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Research article

THE EFFECT OF VERAPAMIL AND DILTIAZEM ON CARDIAC STIMULANT EFFECT OF ADRENALINE AND CALCIUM CHLORIDE ON ISOLATED FROG HEART

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ABSTRACT

Background: Calcium channel blockers block voltage dependent L-type of calcium channel and thus reduce the frequency of opening of these channels in response to depolarization**.** The result is a marked decrease in transmembrane calcium current associated with long lasting relaxation of vascular smooth muscle, reduction in contractility in cardiac muscle, decrease in pacemaker activity in the SA node and decrease in conduction velocity in the AV node. Among Calcium channel blockers verapamil, is cardio selective, nifedipine is vascular smooth muscle selective, while diltiazem exhibits intermediate selectivity. **Methods:** In the present study, the effect of two Ca^{++} channel blocker, Verapamil and Diltiazem were compared on the isolated frog heart by using adrenaline & calcium chloride as standard on frog heart contractility. **Results and conclusion:** Adrenaline and calcium chloride increased the amplitude of contraction of isolated perfused frog heart. The L- type of Ca^{2+} channel blockers verapamil and diltiazem produced dose dependent (2µg, 4µg, 8µg, and 16µg) reduction in the amplitude of contraction produced by calcium chloride in isolated perfused frog heart. There was no statistical significant difference ($p > 0.05$) between the inhibitory effect of diltiazem and verapamil on calcium chloride induced contraction of isolated frog heart.

Keywords : Verapamil , Diltiazem,Cardiac stimulant effect, Adrenaline, $Cacl_2$

INTRODUCTION

The incidence of ischemic heart diseases is high all over the world especially in urban population[1]. Risk factors are age, male sex, hyperlipidemia, smoking, hypertension, diabetes and family history[2]. Calcium channel blockers are used for treatment of heart diseases which include angina, hypertension & arrhythmia [3]. Among Calcium channel blockers verapamil, is cardio selective (↓HR, contractility,& conduction velocity), nifedipine is vascular smooth muscle selective, while diltiazem exhibits intermediate selectivity.[4] so this study was planned to

compare the cardiac depressant effect of the two calcium channel blockers verapmil and diltiazem.

Aims and Objectives The aim of the present study was to compare cardiac depressant effects of two L-type of calcium channel blockers, verapamil & diltiazem in Calcium chloride-induced inotropic effect on isolated frog (*Rana tigrina*) heart preparation.

MATERIAL AND METHODS

The study was conducted in the Amphibian Laboratory in the department of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally during the period from 13/10/2009 to 12/04/2011.[5] Frogs (*Rana tigrina*) 12 in numbers, weighing about 150 – 250g, reared in the Central animal house of the Kamineni Institute of Medical Sciences (KIMS) were used. The present study was approved by Institutional Animal Ethcs Commeette.

Double pithed frog was fastened over the frog board and the heart was removed and mounted using standard procedures described by Ramesh KV et al[5] The Normal contraction of the heart was recorded for 3 minutes by using frog ringer solution. Adrenaline 2µg was added into the vertical limb of the Syme's cannula and response was recorded to test the sensitivity of the tissue.

Calcium chloride 2 mg was added to symes cannula and increase in responses were recorded. Then 2 µg verapamil was added to the Syme's cannula and the contraction of the heart was recorded and the difference from normal contraction (inhibition in height of contraction) was recorded. The procedure was repeated by adding calcium channel blocker verapamil in the dose of 4, 8, 12, and 16 µg respectively. The procedure was repeated in six frog hearts. The above procedure was repeated with diltiazem in the same dose (2, 4, 8, 12, and 16 µg) respectively.

Calcium chloride solution (standard) 2 mg was added each time in to ringer solution because calcium channel blockers verapamil & diltiazem act on calcium chloride induced heart contraction.[6]

Drugs used in the experiment:

a) Diltiazem 5mg/ml vial (Dilgard cipla)
b) Verapamil 5mg/2ml amp (Samarth life science pvt. Ltd.)
c) Adrenaline 1mg/ml amp (Neon laboratories pvt. Ltd.)
d) Calcium chloride (1%) 10mg/ml (Accord labs)

RESULTS

The effect of diltiazem (2µg, 4µg, 8µg, 16µg) pretreatment on calcium chloride induced increase in the amplitude of contractions was also calculated. Diltiazem pretreatment reduced the $CaCl_2$ produced increase in amplitude of contraction in dose dependent quantity, i.e 2µg, 4µg, 8µg, 16µg.

