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SOME PHARMACOLOGICAL ASPECTS OF ULTRA-SHORT ACTING B-BLOCKER (ESMOLOL)

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INTRODUCTION

Esmolol is an ultra short-acting beta 1- adrenergic-receptor antagonist reported to have no intrinsic sympathomimetic activity. It has been successfully used in lowering the ventricular rate and rate-pressure product in patients with myocardial infarction, postmyocardial infarction angina, or acute unstable angina (Kirshenbaum et al., 1985). In anaesthetized dogs, esmolol produced steady-state beta-blockade within 20 minutes of initiation of 3 hours i.v. infusions and did not produce alpha-blockade (Gorczynski and Vuons 1984).

The aim of the present work is to investigate the effect of esmolol on some cardiovascular and respiratory functions. In addition. Its effect on duodenal and uterine smooth muscles was also studied,

MATERIALS AND METHODS

Drug:

Esmolol hydrochloride (Brevibolic®), was provided from Baxter-Travenol Laboratories, USA, as ampoules,

containing 2.5 g esmolol / 10 ml each. The solvent contains 25% propylene glycol, 25% alcohol and water for injection. Esmolol was buffered with 17.0 mg sodium acetate and 0.00715 ml glacial acetic acid, sodium hydroxide and or/ hydrochloric acid added, as necessary to adjust pH.

Methods:

(A) Cardiovascular effects:

Isolated guinea pig auricles, were prepared according to the technique described by Chapman et al., (1972). After recording the normal beats using T2 isotonic transducer connected with MD2 Oscillograph (Bioscience, Washington), different concentrations of esmolol hydrochloride were tested every 20 minutes, their effects and duration of action were demonstrated.

Isolated rabbit's heart was prepared according to Chapman et al., (1972), using Gunn's apparatus. The rhythmic contractions of heart were recorded using T2 isotonic transducer recording on Oscillograph MD2. Graded concentrations of esmolol were injected every 5 min. in 10 ml cannula and their effects were recorded. Trials were also made to determine the potency of esmolol in comparison with that of propranolol (Inderal) on isolated rabbit's heart.

Systemic blood pressure and ECG according to Chapman et al., (1972) were recorded in pentobarbital sodium (30 mg/kg b. wt., i.v.) anaesthetized, spontaneously breathing dogs. ECG was recorded by using a standard Lead. II. The blood pressure was recorded using a four channel Oscillograph (Bioscience). Doses of esmolol hydrochloride ranging from 7.5×10^{-5}-6×10^{-3}M/kg b. wt. were injected intravenously every 15 minutes, and their effects on blood pressure, duration of action and ECG were demonstrated. Trials were

also made to determine the antiarrhythmic effects of esmolol hydrochloride when injected intravenously in a dose 1.5×10^{-4}, 3×10^{-4} and 6×10^{-4} M / kg b. wt. in anaesthetized dogs before and after induction of arrhythmia with adrenaline. After recording the normal ECG, esmolol was given (0.5 minute) before the induced arrhythmia with adrenaline. ECG changes were recorded at 0.5, 2, 5, 10, 15, 20 and 30 minutes after the induced arrhythmia with adrenaline. Moreover, in another experiment, esmolol was given (0.5 minute) after the induced arrhythmia with adrenaline and the ECG changes were recorded before, at once and after (0.5 min.) adrenaline injection, then at 0.5, 2, 5, 10, 15, 20 and 30 minutes post injection of esmolol. The arrythmogenic effects of adrenaline tested are recorded alone in the absence of esmolol.

(B) Respiratory effects:

Effect of different concentrations of esmolol on rat's phrenic nerve-diaphragm was studied according to the method of Bülbring (1946). After recording the normal contractions using T2 isotonic tranceducer connected with MD2 Oscillograph (Bioscience), increased graded concentrations of esmolol every 10 minutes were added and their effects were demonstrated.

(C) Effect on other isolated smooth muscle preparations:

Pieces of rabbit's duodenum and uterus of rats at various stages of sex cycle (non-oestrus and oestrus) and at early and late pregnancy were suspended in glass jar bath of 50 ml capacity containing the specific oxygenated physiological solution at 37 and 38-39°C, respectively (Robella, et al., 1928). Before testing the effects of esmolol hydrochloride, the normal rhythmic contractility of each organ was

recorded. The T2 isotonic transducer connected with Oscillograph MD2 (Bioscience) was used for recording the contractions of each preparation. Different graded concentrations of esmolol every 20 minutes were added and their effects were demonstrated.

RESULTS

Cardiovascular effects:

Esmolol in concentations of 6×10^{-8} to 3.6×10^{-6} M/ml bath caused a marked negative inotropic activity on the isolated guinea pig auricles. The onset, intensity and duration of action were positively correlated with the drug concentration (Table 1).

Esmolol in concentrations of 3.77×10^{-7}, 7.5×10^{-7}, 1.5×10^{-6}, 3×10^{-6}, 6×10^{-6}, 1.5×10^{-5}, 3×10^{-5}, 6×10^{-5}, 1.5×10^{-4}, 3×10^{-4}, 6×10^{-4}, 1.2×10^{-3}, 2.4×10^{-3}, 4.8×10^{-3}, 6×10^{-3}, 1.2×10^{-2} and 2.4×10^{-2} M/ml cannula induced a reduction in amplitude and frequency contraction of the isolated rabbit's heart (i.e. negative inotropic and chronotropic activities). This reduction was concentration dependent (Fig. 1). Attempts made to explore the cardio-inhibitory activity of esmolol in comparison with propranolol (Inderal) on the isolated rabbit's heart. It was noticed that esmolol (1.2×10^{-4} M/ml cannula) produced it cardio-inhibitory effect similar to propranolol (3.3×10^{-6} M/ml cannula) with their reduction in amplitude (45.54 and 46.02%) and rate of contraction (15.38 and 15.38 %), respectively (Fig. 1).

On i.v. administration of esmolol in dogs, the mean systolic and diastolic blood pressure were significantly decreased (1.94 to 14.94% and 6.14 to 26.45% respectively). The changes and duration of action were dose-dependent (Table 2). After i.v. injection of esmolol (6×10^{-4} M/kg b. wt.), the average duration of reduction of systolic and diastolic blood pressure were 4.93 ± 0.05 minutes (Fig.2).

