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PROTECTIVE EFFECT OF CLONIDINE AGAINST THE CARDIOTOXIC EFFECTS OF OUABAIN IN CAT

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Abstract : Cardiac arrhythmias and cardiac arrest were induced in pentobarbitone anaesthetised cats by slow intravenous infusion of ouabain. The dose of ouabain required for the induction of the stages of arrhythmias and caridiac arrest and the maximum pressor effect induced by ouabain were assessed in control and clonidine pretreated cats. Clonidine caused significant delay in the onset of cardiotowic effects of ouabain and inhibition of the maximum pressor effect of ouabin. The inhibition of cardiotoxic and pressor effects of ouabain may be the result of clonidine's effect on the neural components of ouabain action.

Key words : arrhythmias cardiotoxicity clonidine ouabain

INTRODUCTION

Clonidine, a centrally acting antihypertensive agent, decreases the blood pressure by inhibiting the spontaneous discharges from the splanchnic and cardiac nerves (1). Its major actions are mediated through the stimulation of central alpha^2 adrenoceptors, the net result of which is a diminished sympathetic outflow (2). The ability of cardiac glycosides to increase the release of catecholamines and other neurotransmitters from a variety of tissues has been well documented (3, 4), and this is considered to be the major contributor to the cardiac abnormalities caused by them. It has been demonstrated that selective alpha^2 adrenoceptor stimulation and alpha^1 adrenoceptor blockade protect against ventricular arrhythmias induced by digitalis glycosides (5, 6). Considering the above findings, the present study was undertaken to evaluate the effect of clonidine on the cardiotoxic and pressor effects of ouabain in cat.

METHODS

Mongrel cats of either sex weighing between 2.0-3.5 Kg were utilized in this study. The method described by Sekiya and Vaughan Williams (7) was used with some modifications to induce cardiac arrhythmias, cardiac arrest and pressor effect in cats. The animals were anaesthetised with pentobarbitone sodium (50 mg/kg) injected intravenously. Positive pressure artificial respiration was maintained throughout the experiment through the tracheal cannula by means of a Palmer respiratory pump. Respiratory rate was adjusted at 30 strokes/minute and volume at 10 ml/kg body weight. The left femoral vein was cannulated and connected to a Palmer slow infusion pump for the administration of ouabain. The left common carotid artery was cannulated and connected to a mercury manometer for the recording of blood pressure. ECG (Limb lead II) was recorded on a BPL Cardiart machine and heart rate was monitered from the ECG signals. Clonidine was administered (iv) 10 min before the starting of the ouabain infusion. Ouabain solution (100 μg/ml) was continuously infused at a rate of 0.5 ml/min. The onset of early arrhythmias (appearance of octopic beats, prolonged P-R intervals, P wave nt followed by QRS complex), ventricular fibrillation and cardiac arrest were noted. The amount of ouabain required per kg body weight, to produce these stages of arrhythmia and cardiac arrest were calculated in control and clonidine pretreated cats.

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The peak rise in blood pressure due to ouabain was noted in each experiment. Clonidine (Unichem) was dissolved in normal saline and was administered at doses of 100 and 200 μg/kg (iv). The results were expressed as mean ± SEM and were statistically analysed using Student's 't' test.

RESULTS

(a) *Haemodynamic effects of Clonidine :* Intravenous injection of clonidine produced a rise in blood pressure. The full pressor effect to clonidine was obtained within 2 min of administration and thereafter the blood pressure started falling gradually. The rise in blood pressure was accompanied by significant bradycardia. The blood pressure readings 10 min after clonidine administration were not significantly different from control values. The reduction in heart rate caused by clonidine was maintained at significantly lower levels even after 10 min. The haemodynamic profile of intravenously administered clonidine in cats is shown in Table I.

TABLE I : Haemodynamic effects of clonidine in cat

	'n'	*Clonidine* (μg/kg)	*Predrug*	*Postdrug* 1 min	*Postdrug* 10 min
Blood pressure (mm/Hg)	5	100	134±7	169±5	135±5
	6	200	127±6	176*±3	129±5
Heart Rate (bt/min)	5	100	227±8	176*±10	174*±11
	6	200	216±20	136*±9	140*±6

Values are expressed as mean±SEM. *p<0.001 compared to predrug values.

(b) *Effect of clonidine on ouabain induced cardiotoxicity :* Ouabain infusion produced rise in blood pressure and initial abnormal rhythms in all animals. This initial arrhythmia was followed by ventricular fibrillation and cardiac arrest. Clonidine at doses of 100 and 200 μg/kg, given intravenously failed to protect the animals against initial arrhythmias. Even though 100 μg/kg clonidine showed some delay in the incidence of ventricular fibrillation and cardiac arrest, it was not significant statistically. Clonidine at a dose of 200 μg/kg produced statistically significant delay in the onset of ventricular fibrillation and cardiac arrest. The amounts of ouabain required to produce the arryhthmic stages and cardiac arrest in cats are shown in Table II.

