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Protective action of clonidine against the arrhythmogenic and lethal effects of ouabain in guinea-pigs

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1 Clonidine (1.25, 2.5 and 5.0 $\mu g\,kg^{-1}$) was studied for its effect on the cardiac arrhythmias and lethality induced by slow intravenous infusion of ouabain in guinea-pigs.

2 Clonidine produced significant delays in the onset of the arrhythmic stages and lethality. However, clonidine did not offer any such protection in reserpinised guinea-pigs, whereas its effects were unaltered in atropinized guinea-pigs.

3 Idazoxan (100 $\mu g\,kg^{-1}$, i.v.) abolished the antiarrhythmic effect of clonidine whereas corynanthine (1 $mg\,kg^{-1}$, i.v.) had no such effect.

4 Clonidine inhibited the rate of the ouabain-induced rise in blood pressure and the peak pressor response.

5 In isolated paced left atria of the guinea-pig, clonidine (3.75×10^{-4} M) did not offer any protection against rapid and/or irregular extrasystolic contractions induced by ouabain.

6 It is concluded that the antiarrhythmic effect of clonidine is due to its effects on the indirect neural components of digitalis toxicity mediated by the stimulation of α_2-adrenoceptors, without any direct anti-arrhythmic effect on the myocardium.

Keywords: Clonidine; arrhythmia; digitalis; ouabain-induced cardiotoxicity

Introduction

Digitalis, one of the most widely used drugs in the treatment of congestive heart failure, frequently produces a wide variety of cardiac arrhythmias, when high plasma concentrations are reached (Smith *et al.*, 1984). The pathophysiology of digitalis-induced arrhythmias involves glycoside-induced centrally mediated alterations of the autonomic nervous system (Roberts *et al.*, 1967; Saxena & Bhargava, 1975; Gillis & Quest, 1980) apart from the well established direct action on the myocardium (Ferrier, 1977). The role of the sympathetic nervous system in the genesis and perpetuation of cardiac arrhythmias induced by cardiac glycosides is receiving particular attention at the moment, in order to understand and prevent the occurrence of these life-threatening cardiac arrhythmias. Surgical or pharmacological procedures that decrease sympathetic nerve function also decrease digitalis toxicity. Even though many groups of drugs which decrease sympathetic tone, like β-adrenoceptor antagonists (Kelliher & Roberts, 1974; Hernandez & Serrano, 1982; Tripathi & Thomas, 1986), ganglion blocking agents (Gillis *et al.*, 1975), drugs interfering with catecholamine storage and release (Levitt & Roberts, 1967; Saito *et al.*, 1974) were studied and found effective against cardiac arrhythmias induced by various cardiac glycosides, there has been no serious attempt to study the effect of α_2-adrenoceptor agonists against digitalis-induced cardiotoxic effects. Numerous studies have proposed that clonidine reduces blood pressure by a reduction in sympathetic tone through activation of central α_2-adrenoceptors (Schmitt, 1977; Isaac, 1980; Van Zwieten & Timmermans, 1983). Relatively high doses of clonidine were reported to show antiarrhythmic properties against ouabain-induced arrhythmias (Pace & Gillis, 1976; Lechat & Schmitt, 1982; Thomas & Tripathi, 1986). The present study aimed to examine the effect of lower doses of clonidine (which act specifically on α_2-adrenoceptors) against ouabain-induced arrhythmias and lethality and to examine the nature of its antiarrhythmic action.

Methods

Arrhythmias and lethality induced by intravenous infusion of ouabain in guinea-pigs