Table (1): percentage reduction (R %) in amplitude (mm) of isolated guinea pig's auricle in response to esmolol hydrochloride (Mean ± S.E., n = 6)

Concentration (Molar/ml bath)	Duration of action (minutes)	Normal	Amplitude (mm)					
			1 minute		5 minutes		10 minutes	
			mm	R %	mm	R %	mm	R %
$6x10^{-8}$	11.92±0.24	2.70±0.07	2.20±0.02	18.52	1.86±0.19	31.11	2.64±0.45	2.22
$1.2x10^{-7}$	12.58±0.15	2.80±0.10	1.76±0.09	37.14	1.90±0.06	32.14	2.34±0.19	16.43
$2.4x10^{-7}$	13.33±0.17	2.52±0.12	1.44±0.23	42.86	1.84±0.14	26.98	1.96±0.28	22.22
$4.8x10^{-7}$	15.17±0.41	2.52±0.12	1.10±0.10	56.35	1.38±0.30	45.24	1.08±0.20	57.14
$6x10^{-7}$	16.08±0.15	2.72±0.12	1.00±0.05	63.24	1.34±0.24	50.74	0.98±0.17	63.40
$1.2x10^{-6}$	17.0±0.22	2.86±0.06	1.10±0.24	61.54	1.34±0.24	53.15	0.62±0.10	78.32
$2.4x10^{-6}$	18.67±0.11	2.86±0.06	1.30±0.15	54.55	0.94±0.06	67.13	0.36±0.04	87.41
$3.6x10^{-6}$	19.0±0.22	2.52±0.12	1.02±0.08	59.52	0.80±0.08	68.25	0.30±0.03	88.10

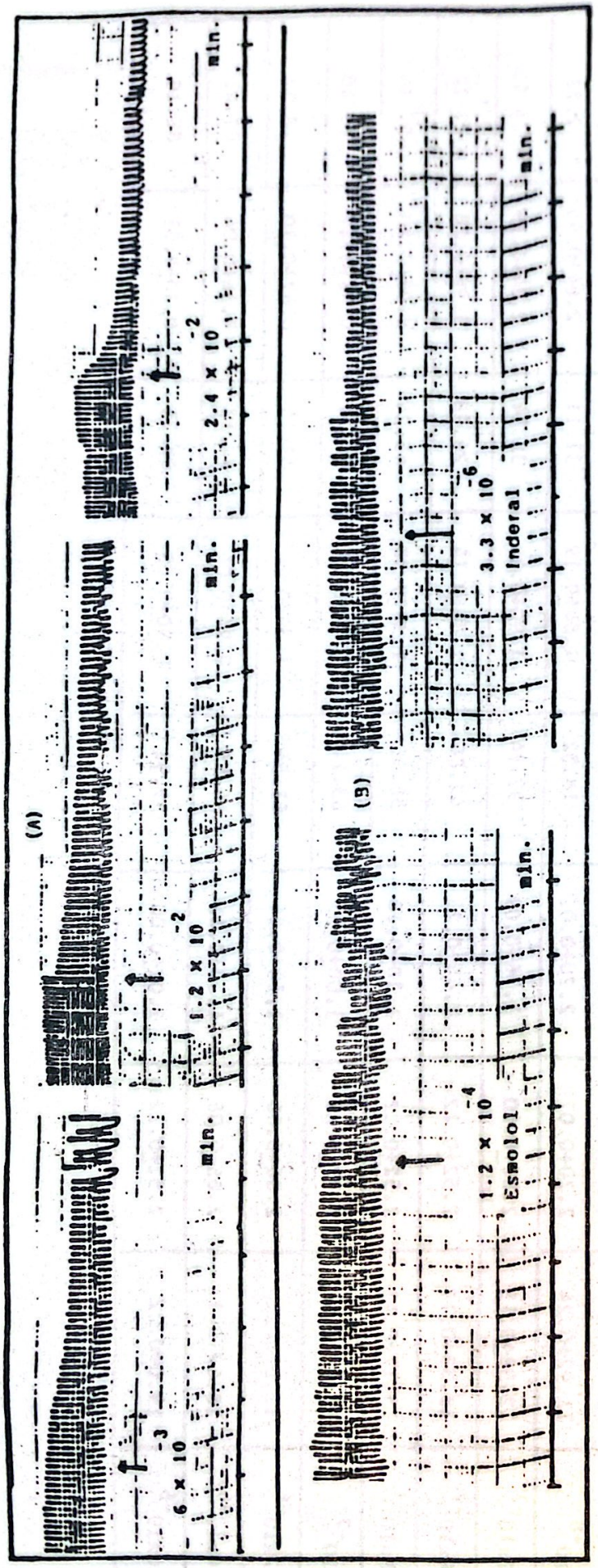

Fig. 1: Effect of esmolol (6×10^{-3} , 1.2×10^{-2} and 2.4×10^{-2} M/ml bath) on isolated rabbit's heart (A).
(B): 1.2×10^{-4} M/ml bath of esmolol was equal to 3.3×10^{-6} M/ml bath of propranolol (Inderal) on their effect on isolated rabbit's heart . Time marks. 1 min.

Table (2): Mean values of arterial systolic blood pressure (ASP) and arterial diastolic blood pressure (ADP) before and after a single i.v. injection of different doses of esmolol and duration of action in anaesthetized dogs. (n = 6).

Dose (Molar/ kg b.wt)	Duration(mins)	ASP (mm Hg)			ADP (mm Hg)		
		Before	After	dec. %	Before	After	dec. %
$7x10^{-5}$	0.27 ± 0.01	120.0 ± 0.58	117.7 ± 0.42	1.94	85.5 ± 0.72	80.3 ± 1.01	6.14
$1.5x10^{-4}$	0.57 ± 0.02	118.0 ± 0.52	115.7 ± 0.21	1.98	81.7 ± 0.80	77.3 ± 0.83	5.41
$3 x 10^{-4}$	0.85 ± 0.02	118.3 ± 0.42	115.3 ± 0.21	2.47	71.1 ± 0.47	65.3 ± 0.36	8.20
$6 x 10^{-4}$	0.99 ± 0.01	117.5 ± 0.65	114.08± 0.24	2.91	80.3 ± 0.70	74.4 ± 0.38	7.27
$9 x 10^{-4}$	1.50 ± 0.03	119.2 ± 0.21	112.1 ± 0.42	5.95	82.5 ± 0.61	70.4 ± 0.82	14.64
$1.2x10^{-3}$	2.20 ± 0.03	119.2 ± 0.59	112.7 ± 0.42	5.45	83.6 ± 0.80	76.0 ± 0.45	9.07
$1.8x10^{-3}$	2.50 ± 0.04	121.8 ± 0.31	111.2 ± 0.60	8.75	89.2 ± 0.59	74.2 ± 0.65	16.82
$2.4x10^{-3}$	3.03 ± 0.03	122.8 ± 0.21	107.8 ± 0.48	12.21	91.7 ± 0.56	70.5 ± 0.55	23.09
$3.0x10^{-3}$	4.77 ± 0.06	120.1 ± 0.08	103.8 ± 0.46	13.53	92.8 ± 0.54	68.8 ± 0.79	25.79
$6.0x10^{-3}$	4.93 ± 0.05	137.3 ± 0.25	116.8 ± 0.79	14.94	115.0 ± 0.52	84.6 ± 1.08	26.45

