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PRAZIQUANTEL- INDUCED TRANSIENT HYPOTENSION, DEPRESSED RESPIRATION AND ALTERED ELECTOCARDIOGRAM (ECG).

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ABSTRACT

A relaxant effect was achieved by praziquantel on the rat thoracic aortic strip preparations which might be of cholinergic nature.

Praziquantel produced an acetylcholine-like effect on the perfused rabbit's heart.

A transient hypotensive effect and respiratory depression and altered ECG were traced. These effects revealed the peripherel cholinergic effects of the drug.

INTRODUCTION

Helminthiasis is a common problem in Veterinary practice affecting animals as well as birds reducing the growth rate, body gain, milk production and even egg-production in laying hens.

Praziquantel is a new anthelmintic drug with a broad spectrum activity aganist cestodes pathogenic to man (Frohberg and Schenching 1981, Flisser et al 1990) and animals (Thomas and Gonnert, 1977), many kinds of trematodes (Groli, 1984) and Schistosomes (Tahani et al 1988).

Literatures on the pharmacodynamics of the drug are relatively spare.

Hence, the present study was carried out to investigate the effect of praziquantel on cardiovascular and respiratory systems.

MATERIAL AND METHODS

The method described by Furchgott (1960) was adopted for studying the effect of praziquantel on isolated rat thoracic aorta preperation. A spiral strip of about 3 cm length of aorta was mounted in 50 ml organ bath in kreb's solution at 37°C aerated with air.

The isolated perfused rabbit's heart and coronary outflow were performed by using the modified Gunn's apparatus for mammalian heart as described by Langendorff (1895).

For investigating the effect of praziquantel on the blood pressure, respiration and electrocardiogram (ECG), the method described by Jackson (1937) was adopted using mongrel dogs anaesthetised with pentobarbital sodium (30 mg/kg B. vet). The femoral artery and femoral vein were cannulated. Heparin (500 units/kg B. wt) was injected intravenously as anticoagulant.

The blood pressure was recorded using strain gauge blood pressure transducer PT 400 connected to MD4 Osciliograph. The electrocardiogram needle electrodes were inserted under the skin of the two fore and hind limbs. Lead II of E.C.G. Coupler were used for recording E. C.G. tracings.

Statistical analysis:

Student "T" test were carried out according to Snedecor (1971).

Drugs:

The following drugs were used, praziquantel (Droncit, Bayer A.G., Leverkusen, Germany), Acetyl-choline chloride (Roche, Switzerland), atropine sulphate (Meaform Smith, Edinburgh, England), Heparin (Sigma Co., U.S.A.), Histamine Dihydrogen phosphate (BDH, England), Isoprenaline (Sigma Co., USA), mepyramine maleate (M&B, England), Nicotine sulphate (Morgan-Laboratories, Egypt), Noradrenaline (Holly- wood CA, U.S.A), Pentobarbitone Sodium (Abbot, USA) & Propranolol hydrochloride (I.C.I., England).

RESUTLS

(A) Effects on thoracic aorta:

Praziquantel produced a dose-dependant inhibitory effect on the rat thoracic aorta. Small doses (0.8 and 1.6 mg/ml) induced slight inhibition of rat thoracic aorta, whereas, large doses (3.2, 6.4 and 12.8 mg/ml) elicited a marked relaxation. (Fig. 1)

Several attempts were made to investigate the site of action of the drug. Noradrenaline produced its stimulatory effect in the presence of the drug indicating the absence of an-alpha adrenergic blocking activity of the drug was excluded since the drug produce its expectant inhibitory effect in the presence of propranolol and mepyramine respectively Praziquantel

has been found to possess an acetylcholine like activity as the drug failed to produce its effect in the presence of atropine sulphate (Fig. 2 A,B,C,D)

(B) Effects on the heart muscle:

Effects on isolated perfused rabbit's heart:

Praziquantel produced a dose dependant hihibitory activity of myocardium. Small doses (0.8 and 1.6 mg/ml) induced slight inhibition., while large doses (3.2 and 6.4 mg/ml) elicited a marked ihibition of the myocardial contraction (Fig 3).