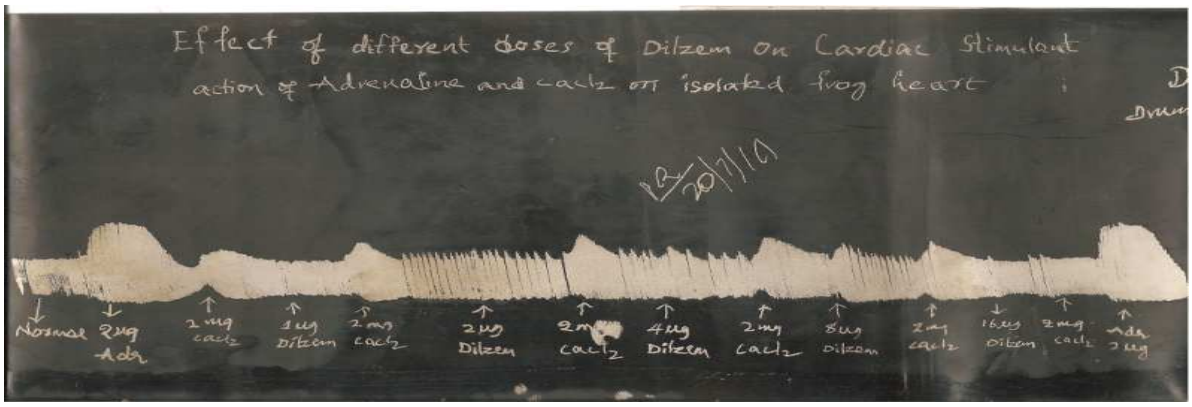

Fig.1: **Inhibitory effect of Diltiazem.**

Adrenaline (2µg) was added to the biophase to conform the normal functioning of heart as adrenaline is a standard drug which increases the contraction of heart. Subsequently 2 mg of calcium chloride was added to the biophase and the increase in contraction of heart compared to the normal contraction was recorded.

Verapamil pretreatment reduced the $CaCl_2$ produced an increase in amplitude of contraction in dose dependent quantity, i.e. 2µg, 4µg, 8µg, 16µg.

Pre-treatment with diltiazem and Verapamil in the above quantities had not modified the adrenaline induced increase in amplitude of contractions suggesting more doses of Verapamil and diltiazem pre-treatment for blocking the adrenaline response or probably L type of Calcium channels may not be involved in adrenaline response in isolated perfused frog heart.

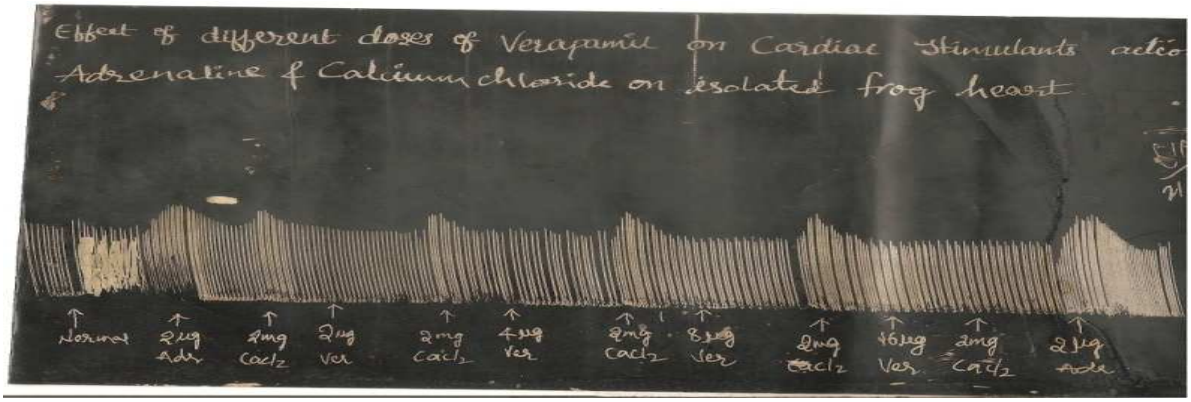

Fig.2: Inhibitory Effect of Verapamil

Table 1: Comparison of antagonist effect of diltiazem versus verapamil

Sr.No	Dose (µg)	Diltiazem Height of contraction (mm)	Verapamil Height of contraction (mm)	t value	p value
1	2	30.83±2.37	24.00±2.76	1.87	0.09
2	4	29.16±2.30	23.33±3.38	1.42	0.18
3	8	27.33±2.40	20.50±3.17	1.71	0.11
4	16	23.16±4.05	20.83±3.02	0.461	0.65

*Data presented as mean ±SD

Comparison of antagonism of $CaCl_2$ produced an increase in amplitude of contraction by diltiazem and Verapamil showed no statistical significance (P>0.05) by applying student unpaired‘t’test

DISCUSSION

Adrenaline (2µg) and $CaCl_2$ (2mg) administration through the Symes cannula in the biophase produced an increase in amplitude of contraction of isolated perfused frog heart preparations. Pre-treatment with the known L-type Ca^{++} channel blockers diltiazem and verapamil reduced the $CaCl_2$ responses in dose dependent quantity. Both diltiazem and verapamil in the doses of 16µg completely blocked $CaCl_2$ induced increase in the amplitude of contractions.

Comparison of antagonism of $CaCl_2$ produced an increase in amplitude of contraction by Diltiazem

and Verapamil showed no statistical significance (P>0.05) by applying student unpaired "t" test.

SUMMARY AND CONCLUSION

Adrenaline and calcium chloride increased the amplitude of contraction of isolated perfused frog heart. The L- type Ca^{++} channel blockers verapamil and diltiazem produced dose dependent (2µg, 4µg, 8µg, and 16µg) reduction in the calcium chloride produced increase in amplitude of contraction of isolated perfused frog heart. There was no statistical significant difference ($p > 0.05$) between the inhibitory effect of Diltiazem and Verapamil on $CaCl_2$ induced contraction on isolated frog heart. Further studies are needed to explore the role of calcium channels in the adrenaline induced positive inotropic effect (increase in amplitude of contraction)

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