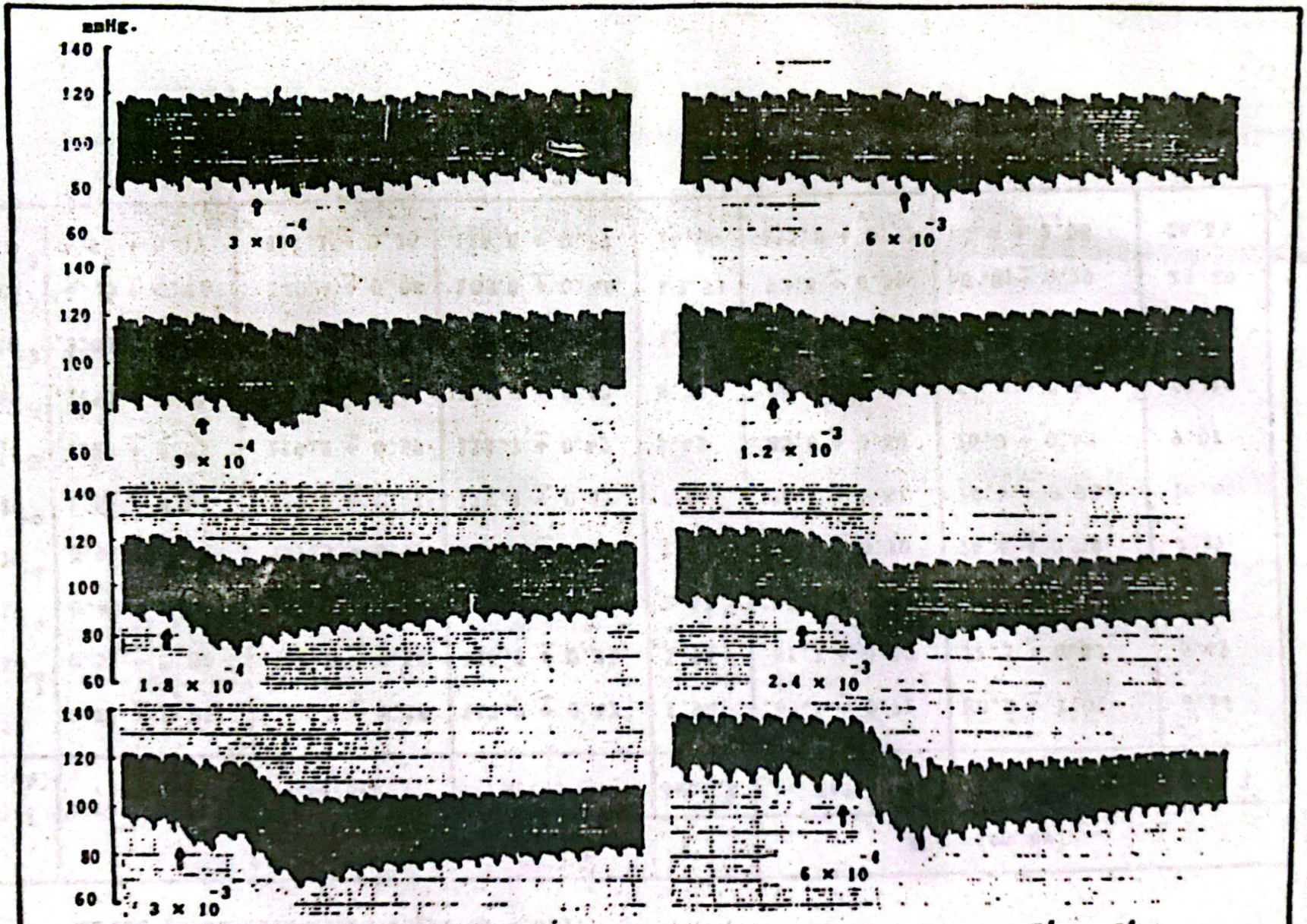

Fig. 2: Effect of the intravenous injection of esmolol (3×10^{-4}, 6×10^{-4}, 9×10^{-4}, 1.2×10^{-3}, 1.8×10^{-3}, 2.4×10^{-3}, 3×10^{-3} and 6×10^{-3} M/kg b. wt.) on blood pressure in an anaesthetized and breathed spontaneously dogs . Time marks. 15 seconds .

The electrocardiographic pattern following i.v. injection of gradual doses of esmolol (7.5×10^{-5} to 6×10^{-3} M/kg b. wt.), in anaesthetized, and spontaneously breathing dogs was studied. As shown in Table 3, there was an increase in the amplitude of P-wave and T-wave, prolongation of P-R, T-wave, P-wave and P-T intervals. Furthermore, the amplitude and duration of QRS complex were decreased. These findings occured immediatly after injection and were dose-dependent.

Antiarrhythmic effects of esmolol when administered intravenously in doses of 1.5×10^{-4}, 3×10^{-4} and 6×10^{-4} M/kg b. wt. in anaesthetized dogs before and after adrenaline injection (1×10^{-1} M/kg b. wt.) were incorporated in Table (4 and 5), respectively. The curative and protective effects of esmolol (before and after induced arrhythmia by adrenaline) are represented as a decreases in amplitude of the QRS complex, P-R and P-T intervals. Furthermore, the duration of T-wave are increased. The onset and duration of the curative action of esmolol were positively correlated with their dosage. The arrythmogenic effects of adrenaline in the absence of esmolol in anaesthetized dogs was studied. Adrenaline increases the amplitude of the P-wave, QRS complex and T-wave, prolongation of P-wave, QRS complex, P-R and P-T intervals. Furthermore, the duration of T-wave are decreased and the average duration of the induced arrhythmias was 37-40 minutes. Esmolol in a dose of 6×10^{-4} M/kg b. wt., showed better protection (more than 30 minutes) when administered i.v. after adrenaline before it (10 minutes only).