TABLE II : Effect of clonidine on the doses of ouabain required to produce early arrhythmias (EA), ventricular fibriliation (VF) and cardiac arrest (CA) in cat.

Drug/Dose	*n*	*EA*	*VF*	*CA*
Control (N. Saline)	6	174.57±8.75	237.16±5.10	255.81±7.36
Clonidine				
100 μg/kg	5	167.66±12.77	248.37±13.60	273.24±17.56
200 μg/kg	6	181.95±4.32	300.73*±11.12	317.89*±9.31

Values are expressed as mean±SEM of the doses of ouabain (μg/kg, body weight). * P < 0.001 compared to controls

(c) *Effect of clonidine on the pressor effect of ouabain :* The peak pressor effect induced by ouabain infusion was found to be just prior to the incidence of ventricular fibrillation in control and

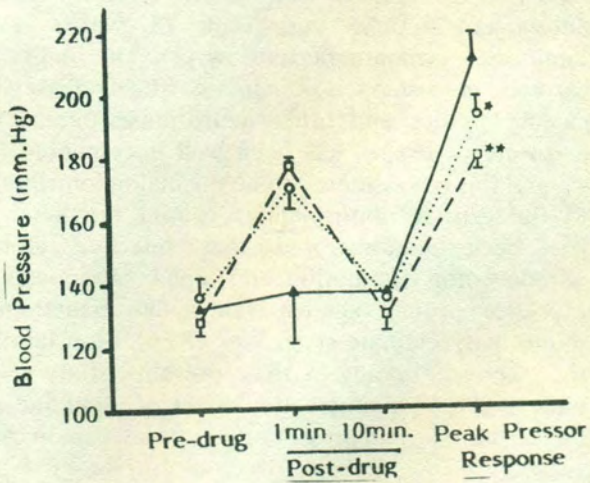

Fig. 1: Effect of clonidine on the pressor effect inducer by ouabain

▲ ▲ Control ○ ○ Clonidine 100 μg/kg
□ □ Clonidine 200 μg/kg. Values are represented as mean ± SEM of 5-6 experiments.
*P<0.01 **P<0.001 compared to control.

drug treated animals. Clonidine produced a dose dependent inhibition of this maximum pressor effect. The pressor response induced by ouabain in control animals and its inhibition in cats pretreated with clonidine are shown in Fig 1.

DISCUSSION

Activation of the presynaptic alpha^2 adrenoceptors leads to reduction in the secretion of noradrenaline per nerve impulse (8). Clonidine a preferential alpha^2 adrenoceptor agonist decreases sympathetic tone through its action on the central nervous system (9). It was suggested that the reduction in sympathetic tone caused by clonidine is not only the result of reduction in the release of noradrenaline from the sympathetic nerve endings but also through a decrease in the fuction of the adrenal medulla (10).

In the present study, clonidine protected cats from the ouabain induced cardiac arrhythmias and cardiac arrest by increasing the dose of ouabain required to produce these stages. The incidence of these arrhythmias and cardiac arrest and the general pattern of arrhythmias were not altered by clonidine in these experiments.

The cardotoxic effects of digitalis involve different components such as direct effects on the mycordium, the sympathetic nervous system and the adrenal medulla (11). Cardiac glycosides cause an increase in transmitter overflow from nerve endings both in brain and a variety of other tissues (12, 13, 14). There appears to be a close correlation between the ability of clonidine to reduce sympathetic tone and its protection in digitalis induced arrhythmias, which are mediated mainly through sympathetic stimulation and release of catecholamines (15). Changes in the heart rate can alter the onset of action of digitalis and its uptake into the myocardium (16). Bradycardia delays the onset of action and decreases the myocardial uptake of digitalis, whereas tachycardia enhances both. Clonidine produced a dose dependent reduction in the heart rate of anaesthetised cats. This presumably had some effect in the delayed toxicity of ouabain.

It was further observed in this study that clonidine inhibited ouabain induced pressor response in a dose dependent manner. The peak pressor effect due to ouabain was shortly before or during the first signs of cardiac abnormalities. The pressor effect of ouabain is considered primarily to be the result of the activation of the sympathetic system (5). So the inhibition of the pressor response of ouabain by clonidine may reflect inhibition of neurally mediated effects of ouabain. Clonidine decreases noradrenaline release rate, an effect blocked by yohimbine, an alpha^2 adrenoceptor blocker and not by corynanthine, an alpha^1 adrenoceptor blocker (17). And this can be the major factor which played a significant role in delaying the cardiotoxic effects of ouabain in cat. It is possible that there is correlation between the reduction of the pressor effect and the reduction in the ouabain cardotoxicity; and both these effects are caused by the effect of clonidine on the neural components of ouabain action.

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