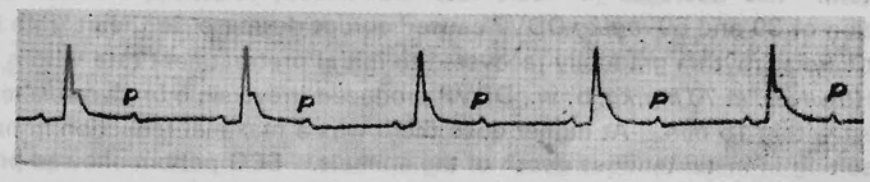

Fig. 4 : ECG of rat treated with 90 *mg/kg* of DDVP showing prolonged P-R intervals and second degree AV block. Alternate P wave with missing QRS complex are indicated. Heart rate : 130.5 BPM, Amplitude ; I *cm/mv,* chart speed : 50 *mm/sec.*

Acetylcholinesterase activity in brain and heart was significantly reduced at all doses of DDVP treatment. The degree of cholinesterase inhibition was more marked in brain than in heart and was found to be dose-dependent (Table III).

At higher doses (70 and 90 *mg/kg*, b.w.) the cholinesterase activity was reduced by 90-92% and 86-88% in brain and heart respectively 5-15 min after DDVP administration.

TABLE III : Effect of DDVP on acetylcholinesterase activity of brain and heart of albino rats

Dosage (mg/kg)	*Duration of post-injection (min)*	*Acetylcholinesterase activity (μm substrate hydrolysed/min/g)*	
		Brain	*Heart*
0	30	3.19± 0.69	1.87 ± 0.07
30	30	0.56 ±0.06[a] (82.5%)	0,83 ± 0.08[a] (55.6%
50	30	0.36 ± 0.05[a] (88.6%)	0.56 ±0 08[a] (70.0%)
70	15	0.30±0.06[a] (92.4%)	0.25±0.02[a] (86.4%)
90	5-8	0.24 ± 0.04[a] (92.4%)	0.20 ± 0.05[d] (88.9%)

Values are mean and S.D, of five animals. Figures in parenthesis denote per cent inhibition of enzyme activity over control.

[a] Signfcantly different from controls $P < 0.01$

DISCUSSION

Intraperitoneal administration of DDVP induced bradycardia, cardiac arrest and inhibition of cholinesterase activity in brain and heart of albino rats. These responses were dose-dependent and could be related directly to the degree of cholinesterase inhibition. The transient and reversible nature of bradycardia observed at lower doses of DDVP treatment could be due to lesser degree (50-70%) of cholinesterase inhibition in heart. Moreover, the sharp and irreversible decrease in heart rate, culminating in cardiac arrest at higher doses could be attributed to the high degree of inhibition (more than 85% and 90%) of cholinesterase activity in heart and brain respectively. It has been reported that in acute organophosphate poisoning, death was related to the cardiac and circulatory failure, and these responses were mainly attributed to the accumulation of

acetylcholine at the cholinergic synapses in the heart (4, 5,9,11,12,). Thus the impairment of cardiac function during acute DDVP poisoning could be due to the accumulated acetylcholine in brain and heart as a result of cholinesterase imhibition. However, Marosi *et al.* (8) demonstrated that cardiac failure in dimethoate induced poisoning was not directly related to the cholinestrerase inhibition but as a result of direct toxic effects on myocardium. Our results suggest that the cardiotoxic responses of Dichorvos in rats may be directly related to the inhibition of cholinesterase activity.

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