An attempt was made to locate the site of action of the drug on the isolated rabbit's heart.

The possibility of beta-adrenoceptor blocking effect of the drug was tested by adding isoprenaline (20 ug/ml) in the presence of praziquantel (3.2 mg/ml). Isoprenaline produced its stimulatory effectt indicating the absence of beta- adrenoceptor blocking effect of the drug (Fig. 4, A).

The probability of an acetylcholine-like effect of the drug was tested by blocking the muscarinic receptors with atropine sulphate (10 ug/ml). Complete blockage was tested by acetylcholine (10 ug/ml). The addition of praziquantel (3.2 mg/ml) failed to produce its inhibitory effect indicating the acetylcholine like effect of paziquantel on the isolated perfused rabbit's heart (Fig. 4,B)

(C) Effects on coronary outflow:

Praziquantel (3.2mg/ml) caused about 18% increase in the coronary outflow after one minute from the addition of the drug. The

increase reached 34%, 66% after 5 minutes and 10 minutes respectively and achieved its maximum of 100% after 15 minutes. The flow then dropped to attain its initial control level after 30 minutes (Fig. 5)

Acetylcholine (10 ug/ml) caused an increase in the coronary outflow of 100% after one minute and the flow then dropped to attain its initial level after 5 minutes (Fig. 5).

(D) Effects on Blood pressure and respiration:

Different doses of the drug were injected intravenously in the femoral vein. It was observed that praziquantel in dose of 20, 40 80 and 160 mg/kg B. wt. induced slight transient hypotensive effect (11, 18, 28 and 33 mm Hg respectively) and slight respiratory depression (Fig. 6).

Praziquantel in doses of 320 and 680 mg/kg B.wt produced marked transient hypotensive effect (40, 50 mm Hg respectively)

An attempt was made to investigate the hypotensive effect of praziquantel. The possibility of histamine-like effect was tested by blocking the histaminic receptors (HI) with mepyramine maleate (20 ug/kg B. wt.). Praziquantel (320 mg/kg B. wt.) induced its hypotensive effect in the presence of mepyramine maleate, indicating the absence of histamine- like effect of praziquantel (Fig. 7,A).

The possibility of beta-adrenoceptor stimulant effect was tested by blocking the beta-adrenoceptors with propranolol (10 ug/kg B. wt.). Complete blockage was tested by isoprenaline (1 ug/kg B. wt.).

Praziquantel (320 mg/kg B. Wt) induced hypotensive effect in the presence of propranolol indicating the absence of beta- adrenoceptor agonist activity of the drug (Fig. 7,B).

The probability of an alpha-adrenoceptor blocking activity was tested by noradrenaline (2 ug/kg B. Wt.) in the presence of praziquantel (320 mg/kg B. wt.). Noradrenaline produced its hypotensive effect indicating the absence of any alpha-adrenoceptor blocking activity of the drug (Fig. 7,C).

The possibility of ganglionic blocking activity was tested by injecting a small dose of nicotine sulphate (2 ug/kg B. wt.) in the presence of praziquantel (320 mg/kg B. wt.). Nicotine induced its hypertensive effect indicating the absence of ganglionic blocking activity of the drug (Fig. 7,D).

The possibility of cholinergic activity was tested by blocking the peripheral cholinergic receptors with atropine sulphate (10 ug/kg B.wt.). Praziquantel (320 mg/kg B. wt) failed to induce its hypotensive effect in the presence of atropine sulphate indicating the peripheral cholinergic effect of the drug (Fig. 7,E).

(E) Effects on electrographic pattern (ECG):

Praziquantel in doses of 40,80 and 160 mg/kg B. wt produced no changes in the ECG pattern. Increasing the dose of the drug to 320 and 640 mg/kg B. wt prolonged the P. R. interval indicating slowed conduction in the auriculoventriculr node (Fig 8).

Bradycardia was observed after injecting praziquantel in large doses (320 and 640 mg/kg B.wt). Moreover, praziquantel prolonged the ST segment reflecting a prolonged depolarization and repolarization of the ventricular myocardial cells which leads to bradycardia.

DSCUSSION

It was evident from the present work that praziquantel produced a dose dependant inhibitory effect on the vascular smooth muscles rat thoracic aorta.