Albino guinea-pigs of either sex in the weight range of 350–450 g were used in this study. The method described by Thomas & Tripathi (1986) was employed. The animals were anaesthetized by an intraperitoneal injection of pentobarbitone sodium (60 $mg\,kg^{-1}$). Positive pressure artificial respiration was maintained throughout the experiment by means of a rodent respiratory pump (Palmer) at the rate of 45 strokes min^{-1} and volume was adjusted at 1.0 ml 100 g^{-1} body weight. The left common carotid artery was cannulated and connected to a Bentley-Trantec physiological pressure transducer and the blood pressure was recorded on a Gemini Recorder (Ugo Basile, Model 7070). The right jugular vein was cannulated for the infusion of ouabain and administration of test drugs. Limb lead II ECG was recorded on a Grass Polygraph (Model 7D) and heart rate was calculated from ECG signals. Ouabain solution (80 $\mu g\,ml^{-1}$) was continuously infused at the rate of 100 $\mu l\,min^{-1}$. The amount of ouabain required per kg body weight for the onset of ventricular premature beats (VPB), ventricular tachycarrhythmias (VT) (denoted by ventricular tachycardia or ventricular fibrillation associated with a sudden fall in blood pressure) and lethality (L) was determined in control and clonidine-treated animals.

Pressor effect induced by ouabain

During the course of the experimental procedure described above, blood pressure was recorded every 2 min of ouabain infusion until the onset of VT. The rate of rise of blood pressure induced by ouabain and the peak pressor effect attained was noted for control and clonidine (2.5 $\mu g\,kg^{-1}$)-treated groups.

Interaction studies

In order to study the nature of the antiarrhythmic action of clonidine, the following sets of experiments were conducted using the method described above.

(1) Two groups of six guinea-pigs each were given reserpine (5 $mg\,kg^{-1}$, i.m.) 24 h before the experiment. The first group was administered clonidine at a dose of 2.5 $\mu g\,kg^{-1}$, i.v. and the rest given normal saline 10 min prior to the ouabain infusion.

(2) Corynanthine hydrochloride (1 $mg\,kg^{-1}$) was administered intravenously to six animals 10 min before clonidine (2.5 $\mu g\,kg^{-1}$), while another three groups of six animals each

were administered clonidine, corynanthine and normal saline respectively.

(3) Idazoxan (100 $\mu g\,kg^{-1}$, i.v.) was administered to six guinea-pigs and after 10 min, clonidine was given at a dose of 2.5 $\mu g\,kg^{-1}$, i.v. Another three groups of six animals each were also studied, one as control and the others were treated with clonidine and idazoxan.

(4) One group of five animals was pretreated with atropine sulphate (2 $mg\,kg^{-1}$, i.v.) and another five animals with atropine and clonidine (2.5 $\mu g\,kg^{-1}$) before the infusion of ouabain.

Ouabain-induced arrhythmias in paced guinea-pig left atria

Guinea-pigs of either sex (350–450 g) were killed by a hammer blow on the head and the heart was quickly excised and transferred to a Petri dish containing Ringer Locke solution (composition in mM: NaCl 154, KCl 5.6, $CaCl_2$ 2.2, $NaHCO_3$ 6.0 and glucose 5.5). The left atrium was dissected free and hung vertically with the base anchored to a stimulating electrode and the other end tied to an isometric transducer (type DYO, Ugo Basile, Italy), in a 50 ml organ bath containing Ringer Locke Solution at 37 ± 1°C and buffered to pH 7.4 by saturation with oxygen. After a lapse of 10 min, the atrium was driven at a constant rate of 1 Hz at intervals of 1000 m and duration of 2 ms at twice the threshold voltage delivered by a square wave pulse generator (Grass, Model S44, U.S.A.).

After an initial stabilization period of 45 min during which the tissue was washed every 15 min and the threshold voltage checked, ouabain at a concentration of 1.0×10^{-6} M was added and the atrial contractions were recorded continuously on a Ugo Basile Microdynamometer. The time taken for the development of arrhythmia (spell I), defined as 30 s of continuous rapid and/or irregular extrasystolic contractions, was noted. The tissue was washed four times and allowed to stabilize for 60 min. During this period, the tissue was washed every 15 min and the threshold voltage checked. At the end of this stabilization period, ouabain (1.0×10^{-6} M) was once again added and the onset and duration of arrhythmic contractions (spell II) were noted ($n = 6$).

In another set of experiments, clonidine at concentrations of 3.75×10^{-6} M, 3.75×10^{-5} M and 3.75×10^{-4} M ($n = 5$ for each concentration in separate experiments) was added to the bath after spell I and the onset and duration of spell II were noted.