Respiratory effect:

Esmolol in concentrations of 6×10^{-6}, 1.2×10^{-5}, 2.4×10^{-5}, 4.8×10^{-5}, 9.6×10^{-5}, 1.9×10^{-4}, 3.86×10^{-4} and 7.7×10^{-4} M/ml bath was had no effect on the twitches of isolated rat phrenic nerve-diaphragm preparation by indirect stimulation. Esmolol (1.5×10^{-3} and 3×10^{-3} M/ml bath) decreased

Table (3): Effect of intravenous injection of different doses of esmolol hydrochloride on the electrocardiogram of pentobarbital anaesthetized dogs (n = 6).

Parameter	Before	2 minutes after esmolol hydrochloride injection									
		Dose (Molar / kg b.wt.)									
		$.7.5x10^{-5}$	$1.5x10^{-4}$	$3x10^{-4}$	$6x10^{-4}$	$9x10^{-4}$	$1.2x10^{-3}$	$1.8x10^{-3}$	$2.4x10^{-3}$	$3x10^{-3}$	$6x10^{-3}$
P-wave: amplitude(mm)	1.17±0.11	0.92±0.05	0.58±0.07	3.25±0.00	4.13±0.08	4.03±0.03	3.75±0.11	3.58±0.08	3.50±0.00	4.42±0.08	4.75±0.08
duration(msec)	46.33±4.01	43.33±3.33	53.33±4.22	66.71±3.68	70.00±0.00	70.00±0.00	78.33±1.67	78.33±1.67	78.33±1.67	78.33±1.67	80.00±0.0
P-R interval(msec)	103.33±3.33	100.67±4.22	116.67±6.15	120.0±0.00	120.0±0.00	120.0±0.00	120.67±4.22	140.00±0.00	140.00±0.00	140.0±0.00	160.00±0.00
P-T interval(msec)	233.33±4.22	240.0±0.00	253.33±4.22	260.0±0.00	260.0±0.00	260.0±0.00	260.0±0.00	260.0±0.00	260.67±4.22	260.67±4.22	260.67±4.22
QRS complex: amplitude(mm	12.5±0.45	13.25±0.36	12.02±0.33	11.83±0.11	11.75±0.44	11.08±0.37	11.0±0.37	10.67±0.25	10.67±0.33	10.67±0.33	10.67±0.33
duration(msec)	80.0±0.00	80.0±0.00	80.0±0.00	80.0±0.00	43.33±3.33	40.0±0.00	36.67±3.33	33.33±4.22	30.00±4.47	28.33±4.01	25.0±3.42
T-wave: amplitude(mm)	0.98±0.04	0.78±0.04	0.78±0.04	1.38±0.04	2.0±0.00	2.0 ±0.00	2.5±0.00	2.5±0.00	2.5±0.00	2.5±0.00	2.5±0.00
duration(msec)	86.67±4.22	103.33±3.33	103.33±3.33	120.0±0.00	120.0±0.00	120.0±0.00	130.0±0.00	140.0±0.00	180.0±0.00	180.0±0.00	180.0±0.00

Table (4): Curative and protective effect of esmolol hydrochloride ($1.5x10^{-4}$, $3x10^{-4}$ and $6x10^{-4}$ M/kg b.wt.) before dysrrthythmias induced by adrenaline in anaesthetized dogs. (n = 6).