It had been shown that noradrenaline, an alpha-adrenoceptor stimulant, produced its stimulatory effect in the presence of praziquantel. It was found also that praziquantel produced its inhibitory effect after blocking the beta-adrenoceptors with the non-selective beta-adrenoceptor blocker, propranolol or histaminergic receptor sites with HI blocker, mepyramine maleate. The previous results suggested the absence of alpha-adrenoceptor blocking effect, beta-adrenoceptor agonist or histaminic activities of praziquantel on the vascular smooth muscles.

On similar ground, it has been shown that the relaxant effect of praziquantel on the rat thoracic aorta was abolished in the presence of the peripheral cholinergic receptor blocker, atropine sulphate.

Our results confirmed the results obtained by Jim and Triggle (1979). they clearly found that praziquantel produced a stimulant effect on guinea pig ileal muscles in a manner dependant on the extracellular calcium concentration.

Praziquantel has been found to elicit a dose-related negative inotropic activity on the isolated perfused rabbit hearts. The effect is presumed not to be due to an interaction with beta-adrenergic receptors sites since beta-agonist, isoprenaline elicited its expectant stimulatory effect in the presence of the drug. Moreover, an interaction of praziquantel with the central nicotinic receptors could be ruled out by the fact that drugs interacting with nicotinic receptors as ganglionic blockers could possibly stimulate the isolated heart preperations (Corn and Edge, 1958).

Furthermore, an effect on peripheral cholinergic receptors could not be ignored since, the depressant activity of the drug was completely obtunted after pretreatment with the peripheral cholinergic antagonist (atropine sulphate).

Harder et al (1987) had reported that praziquantel enhances calcium permeability by memberane perturbation. Other investigators have found that the drug increase the rates of force develpment and relaxation of isolated rat atria and that effect was blocked by calcium channel blockers (Chubb et al, 1978). Also, chineese investigators have reported that precipitation of heart rhythimc agents (Shao et al, 1981). The effect of praziquantel has been studied on isolated guinea pig left atria by Khayyal et al (1987). They found that praziquantel caused concentration dependant increase in the force of contraction of the isolated left atria, an effect which may be due to an increase in Ca^{++} fluxes. The previous workers also found that praziquantel antagonised the cardiotonic effect of the cardiac glycosides on the guinea pig atria. This antagonism is

neighter due to an slteration of Ca^{++} concentration in cell nor to direct action on Na^{+}, K^{+} ATPase, not to inhibition of binding of cardiac glycosides to heart tissues. This interaction may involve an enhancement of K+ fluxes in cardiac cells under the influence of praziquantel.

Praziquantel evoked a dose-dependant fall in both systolic and diastolic blood pressure and respiratory depression. It seems unlikely that the hypotensive effect of praziquantel could be explained on the basis of histmine-like effect or the release of tissue bound histamine by the drug, since the hypotension and respiratory depression were still observed in the presence of histaminic blocker (mepyramine maleate).

It was found also that praziquantel produced its hypotensive effect and respiratory depression after blocking the beta-adrenoceptor agonist activity of the dryg. Noradrenaline (alpha-adrenoceptor agoisnt or nicotine sulphate in small dose (central cholinergic receptor agoinst) produced their hypertensive effect in the presence of praziquantel and gave an additional evidence for absence of any alpha-adrenoceptor or central cholinergic receptore blocking activity of the drug.

Eventhough, needless to say that an interaction of the drug as ganglionic blocker with central cholinergic receptors could possibly mediate this drug induced hypotension is excluded since ganglionic blockers often stimulate the isolated heart preperation (Corn and Edge, 1958).

A possible interaction with the peripheral cholinergic receptors in the blood vessels, heart and respiratory and respiratory depression after

pretreatment with peripheral cholinergic receptors antagonist (atropine sulphate).