Drugs

The following drugs were used in this study: clonidine hydrochloride (Unichem Laboratories), corynanthine hydrochloride (Sigma), idazoxan (Reckitt & Colman), ouabain octahydrate (Sigma), reserpine and atropine sulphate (Boehringer Ingelheim). All drugs except reserpine were dissolved in normal saline for injection. Reserpine was dissolved in minimum amount of glacial acetic acid, the pH adjusted to 5.5 by 0.1 N NaOH and diluted with distilled water to give a concentration of 1 $mg\,ml^{-1}$.

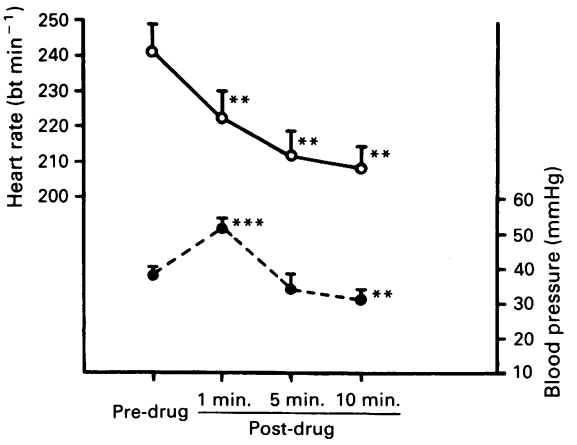

Figure 1 The effect of clonidine on heart rate (○) and blood pressure (●) in guinea-pig. Values are represented as mean of 5–6 experiments with s.e.mean by vertical bars. ** $P < 0.01$; *** $P < 0.001$. Clonidine 2.5 $\mu g\,kg^{-1}$.

Statistical analysis

Statistical analysis was performed by use of Student's t test. Significance was established when the probability value was less than 0.05. All values were expressed as mean ± s.e.mean.

Results

Haemodynamic effects of clonidine

Guinea-pigs anaesthetized with sodium pentobarbitone showed a basal mean arterial blood pressure of 38 ± 2 mmHg and heart rate of 241 ± 8 beats min^{-1}. Clonidine (2.5 $\mu g\,kg^{-1}$) on intravenous administration, produced an immediate significant reduction in the heart rate ($P < 0.01$). Further lowering was seen at the end of 5 and 10 min periods ($P < 0.01$). A biphasic response was observed on blood pressure. The initial statistically significant rise was transient and was followed by a gradual fall. The blood pressure value at the end of 10 min was significantly lower ($P < 0.01$) when compared to the control value (Figure 1).

Effect of clonidine on cardiac arrhythmias and lethality

Ouabain infusion produced initial bradyarrhythmias, ventricular premature beats, ventricular tachycardia (mostly associated with spells of ventricular fibrillation) and cardiac arrest in guinea-pigs. Initial bradyarrhythmias occurred almost at the same time as VPB and in some cases VPB was the first arrhythmic stage. Clonidine at a dose of 1.25 $\mu g\,kg^{-1}$ significantly increased the dose of ouabain required to cause VT. However, at this dose level, there was no significant alteration in the dose of ouabain required to produce VPB. At doses of 2.5 and 5.0 $\mu g\,kg^{-1}$ clonidine, there were significant increases in the dose of ouabain needed to elicit VPB and VT. Similarly, these doses caused a significant increase in the lethal dose of ouabain, whereas there was no significant difference at 1.25 $\mu g\,kg^{-1}$ dose level (Table 1).

Table 1 Effect of clonidine on ouabain-induced cardiac arrhythmias and lethality in guinea-pigs

Drug ($\mu g\,kg^{-1}$)	n	*VPB*	*VT*	*L*
Control	6	183.3 ± 11.2	209.4 ± 16.7	298.0 ± 6.0
Clonidine				
1.25	6	181.3 ± 5.2	282.0 ± 24.9*	337.9 ± 22.1
2.50	6	239.3 ± 11.6**	342.1 ± 13.9***	411.4 ± 14.4***
5.00	6	244.6 ± 13.6**	372.1 ± 10.9***	459.5 ± 15.8***

Unpaired 't' test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Values are expressed as mean ± s.e.mean of the doses of ouabain ($\mu g\,kg^{-1}$ body weight) required to cause ventricular premature beats (VPB), ventricular tachyarrhythmias (VT) and lethality (L).

