PROTECTIVE EFFECT OF ST-93 AGAINST OUABAIN INDUCED ARRHYTHMIAS IN GUINEA PIGS[1, 2].

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Summary : ST-93, a clonidine analog was studied for its antiarrhythmic activity in anaesthetised guinea pigs against ouabain induced arrhythmia. The amount of ouabain required ($\mu g/kg$) for the production of ventricular premature best, Ventricular fibrillation and cardiac arrest was recorded in control and drug treated group of animals. Both ST-93 and clonidine produced significant antiarrhythmic effect in guinea pigs. This protective effect was significantly blocked by yohimbine, suggesting that the antiarrhythmic effect is mediated through presynaptic alpha$_2$-adrenoceptors.

Key words : ST-93 ouabain arrhythmia guinea pig

INTRODUCTION

In the recent past a great number of clonidine analogs have been synthesised and tested for various pharmacodynamic activities. Tolonidine (ST 375), ST 93 and ST 363 have been reported to produce hypotension and bradycardia (3). Alpha-adrenoceptor effects of flutonidine, ST-93, tolonidine and alinidine (ST 567) on various tissues have been recently reported (4,5,9,). Post synaptic and presynaptic alpha-adrenoceptor effects of clonidine are well known. Clonidine has been classified as selective alpha$_2$-adrenoceptor agonist (7), and due to this effect, reduced the arrhythmogenic effects of ouabain in guinea pigs (8). Furthermore, alinidine has also been shown to abolish certain experimental arrhythmias in dogs (1,2).

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In view of the above reports on newer imidazolidine analogs, the present study was aimed to observe the effect of ST 93 (2, chloro, 6-methyl, phenyliminoimidazolidine, hydrochloride) against ouabain induced-arrhythmia in guinea pigs.

MATERIAL AND METHODS

The method for prodction of arrhythmia used was as described by Thomas and Tripathi (11). Albino guinea pigs of either sex (350-450 *g*) were anaesthetized with pentobarbitone sodium (60 *mg/kg*, ip). Positive pressure artificial respiration was maintained throughout the experiment by means of a rodent ventilator at a rate of 45 min and stroke volume, (*1 ml/100 g*). The right jugular vein was cannulated for infusion of ouabain and injection of drugs. Limb lead II ECG was recorded on a Grass polygraph and heart rate was monitored from the ECG signals. Blood pressure was recorded from left carotid artery with Gould Statham pressure transducer. Ouabain solution (80 *μg/ml*) was continuously infused at the rate of 100 *μg/min*. Amount of ouabain required (*per kg* body weight) for the occurence of ventricular premature beats (VPB), ventricular fibrillation (VF) and cardiac arrest (CA) was determined in control (normal saline) and drug treated animals.

Drug treatment : Group I animals were given clonidine (2.5, 5 and 10 *μg/kg, iv*). 10 min before the ouabain infusion. Group II animals were given ST 93 (2.5, 5 and 10 *μg/kg, iv*) 10 min before the ouabain infusion. Group III animals were pre-treated with yohimbine (2 *mg/kg, iv*) 15 min before ouabain infusion. Group IV and V animals were pretreated with yohimbine (2 *mg/kg, iv*) and 15 min later either clonidine (5 *μg/kg*) or ST 93 (5 *μg/kg*) was administered; ouabain infusion was started 10 min after the last treatment. All control animals received equivalent volume of normal saline and 10 min later, ouabain infusion was started.

Blood pressure and heart rate were recorded immediately before a drug treatment and 15 min after the administration of drugs.

Drugs used : Clonidine (Cipla, India), ST 93 (Boehringer Ingelheim, W. Germany), Yohimbine Hcl and ouabain (Sigma) were dissolved in normal saline prior to use.

RESULTS

Haemodynamic effects : The initial mean arterial blood pressure and heart rate of control animals were 51.9 ± 2.4 mm Hg and 242.5 ± 8.3 beats/min, respectively. Infu-

sion of ouabain induced a pressor response. The effect was maximal when the first ventricular arrhythmia occured. The pressor response amounted to 88.8 ± 3.5 mm Hg. Clonidine and ST 93 (*5 μg/kg*) produced significant reduction in blood preasure and heart rate (Table I). Yohimbine (*2 mg/kg*) *per se* had no significant effect on both the parameters. Clonidine and ST 93 induced reduction in heart rate and blood pressure were significantly ($P<0.01$) antagonized by yohimbine pretreatment.