Parameter	Dose (Molar /kg b.wt.)	Normal	Pretreatment of esmolol after(0.5 min	Time in minutes after adrenaline injection						
				0.5	2	5	10	15	20	30
P-wave: amplitude (mm.) duration (msec.)	1.5×10^{-4}	1.17±0.11 40.33±4.01	2.75±0.11 40.0±0.0	3.50±0.0 120.0±0.0	3.75±0.11 40.0±0.0	2.75±0.11 40.0±0.0	3.0±0.0 40.0±0.0	2.5±0.0 80.0±0.0	2.5±0.0 80 ±0.0	2.5±0.0 80 ±0.0
P-R interval(msec.) P-T interval(msec.)		183.33±3.33 233.33±4.22	80 ±0.0 200 ±0.0	240 ±0.0 380 ±0.0	80 ±0.0 180 ±0.0	80 ±0.0 180 ±0.0	80 ±0.0 200 ±0.0	180 ±0.0 480 ±0.0	180 ±0.0 440 ±0.0	180 ±0.0 440 ±0.0
QRS complex: amplitude(mm.) duration(msec.)		12.5±0.45 80 ±0.0	10.00±0.15 80 ±0.0	20 ±0.0 380 ±0.0	8.83±0.11 80.0±0.0	8.83±0.11 80 ±0.0	8.02±0.15 80 ±0.0	14.33±0.11 320 ±0.0	10.50±0.15 300 ±0.0	10.38±0.15 300 ±0.0
T-wave: amplitude(mm.) duration(msec.)		0.08±0.04 80.67±4.22	1.25±0.0 80 ±0.0	10.5±0.13 40 ±0.0	1.0 ±0.0 120 ±0.0	1.0 ±0.0 120 ±0.0	1.5 ±0.0 120 ±0.0	10.5±0.13 80 ±0.0	10 ±0.22 80 ±0.0	10. ±0.22 80 ±0.0
P-wave: amplitude(mm.) duration(msec.)	3×10^{-4}	1.17±0.11 40.33±4.01	2.67±0.11 40 ±0.0	1.5 ±0.0 80 ±0.0	3.5 ±0.0 80 ±0.0	4.0 ±0.0 80 ±0.0	3.5 ±0.0 40 ±0.0	3.0 ±0.0 40 ±0.0	3.0 ±0.0 40 ±0.0	2.0 ±0.0 40 ±0.0
P-R interval(msec) P-T interval(msec)		100 ±0.0 233.33±4.22	100 ±0.0 200 ±0.0	100 ±0.0 240 ±0.0	100 ±0.0 180 ±0.0	100 ±0.0 180 ±0.0	100 ±0.0 200 ±0.0	80 ±0.0 200 ±0.0	80 ±0.0 200 ±0.0	80 ±0.0 200 ±0.0
QRS complex: amplitude(mm) duration(msec)		12.5±0.45 80 ±0.0	11.33±0.11 80 ±0.0	10.00±0.00 80 ±0.0	10 ±0.0 80 ±0.0	8.5 ±0.0 80 ±0.0	8.00±0.00 80 ±0.0	7.75±0.11 80 ±0.0	7.75±0.11 80 ±0.0	7.75±0.11 80 ±0.0
T-wave: amplitude(mm) duration(msec)		0.08±0.04 80.67±4.22	2.5 ±0.0 120 ±0.0	2 ±0.0 80 ±0.0	1.5 ±0.0 80 ±0.0	1.5 ±0.0 100 ±0.0	2 ±0.0 80 ±0.0	2.5 ±0.0 80 ±0.0	3 ±0.0 80 ±0.0	3 ±0.0 80 ±0.0
P-wave: amplitude(mm) duration(msec)	6×10^{-4}	1.17 ±0.11 40.33±4.01	3.83±0.11 40 ±0.0	1.5 ±0.0 120 ±0.0	4 ±0.0 40 ±0.0	3.83±0.11 40 ±0.0	3.83±0.11 40 ±0.0	3.83±0.11 40 ±0.0	3.83±0.11 40 ±0.0	3.83±0.11 40 ±0.0
P-R interval(msec) P-T interval(msec)		100 ±0.0 230 ±0.0	100 ±0.0 180 ±0.0	200 ±0.0 380 ±0.0	80 ±0.0 180 ±0.0	80 ±0.0 180 ±0.0	80 ±0.0 180 ±0.0	80 ±0.0 180 ±0.0	100 ±0.0 180 ±0.0	100 ±0.0 180 ±0.0
QRS complex: amplitude(mm) duration(msec)		12.5 ±0.45 80 ±0.0	9.5 ±0.18 80 ±0.0	20.33±0.33 400 ±0.0	10.00±0.33 80 ±0.0	8.67±0.31 80 ±0.0	8.67±0.31 80 ±0.0	9.58±0.2 80 ±0.0	8 ±0.0 80 ±0.0	8 ±0.20 80 ±0.0
T-wave: amplitude(mm) duration(msec)		0.08±0.04 80.67±4.22	1.5 ±0.0 120 ±0.0	8.83 ±0.17 80 ±0.0	2 ±0.0 120 ±0.0	2 ±0.0 120 ±0.0	2 ±0.0 120 ±0.0	2.5 ±0.0 120 ±0.0	2.5 ±0.0 120 ±0.0	2.5 ±0.0 120 ±0.0

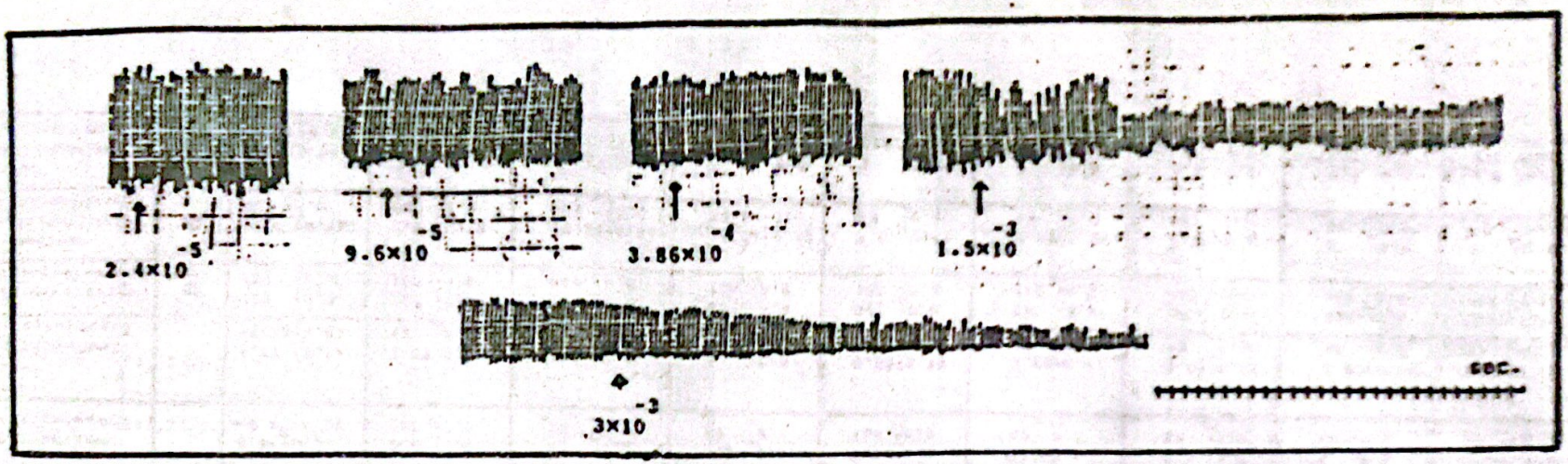

Fig. 3: Effect of esmolol (2.4×10^{-5}, 9.6×10^{-5}, 3.86×10^{-4}, 1.5×10^{-3} and 3×10^{-3} ml bath) on the isolated rat phrenic nerve diaphragm preparation . Chart speed. 2.5 mm / seconds.