Effect of clonidine on the ouabain-induced pressor response

A gradual rise in blood pressure was observed after intravenous infusion of ouabain. The peak pressor response was obtained just before the onset of VT. The rise in blood pressure induced by ouabain and its inhibition by clonidine is shown in Figure 2. The rate of rise of blood pressure was significantly ($P < 0.001$) lower in clonidine pretreated guinea-pigs than in controls. Similarly, the peak pressor response obtained in clonidine pretreated animals was significantly ($P < 0.05$) lower than that of controls (Figure 3). Corynanthine, the α_1-adrenoceptor antagonist could not influence the inhibition of the pressor effect caused by clonidine but idazoxan, the α_2-adrenoceptor antagonist completely abolished it.

Interaction studies

The dose of ouabain needed to induce VPB, VT and L were higher in reserpinised guinea-pigs than in normal controls. In reserpinsed animals, clonidine did not alter the arrhythmogenic and lethal effects of ouabain as the doses of ouabain needed to produce these effects were not significantly different in clonidine-treated, compared to control animals after reserpinization (Table 2). Corynanthine, an α_1-adrenoceptor blocking agent, *per se* did not have any significant effect on ouabain-induced arrhythmias in the guinea-pig. It also failed to modify the antiarrhythmic effect of clonidine significantly. Idazoxan, the specific α_2-adrenoceptor antagonist, showed significant inhibition ($P < 0.05$ for VPB, $P < 0.01$ for VT and L)

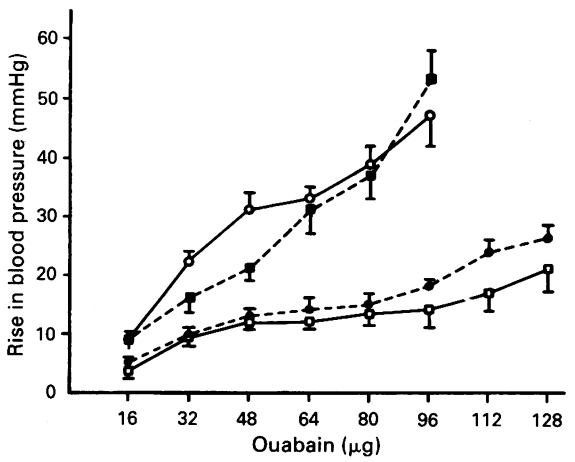

Figure 2 Effect of clonidine on the ouabain-induced rate of rise of blood pressure in guinea-pig. Values are expressed as mean of 5–6 experiments; vertical bars show s.e.mean. Control (○); clonidine ($2.5\,\mu g\,kg^{-1}$) (●) and clonidine after coryanthine ($1\,mg\,kg^{-1}$) (□) and idazoxan ($100\,\mu g\,kg^{-1}$) (■).

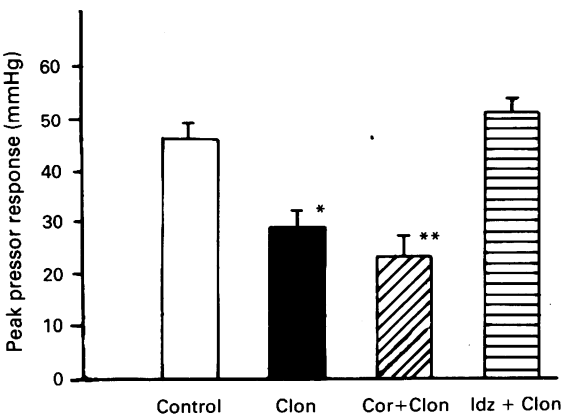

Figure 3 Effect of clonidine on the peak pressor response induced by ouabain: Clonidine (Clon) $2.5\,\mu g\,kg^{-1}$; coryanthine (Cor) $1\,mg\,kg^{-1}$; idazoxan (Idz) $100\,\mu g\,kg^{-1}$. * $P < 0.05$; ** $P < 0.01$.

of the antiarrhythmic effect of clonidine (Table 3). Atropinisation itself did not have any effect on the arrhythmogenic or lethal effect of ouabain whereas it potentiated the effect of clonidine against lethality caused by ouabain. The antiarrhythmic effect of clonidine was not altered significantly by atropine even though there was a general increase in the dose of ouabain needed to induce VPB and VT (Table 2).