Concerning the effect of praziquantel on ECG, the drug in large doses (320 and 640 mg/kg B.wt) prolonged the P.R. interval reflecting slowing of auriculventricular node conduction. This effect together with reduction in heart rate seen in the present study confirm similar findings in rabbits heart and guinea pig auricles, suggesting a muscarinic stimulant activity of praziquantel. Moreover, praziquantel in the present investigation prolonged S.T. segment reflecting a decreased influx of calcium during repolarization which is expected to be a consequence of its cholinomimetic activity. the drug induced shortening of the duration of the action potential (The Q-T- interval), this effect seems to be mediated through the stimulation of muscarinic receptors.

It could be concluded from our results that praziquantel stimulates the peripheral cholinergic receptors in smooth and cardial muscels. Our study strongly emphasizes that further work should adress the clinical implication if any of their cholinergic stiimulatory effects at least in those patient animals suffering from hypertension or receiving hypertensive drugs.

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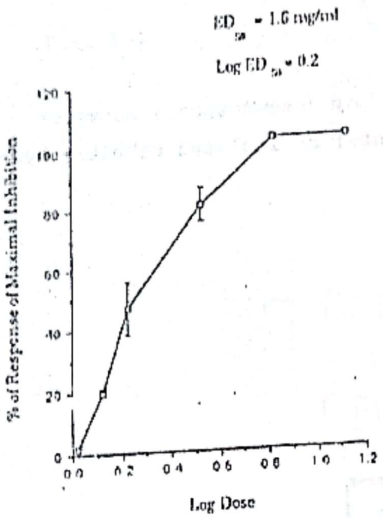

Fig. 1- Log dose-response curve of praziquantel on isolated rat thoracic aorta.

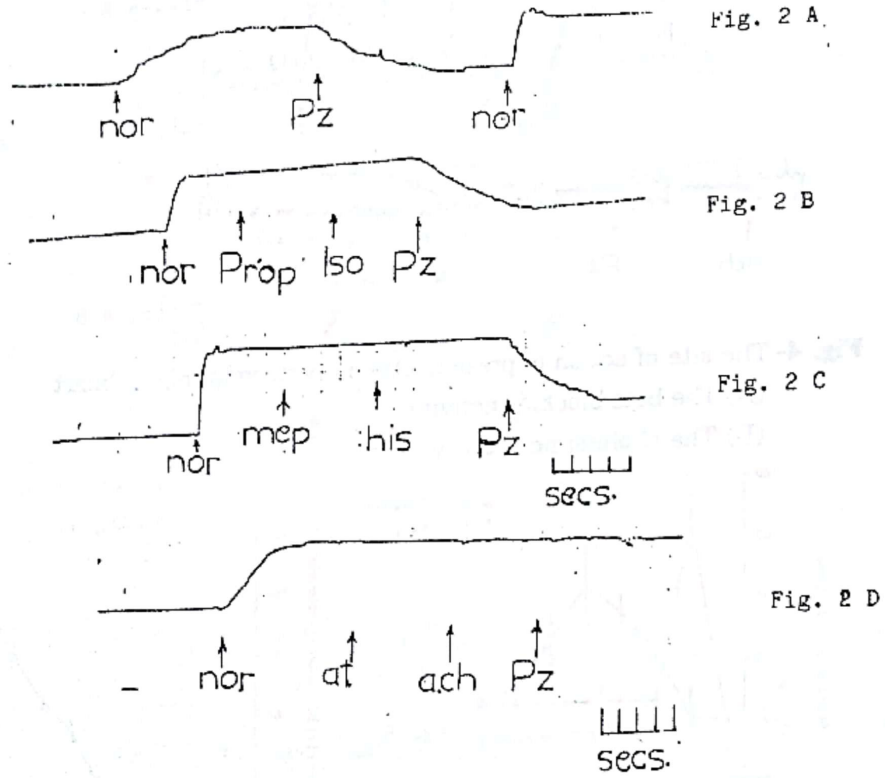

Fig. 2- The site of action of praziquantel on the rat thoracic aorta.

(A) The alpha-blocking activity.

(B) The beta-stimulant activity.

(C) The histaminic activity.

(D) The cholinergic activity.