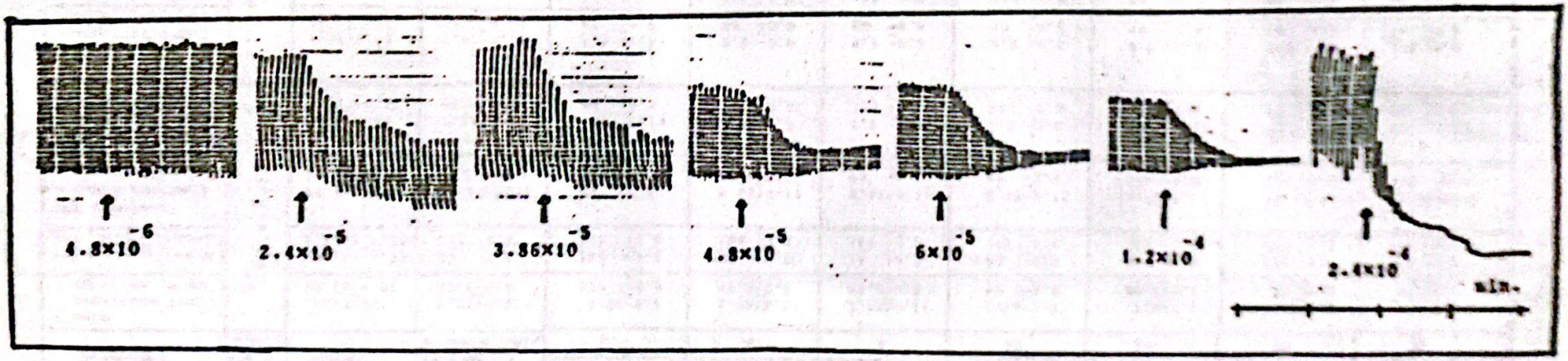

Fig. 4: Effect of esmolol (4.8×10^{-6}, 2.4×10^{-5}, 3.86×10^{-5}, 4.8×10^{-5}, 6×10^{-5}, 1.2×10^{-4} and 2.4×10^{-4} M/ml bath) on contractions of isolated rabbit's duodenum . Time marks , 1 minute .

the amplitude of the indirect muscle twitches (Fig. 3) in comparison with control solvent of the tested drug.

Effect on the other smooth muscles:

Esmolol (up to 9.6×10^{-6} M/ml bath) had no effect on the contraction of isolated rabbit's duodenum, whereas, concentrations from 1.2×10^{-5} to 3.86×10^{-5} M/ml bath, inhibited the amplitude only. Concentrations of esmolol more than 3.86×10^{-5} M/ml inhibited both amplitude and rate of isolated rabbit's duodentum. This effect was dose-dependent (Fig. 4) and the duration of action about 6-8 min. (for 2.4×10^{-5} - 3.86×10^{-5} M/ml) and 12-21 min. (for 4.8×10^{-5} - 2.4×10^{-4} M/ml).

The effects of esmolol on the uterine motility of rats at various stages of sex cycle were demonstrated in (Fig. 5). Concentrations ranged from 1.2×10^{-5} to 2.4×10^{-5} M/ml bath inhibited the force and stimulate the frequency of motility of the isolated uterus of rats at all tested stages (non-oestrus, oestrus, early and late pregnancy). Higher concentrations up to 6×10^{-5} M/ml bath induced marked inhibition in both force and frequency of contraction. The duration of action about 4, 7.5, 13 and 19.5 minutes for the concentrations of 1.8×10^{-5}, 3.6×10^{-5} 4.8×10^{-5} and 6×10^{-5} M/ml bath in all tested stages, respectively.

DISCUSSION

The present study indicated that esmolol induced a negative inotropic activity on both guinea pig's auricle and rabbit's heart. Its potency is 1 / 36.36 as potent as a propranolol. Similar findings were also previously reported by Sochynsky and Hardcastle (1986), who found that, esmolol potency is one over [illegible] as potent as a propranolol. The significant

Table (5): Curative and protective effect of esmolol hydrochloride ($1.5x10^{-4}$, $3x10^{-4}$ and $6x10^{-4}$ M/kg b.wt. after dysrthythmias induced by adrenaline in anaesthetized dogs (n = 6).

Parameter	Dose Molar/kg b. wt.	Normal	Effect of adrenaline after		Time in minutes after esmolol injection						
			At once	0.5(min.)	0.5	2	5	10	15	20	30
P-wave: amplitude(mm) duration(msec)	1.5×10^{-4}	1.17±0.11 98.33±9.01	3.0 ± 0.0 120 ± 0.0	3 ± 0.0 100 ± 0.0	3 ± 0.0 80 ± 0.0	2.5 ± 0.0 80 ± 0.0	2.5 ± 0.0 80 ± 0.0	2.67± 0.11 80 ± 0.0	2.5 ± 0.0 120 ± 0.0	2.5 ± 0.0 120 ± 0.0	2.5 ± 0.0 80 ± 0.0
P-R interval(msec) P-T interval(msec)		103.33±3.33 233 ± 9.22	240 ± 0.0 720 ± 0.0	200 ± 0.0 480 ± 0.0	200±0.0 320 ± 0.0	100 ± 0.0 160 ± 0.0	100 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	240 ± 0.0 800 ± 0.0	240 ± 0.0 840 ± 0.0	80 ± 0.0 160 ± 0.0
QRS complex: amplitude(mm) duration(msec)		12.0±0.45 80 ± 0.0	28.5±0.18 320 ± 0.0	24.0± 0.0 300 ± 0.0	20.3± 0.22 280 ± 0.0	9.0 ± 0.0 80 ± 0.0	8 ± 0.0 80 ± 0.0	8.75± 0.11 80 ± 0.0	17.87±0.21 360 ± 0.0	18 ± 0.0 360 ± 0.0	18.83±0.21 100 ± 0.04
T-wave: amplitude(mm) duration(msec)		0.88 ± 0.04 86.67± 9.22	10.33±0.11 80 ± 0.0	9.5 ± 0.0 80 ± 0.0	9.5 ± 0.0 80 ± 0.0	1.0 ± 0.0 100 ± 0.0	1.0 ± 0.0 100 ± 0.0	1.42± 0.08 120 ± 0.0	10.3 ± 0.0 80 ± 0.0	10.3± 0.0 80 ± 0.0	1.42 ± 0.08 100 ± 0.0
P-wave: amplitude(mm) duration(msec)	3×10^{-4}	1.17 ± 0.11 98.33±9.01	3 ± 0.0 100 ± 0.0	3 ± 0.0 120 ± 0.0	2.83± 0.11 80 ± 0.0	2.5 ± 0.11 80 ± 0.0	3.17±0.21 80 ± 0.0	3.25±0.11 80 ± 0.0	3 ± 0.0 80 ± 0.0	3 ± 0.0 80 ± 0.0	3 ± 0.0 80 ± 0.0
P-R interval(msec) P-T interval(msec)		100 ± 0.0 233.33±9.22	240 ± 0.0 680 ± 0.0	200 ± 0.0 600 ± 0.0	100 ± 0.0 200 ± 0.0	100 ± 0.0 160 ± 0.0	100 ± 0.0 160 ± 0.0	100 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0
QRS complex: amplitude(mm) duration(msec)		12.5±0.45 80 ± 0.0	26.83± 0.42 520 ± 0.0	28.5± 0.13 360 ± 0.0	10.5±0.18 80 ± 0.0	10.67±0.17 80 ± 0.0	10.25±0.17 80 ±0.0	9.87± 0.11 80 ± 0.0	9.42 ± 0.13 80 ± 0.0	9.42±0.13 80 ± 0.0	9.17 ± 0.29 80 ± 0.0
T-wave: amplitude(mm) duration(mm)		0.88±0.04 86.67±9.22	10.33±0.21 80 ± 0.0	10 ± 0.0 80 ± 0.0	1.5 ± 0.0 120 ± 0.0	1.5 ± 0.0 120 ± 0.0	2.5 ± 0.0 80 ± 0.0	3.0 ± 0.0 80 ± 0.0	3 ± 0.0 80 ± 0.0	3 ± 0.0 80 ± 0.0	3 ± 0.0 80 ± 0.0
P-wave: amplitude(mm) duration(msec)	6×10^{-4}	1.17 ± 0.11 98.33± 9.01	3 ± 0.0 120 ± 0.0	1.5 ± 0.0 160 ± 0.0	3.75± 0.11 80 ± 0.0	3.75± 0.11 80 ± 0.0	3.75± 0.11 80 ± 0.0	3.75± 0.11 80 ± 0.0	3.75± 0.11 80 ± 0.0	3.75±0.11 80 ± 0.0	3.75± 0.11 80 ± 0.0
P-R interval(msec) P-T interval(msec)		100 ± 0.0 230 ± 0.0	240 ± 0.0 720 ± 0.0	240 ± 0.0 720 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0	80 ± 0.0 160 ± 0.0
QRS complex: amplitude(mm) duration(msec)		12.5± 0.45 80 ± 0.0	28 .5± 0.18 520 ± 0.0	25.67±0.33 400 ± 0.0	10 ± 0.0 80 ± 0.0	10 ± 0.34 80 ± 0.0	10 ± 0.0 80 ± 0.0	9.42± 0.2 80 ± 0.0	9.25±0.17 80 ± 0.0	8 ± 0.0 80 ± 0.0	8 ± 0.0 80 ± 0.0
T-wave: amplitude(mm) duration(msec)		0.88± 0.04 86.67±9.22	10.33±0.11 80 ± 0.0	8.5 ± 0.0 80 ± 0.0	2 ± 0.0 120 ± 0.0	2 ± 0.0 120 ± 0.0	2 ± 0.0 120 ± 0.0	2 ± 0.0 120 ± 0.0	2 ± 0.0 120 ± 0.0	2 ± 0.0 120 ± 0.0	2 ± 0.0 120 ± 0.0