Effect of clonidine on ouabain-induced arrhythmias in isolated paced left atria of guinea-pigs

Clonidine at concentrations of 3.75×10^{-6} M, 3.75×10^{-5} M and 3.75×10^{-4} M did not accord any protection against ouabain-induced arrhythmias in isolated paced left atria of guinea-pigs (Table 4), whereas propranolol at a concentration of 1.69×10^{-5} M and lignocaine at a concentration of 3.46×10^{-5} M completely protected the tissues from ouabain-induced arrhythmias.

Discussion

In the present study, clonidine at very low doses significantly increased the ouabain dose required to produce VPB, VT and L. The incidence and pattern of these stages remained unaltered. This result is in conformity with the previous studies with clonidine, even though used in higher doses. Pace & Gillis (1976) used $6–60\,mg\,kg^{-1}$ (i.v.), whereas Lechat & Schmitt (1982) employed $10–300\,\mu g\,kg^{-1}$ (i.v.) and Thomas & Tripathi (1986) used $500\,\mu g\,kg^{-1}$ (i.p.) and reported similar results. Dose-range is a vital factor as far as the specificity of clonidine for α_2-adrenoceptors is concerned. In higher doses, clonidine acts upon α_1-adrenoceptors also (Cavero & Roach, 1978) and exhibits membrane stabilizing properties (Hoefke & Kobinger, 1966). Hence, the present study was done with very low doses of clonidine in an effort to identify its antiarrhythmic activity through its α_2-adrenoceptor stimulant properties.

Central α_2-adrenoceptors in the brain stem have been identified as the target of clonidine-like centrally acting antihypertensive drugs (Kobinger, 1978). Clonidine in lower doses acts specifically on α_2-adrenoceptors and numerous studies have proposed that the drug reduces blood pressure by a reduction in sympathetic tone by activation of central α_2-adrenoceptors (Schmitt, 1977; Isaac, 1980; Van Zwieten & Timmermans, 1983).

Digitalis-induced arrhythmias are the outcome of a complex interplay of actions on the myocardium, the central nervous system and the autonomic nervous system. Since membrane stabilizing properties have been reported for clonidine (Hoefke & Kobinger, 1966) it could in principle act against the direct or indirect components of ouabain toxicity. Left atrial models of ouabain-induced arrhythmias are the result of the direct effect of ouabain as they exclude the indirect centrally mediated reflex effects (Thomas & Varma, 1990). In the present study, clonidine up to a concentration of 3.75×10^{-4} M failed to offer any protective effect in this tissue. In these concentrations, clonidine may be devoid of any membrane stabilizing action and this rules out any direct effect of clonidine on the myocardium as the cause of its antiarrhythmic action. In the same preparation, propranolol at a concentration of 1.69×10^{-5} M and lignocaine at 3.46×10^{-5} M afforded complete protection to the tissue against ouabain-induced arrhythmias. This also indicates that clonidine might be acting upon the indirect components of digitalis toxicity. In reserpinized guinea-pigs, clonidine was unable to alter the arrhythmogenic and lethal doses of ouabain. In reserpinized animals the effect produced by ouabain would be comparable to a situation where indirect (sympathetic) components of its toxic effects are removed or inhibited. Thus the inability of clonidine to alter the arrhythmogenic and lethal effects of ouabain in reserpinized guinea-pigs supports the assumption that it is the indirect

Table 2 Effect of clonidine on ouabine induced arrhythmias in atropinized and reserpinized guinea-pigs