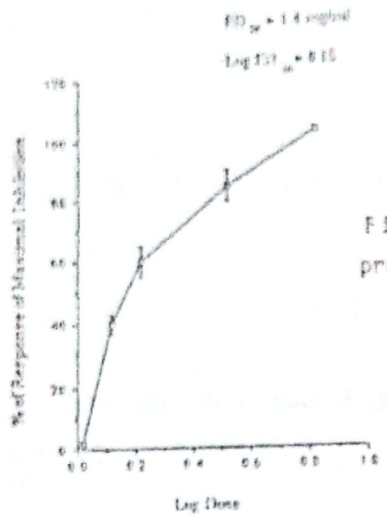

Fig.3: Log dose-response curve of praziquantel on isolated rabbit's heart

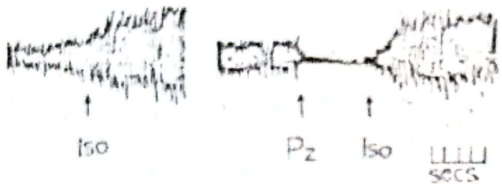

Fig. 4 A

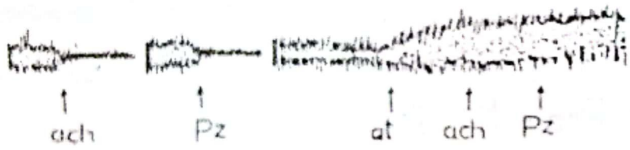

Fig. 4 B

Fig. 4- The site of action of praziquantel on perfused rabbit's heart.
(A) The beta blocking activity
(B) The cholinergic activity

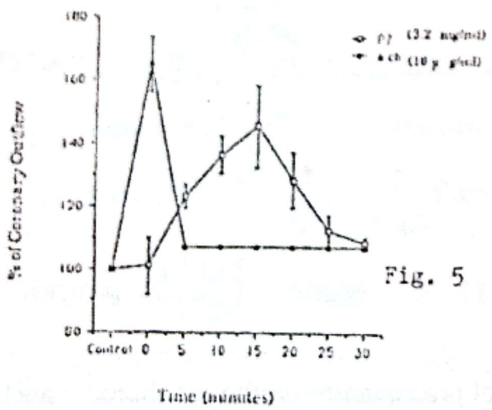

Fig. 5

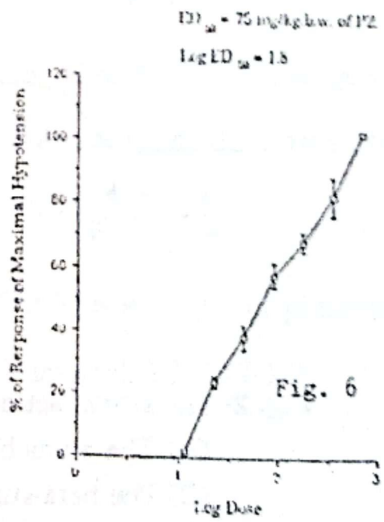

Fig. 6

Fig. 5- The effect of praziquantel on the coronary outflow in comparison with acetyle choline.

Fig. 6- Log dose- response curve of praziquantel effect on the blood pressure of dogs.