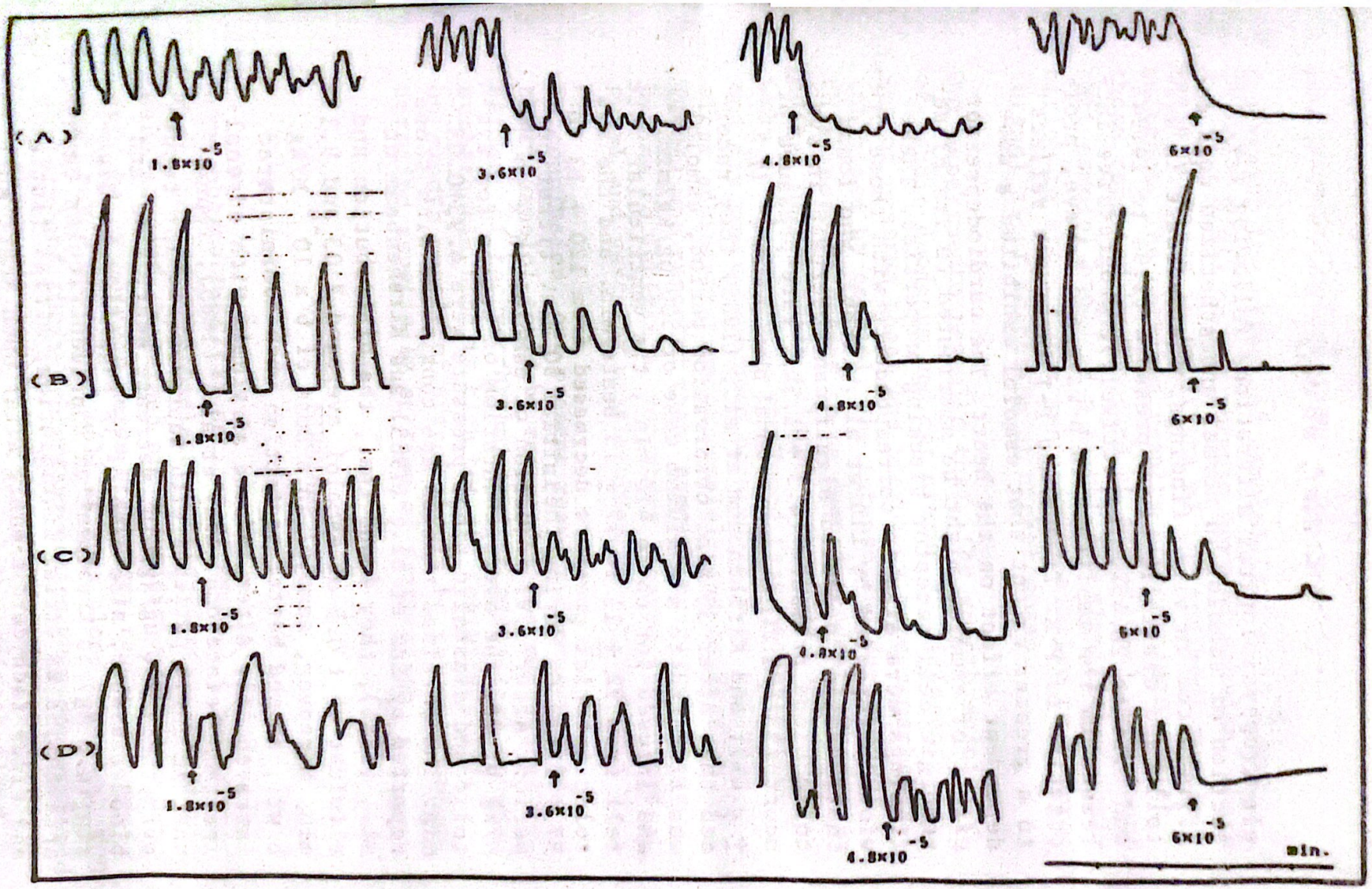

Fig. 5: Effect of esexolol (1.8×10^{-5}. 3.6×10^{-5}. 4.8×10^{-5} and 6×10^{-5} M/ml bath) on contractions of non-oestrus (A). oestrus (B). early pregnant (C) and late pregnant (D) uterus of rat's . Time marks. 1 minute .