Drug (Dose)	n	*VPB*	*VT*	*L*
Control	5	205.5 ± 17.0	238.4 ± 13.0	329.8 ± 18.7
Clonidine ($2.5\,\mu g\,kg^{-1}$)	5	269.1 ± 17.8*	339.0 ± 13.3***	387.8 ± 13.4*
Atropine ($2\,mg\,kg^{-1}$)	5	205.8 ± 7.7	251.4 ± 15.7	354.7 ± 10.2
Atr + clonidine ($2\,mg\,kg^{-1} + 2.5\,\mu g\,kg^{-1}$)	5	291.0 ± 16.6	385.4 ± 21.7	449.2 ± 8.6[a]
Reserpine ($5\,mg\,kg^{-1}$)	6	224.9 ± 8.3	292.2 ± 13.7	389.7 ± 5.1
Reserpine ($5\,mg\,kg^{-1}$) + clonidine ($2.5\,\mu g\,kg^{-1}$)	7	232.6 ± 13.1	324.8 ± 16.2	423.8 ± 10.6

Values are expressed as mean ± s.e.mean of the doses of ouabain ($\mu g\,kg^{-1}$ body weight) required to cause ventricular premature beats (VPB), ventricular tachyarrhythmia (VT) and lethality (L).
* $P < 0.05$; *** $P < 0.001$ compared to control. [a] $P < 0.01$ compared to clonidine (Student's t test).

Table 3 Effect of α-adrenoceptor antagonists on the anti-arrhythmic effect of clonidine

Drug (dose)	n	*VPB*	*VT*	*L*
Control	6	183.6 ± 6.1	232.3 ± 15.4	311.2 ± 14.0
Clonidine ($2.5\,\mu g\,kg^{-1}$)	6	230.8 ± 17.4*	330.8 ± 24.1**	392.8 ± 25.1*
Corynanthine ($1\,mg\,kg^{-1}$)	6	175.4 ± 9.4	253.2 ± 21.4	345.9 ± 26.5
Cor + Clon ($1\,mg\,kg^{-1} + 2.5\,\mu g\,kg^{-1}$)	6	249.1 ± 6.4***	363.1 ± 20.0***	428.8 ± 15.5***
Control	6	210.8 ± 10.5	250.2 ± 10.9	336.0 ± 16.9
Clonidine ($2.5\,\mu g\,kg^{-1}$)	6	287.9 ± 19.3**	369.9 ± 25.8**	426.3 ± 23.2**
Idazoxan ($100\,\mu g\,kg^{-1}$)	6	196.4 ± 14.8	231.4 ± 19.6	322.7 ± 28.9
Idazoxan + clonidine ($100\,\mu g\,kg^{-1} + 2.5\,\mu g\,kg^{-1}$)	6	227.6 ± 13.1[a]	265.0 ± 14.5[b]	324.8 ± 16.0[b]

Values are expressed as mean ± s.e.mean of the doses of ouabain ($\mu g\,kg^{-1}$ body weight) required to cause ventricular premature beats (VPB), ventricular tachyarrhythmia (VT) and lethality (L).
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared to respective controls. [a] $P < 0.05$; [b] $P < 0.01$ compared to respective clonidine values (Student's t test)

components of digitalis toxicity that are acted upon by clonidine.

Clonidine has roughly ten times more affinity for α_2- than for α_1- adrenoceptors (Bousquet & Schwartz, 1983).However, many investigators have demonstrated the involvement of α_1-adrenoceptors in some of the pharmacological actions of clonidine in the periphery (Hoefke & Kobinger, 1966; Drew, 1976) and in the central nervous system (Cavero & Roach, 1978; Timmermans *et al.*, 1979; Hamilton & Longman, 1982). Corynanthine, a preferential α_1-adrenoceptor antagonist (Weitzell *et al.*, 1979; Van Zwieten & Timmermans, 1983) did not alter the antiarrhythmic effect of clonidine in this study, thereby excluding the involvement of α_1-adrenoceptors in its effect. Idazoxan, the highly selective α_2-antagonist (Clifford *et al.*, 1985; Al-Damluji *et al.*, 1988) completely abolished the protective effect of clonidine against the ventricular arrhythmias and lethality pointing to the involvement of α_2-adrenoceptors in this action.