Fig. 7 A

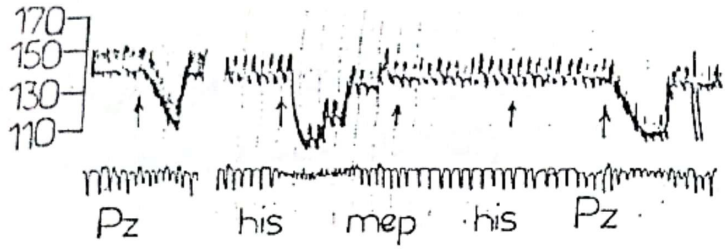

Fig. 7 B

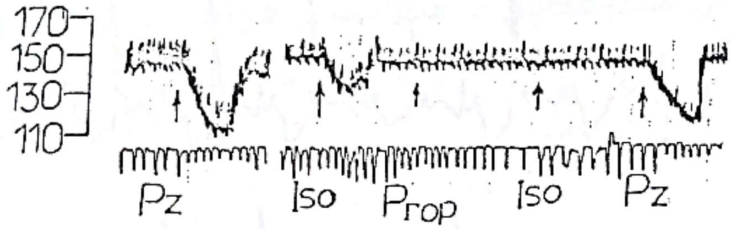

Fig. 7 C

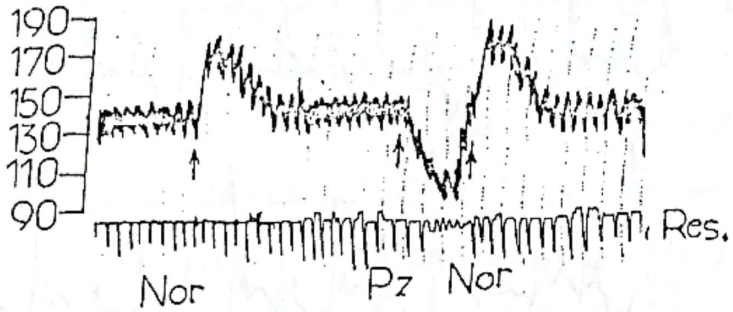

Fig. 7 D

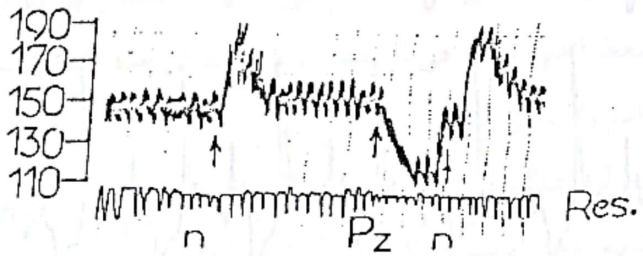

Fig. 7 E

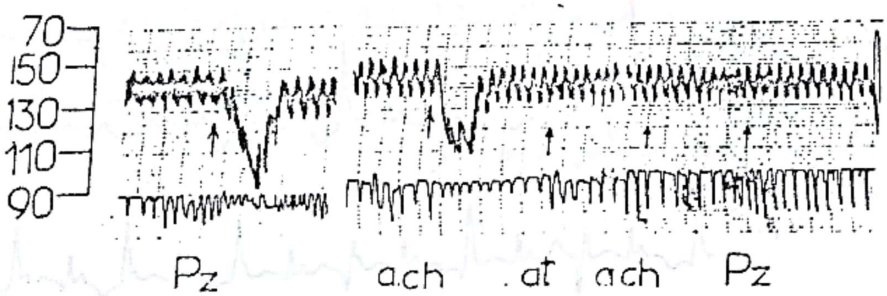

Fig. 7. The site of action of praziquantel on the arterial blood pressure of dogs.

(A) The histamine activity.

(B) The beta stimulant activity

(C) The alpha blocking activity.

(D) The ganglionic blocking activity.

(E) The cholinergic activity.