Interaction between ouabain and alpha-adrenoceptor stimulation : Both the clonidine and ST 93 (2.5, 5 and 10 *μg/kg, iv*) produced a significant increase ($P<0.001$) in the doses of ouabain required for the production of VPB, VF and cardiac arrest (Table II). However, there was no significant difference between 5 and 10 *μg/kg* doses of both clonidine and ST 93 in their protective effect.

Yohimbine (2 *mg/kg*) pretreatment significantly antagonized ($P < 0.001$) the effects of both clonidine and ST 93 treated animals. Yohimbine *per se* did not alter ouabain dose requirement for the occurence of VPB, VF and cardiac arrest.

DISCUSSION

Both ST-93 and clonidine induced significant hypotension and bradycardia in control animals. ST-93 has been reported to produce hypotension and bradycardia in cats. The selective alpha$_2$-adrenoceptor antagonist yohimbine had no such effects. However, it signficantly inhibited the hypotension and bradycardia induced by ST-93. The data suggest that ST-93 induced bradycardia in guinea pigs could be mediated through alpha$_2$-adrenoceptors. The post synaptic and presynaptic ∝-adrenoceptor activity of ST-93 is reported earlier (4,10,12-14).

The protective effect of ST-93 and clonidine against ouabain-arrhythmia was evident, but did not increase beyond dose of 5 *μg/kg*. The results obtained with clonidine are in agreement with the findings of Lechat and Schmitt (8). ST-567, a clonidine analog, is also reported to abolish certain experimental cardiac arrhythmias (1, 2, 6).

Results obtained with yohimbine suggest that ST-93 induced protective effect against ouabain-induced arrhythmia is mediated through stimulation of presynaptic alhha$_2$-adrenoceptors. The activation of central alpha$_2$-adrenoceptors by ST-93, probably decreases the sympathetic tone, thereby affording protection against ouabain arrhythmia.

TABLE I : Haemodynamic effects of clonidine, ST-93 and yohimbine interactions on anaesthetised guinea pigs. Values are presented as Mean ± SEM.

Treatment (*dose, iv*)	*n*	*Blood pressure mmHg.*		*Heart rate beat/min*	
		Initial	*After ouabain*	*Initial*	*After ouabain*
Control (Saline)	15	51.9±2.5	51.8±2.3	242 5±8.3	228.4±7.4
Colonidine (5 μg)	11	56.2±5.1	35.3±3.2**	248.0±8.9	188 2±4.8**
ST-93 (5 μg)	9	62.0±3.3	41.8±2.6**	287.8±4.4	191.5±5.9**
Yohimbine (2 *mg*)	11	59.4±3.6	54.4±3.8	276.2±11 5	253 8±14.8
Yohimbine+ Clonidine (2 *mg*)+ (5 μg)	9	59.3±4.4	49.1±2.6*	252.0±12.6	216.9±5.4*
Yohimbine+ST-93 (2 *mg*) + (5 μg)	8	55.1±1.6	48.5±1.5*	255.5±9.1	223.5±6.3*

* P<0.01
** P<0.001

(unpaired 't' test)

TABLE II : Effect of clonidine and ST-93 and their interaction with yohimbine on ouabain induced arrhythmia in guinea pigs. Values presented are as Mean ±SEM of doses of ouabain (*μg/kg*) required to produce ventricular premature beat (VPB), ventricular fibrillation (VF) and cardiac arrest (CA).

Treatment (*dose, iv*)	*n*	*VPB*	*VF*	*CA*
Control (Saline)	25	172.80±3.80	186.70±4.20	257.10±4.65
Clonidine 2.5	9	246.16±5.17***	338.66±19.24***	415.45±19.10***
5.0	10	287.57±13 70***	361.30±21.07***	435.30±18.40***
10.0	9	307.27±18.9***	377.80±24.58***	453.80±18.04***
ST-93 2.5	9	223.66±13.96***	287.50±17.50**	372.80±19.80*
5.0	9	248.03±5.80**	307.57±12.12***	374.35±7.01***
10.0	9	253.92±7.41***	322.54±10.28***	414.46±12.84***
Yohimbine (2 *mg*)	11	174.38±6.71	208.33±6.84	265.60±6.10
Yohimbine+Clonidine (2 *mg*+5 μg)	10	204.42±8.08[a]	242.35±13.63[a]	304.04±10.50[a]
Yohimbine+ST-93 (2 *mg*+5 μg)	8	197.43±12.79[b]	229.96±13.52[b]	274.93±14.80[b]

*P<0.05 **P<0.01 ***P<0.001 [a]P<0.001 vs Clonidine (5 μg)
[b]P<0.001 vs ST-93 (5 μg) (unpaired 't' test)

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