Table 4 Effect of clonidine on ouabain-induced arrhythmia in isolated paced left atrium of guinea-pig

Drug (M)	n	*Pre-drug* *Onset* (min)	*Post-drug* *Onset* (min)	*Post-drug* *Duration* (min)
Control	6	6.13 ± 0.80	6.45 ± 0.59	>30
Clonidine				
3.75 ± 10^{-6}	5	6.43 ± 0.34	7.60 ± 0.41	>30
3.75 ± 10^{-5}	5	6.73 ± 0.61	5.89 ± 0.94	>30
3.75×10^{-4}	5	6.30 ± 0.84	6.59 ± 0.30	>30
Lignocaine				
3.46×10^{-5}	6	7.15 ± 0.81	—*	—*
Propranolol				
1.69×10^{-5}	6	6.90 ± 0.24	—*	—*

Values are expressed as mean ± s.e.mean of the time taken for the onset of extrasystolic contractions induced by ouabain (1.0×10^{-6} M).
* Complete protection.

Stimulation of central α_2-adrenoceptors by clonidine induces an enhanced vagal tone (Timmermans & Van Zweiten, 1977). There was no inhibition of its antiarrhythmic effect in atropinized guinea-pigs, ruling out enhanced vagal tone as the cause of its antiarrhythmic activity, whereas there was a significant increase in the lethal dose of ouabain in animals treated with atropine and clonidine compared to those treated with clonidine alone, indicating a potentiation of the effect of clonidine. It has been suggested that activation of muscarinic receptors by ouabain can cause the enhancement of catecholamine secretion (Yamada *et al.*, 1989). Whether the muscarinic blockade helped in the potentiation of the protective effect requires further examination and study.

Elevation in blood pressure induced by ouabain results primarily from activation of the sympathetic nervous system (Trzeciakowski, 1985). In the guinea-pig, digitalis glycosides induce the release of catecholamines by an action on the central nervous system and this is responsible for its pressor effects. This pressor effect is produced by the stimulation of

α_1-adrenoceptors and is suppressed by α_1-blockade and not altered by α_2-blockade (Lechat & Schmitt, 1982). In the present study, clonidine significantly inhibited the pressor effects induced by ouabain. The rate of rise of blood pressure and the peak pressor response induced by ouabain were significantly lower in clonidine pretreated guinea-pigs than in controls. The correlation between the inhibition of pressor effects and the reduction in the arrhythmogenic and lethal doses of ouabain indicates that both may be the result of the ability of clonidine to interfere with the neural components of ouabain action. In the interaction studies it was observed that idazoxan abolished the inhibition of the pressor effect caused by clonidine, whereas corynanthiane could not alter it. These results are parallel to their effects on the antiarrhythmic effect of clonidine and support the contention that these two effects are interrelated.

Clonidine causes a diminished release of noradrenaline from the nerve endings supplying the heart by stimulation of peripheral presynaptic α_2-adrenoceptors and decreases plasma catecholamines and peripheral sympathetic tone by stimulation of central α_2-adrenoceptors (Van Zwieten & Timmermans, 1984). Thus it is possible that the protective effect of clonidine against ouabain induced ventricular arrhythmias and lethality is brought about by the same mechanism which is responsible for its antihypertensive effect, i.e. the reduction in the sympathetic tone.

The results of the present study can be summarized as follows. Clonidine in relatively low doses demonstrated significant protection against ouabain-induced ventricular arrhythmias and lethality in guinea-pigs. In isolated paced left atria of the guinea-pig clonidine failed to produce any antiarrhythmic effect against ouabain. The pressor effect induced by ouabain was also inhibited by clonidine. In reserpinized animals, clonidine does not accord any further protection. α_2-Adrenoceptor blockade abolished the antiarrhythmic effect of clonidine whereas α_1-blockade was without any effect. Muscarinic blockade did not alter the antiarrhythmic efficacy of clonidine whereas it potentiated the clonidine-induced protection against lethality caused by ouabain.

It may be concluded that clonidine inhibits the indirect (neural) components of ouabain toxicity by a reduction in sympathetic tone caused by stimulation of α_2-adrenoceptors, without any direct antiarrhythmic actions on the myocardium.

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