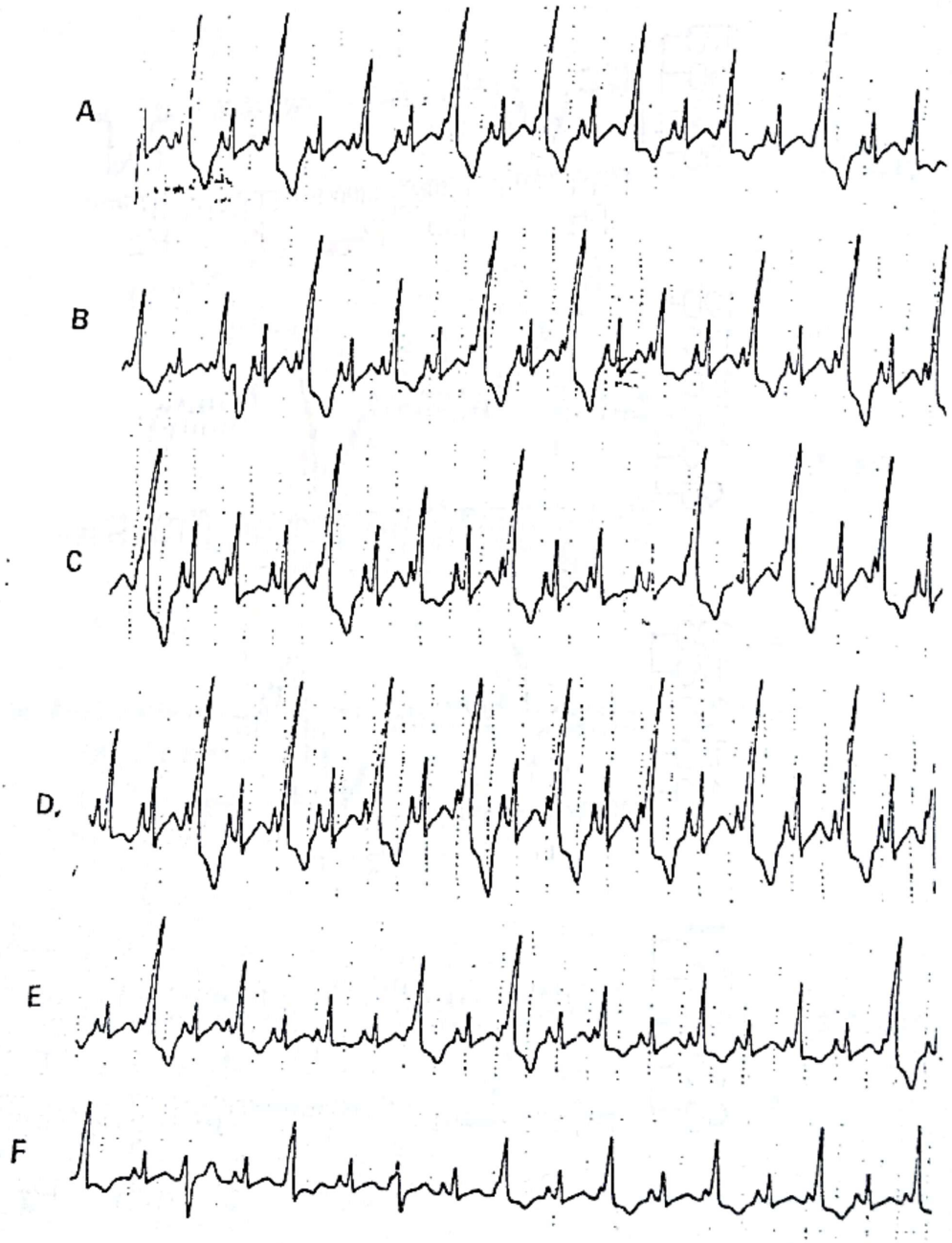

Fig. 8- Effect of praziquantel on Electrocardiograph. (E.C.G.)

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البرازيكوانتيل يحدث إنخفاضا مؤقتا فى ضغط الدم وقلة التنفس وتغير فى رسم القلب

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لقد إتضح من هذه الدراسة أن دواء البرازيكوانتيل يسبب تأثيرا مثبطا على قوة وعدد ضربات القلب المعزول من الأرانب ودراسة كيفية إحداث هذا التأثير ثبت للدواء تأثير مشابها لتأثير الإسيتيل كولين على عضلات القلب.

ولقد وجد أن لبرازيكوانتيل له تأثيرا مثبطا علي الشريان الأورطى المعزول من الفئران وأن هذا التأثير يشابه فعل الإسيتيل كولين علي الأوعية الدموية.

وبدراسة تأثير المادة على ضغط الدم فى الكلاب المخدرة بالبنتوباربيتون وجد انه يسبب هبوطا مؤقتا فى ضغط الدم وتوقفا فى التنفس. ولقد وجد ان هذه التأثيرات مشابهة لفعل الأسيتيل كولين على ضغط الدم والتنفس.

كما إتضح أن إعطاء الدواء فى جرعات كبيرة يحدث تغيرات فى رسم القلب ولقد وجد أن هذه التأثيرات مشابهة لفعل الإسيتيل كولين على رسم القلب.

يستخلص من هذه الدراسة أن البرازيكوانتيل له تأثير مماثل للأسيتيل كولين علي الأوعية الدموية والقلب وضغط الدم والتنفس ورسم القلب لذلك يجب الحذر عند إستخدام هذا الدواء لمرضى القلب والمصابون بإنخفاض ضغط الدم.