electrophysiological alterations following i.v. injection of esmolol in normal anaesthetized dogs confirmed the in vitro findings. The decrease in systolic and diastolic blood pressure (1.94 to 14.94% and 6.14 to 26.45%, respectively), progressive increases in the amplitute in p-wave and T-wave, prolongation of P-R. T-wave and P-T intervals reflect to a greater extent that esmolol exhibited a dose dependent effect on the heart. The cardiodepressor effect of esmolol might be attributed to its B1-adrenergic cell receptor blocking properties. These findings were also in correspondence with those previously reported by Liu et al., (1986), who found that, esmolol produced significant decrease in systolic blood pressure (4.3 $\pm$ 1.5%), rate-pressure product (13.1$\pm$ 1.8%) and mean arterial blood pressure (1.7 $\pm$ 2.0%); and Kirshenbaum et al., (1985) they recorded that after 30 min. observation period, esmolol was titrated to a maxiumum dose of 300 ug/kg/min. and infused for up to 420 min., the ventricular rate fell from 92 $\pm$ 11 to 77 $\pm$ 13 beats/min. and the systolic arterial pressure decreased from 120 $\pm$ 13 to 97 $\pm$ 11 mm Hg during the initial 30 min. titration period. After i.v. injection of esmolol (6×10^{-3} M/kg b. wt) the average duration of action for systolic and diastolic blood pressure were 4.93$\pm$0.05 min. The obtained results are consistent with those reported by Sum et al., (1983) and Kirshenbaum et al., (1985), they found that, the distribution and elimination t 0.5 of esmolol averaged 2.03 and 9.19 min. Moreover, esmolol in a dose of 6×10^{-4} M/kg b wt., showed better protection when administered intravenously after induced arrythmia with adrenaline than before one. Gray et al., (1985), found that in 15/16 patients with supraventricular tachyarrhythmia 200 ug/kg/min. decrease heart rate and blood pressure, also esmolol is supperior to digoxin (0.6 mg) in treatment of supraventricular tachyarrhythmias as atrial fibrillation, atrial flutter and sinus tachycardia-early after open heart surgery when sympathetic tone is high and ventricular response rates may be rapid.

Concerning the effect of esmolol (1.5×10^{-3} and 3×10^{-3} M/ml) on rat phrenic nerve-diaphragm, there was a decrease in amplitute of the indirect muscle twitches. The obtained results are consistent with those reported by Sheppard et al., (1986), who found that esmolol produced a slight and significant inhibition to bronchmotor sensitivity similar to isoproterenol after injection of higher doses.

Our experiments revealed that, the smooth muscles of rabbit duodenum and rat uterus at different stages of oestrus phase and pregnancy were remarkably inhibited by esmolol. The intense and duration of this response seemed to be dose-dependent. These findings were closely related with those reported by Gray et al., (1985), who found that, constipation and dry moutn have been occured in some patients after administration of esmolol; and Angaran et al., (1986) who reported that, esmolol at higher doses begins to inhibit B_2 receptors located in the bronchial and vascular musclature.

In conclusion, our present results demonestrated that, esmolol could be recomended for successful treatment of tachyarrhythmias after adrenaline or when sympathetic tone is high but its inhibitory effect on smooth muscle of uterus should be taken in consideration especially at time of parturation.

SUMMARY

Some pharmacological actions of esmolol,a new ultrashort acting cardioselective beta-adrenergic blocker, were studied on guinea pig's auricles, rabbit's heart, rat's phrenic nerve diaphragm, rabbit's duodenum, rat's uterus as well as dogs blood pressure, ECG pattern and their protective action when administered intravenously before and after induced tachyarrhythmias with adrenaline in pentobarbital anaesthetized dogs was demonstrated.

Esmolol induced a marked negative inotropic activity on guinea pig's auricles. On isolated rabbit's heart, the negative inotropic and chronotropic effects were induced by esmolol in concentrations up to 7.5×10^{-7} M/ml. The inhibitory effect of esmolol potency is 1/ 36.36 as potent of propranolol on rabbit's heart.

In anaesthetized dogs. i.v. injection of esmolol at dosage ranged from 7.5×10^{-5} - 6×10^{-3} M/kg b.wt. produced a significant decrease in systolic and diastolic pressure, while lower doses induced insignificant changes. The electrocardiographic pattern induced by esmolol in dogs were mainly characterized by an increase in the amplitues of p-wave and T-wave, prolongation of P-R, T-wave, P-wave and P-T intervals. Esmolol in a dose of 6×10^{-4} M/kg b.wt. produced a good curative effect when injected intravenously after induced arrhythmias with adrenaline than before injection.

Esmolol inhibited the indirect muscle twiches of rat's phrenic nerve-diaphragm,

Furthermore, esmolol induced a marked inhibition of both amplitutes and frequency of isolated rabbit's duodenum and uterus of rats in concentrations more than 3.86×10^{-5} and 3.6×10^{-5} M/ml, respectively.

REFERENCES

1. Angaran, D.M.; Schultz, N.Z. and Tschida, V.H. (1986): Esmolol hydrochloride : An ultra short-acting, beta-adrenergic blocking agent. Clin. Pharm., 5 (4). 288-303.

2. Bülbring, E. (1946): Observations on the isolated phrenic nerve diaphragm preparation of the rat. Br. J. Pharmacol., 1, 38.

3 . Chapman, R.A.; Howard, L. and Tunstal, J. (1972): Experiments in physiology using Bioscience 400 series, Washington. Oscillograph.

4 . Gorczynski, R.J. and Vuong, A. (1984): Cardiovascular pharmacology of ACC-9089-a novel, ultrashort acting, beta-adrenergic receptor antagonist. J. cardiovasc, Pharmacol., 6 (4), 555-564.

5 . Gray, R.J.; Bateman, T.M.; Czer, S.C. (1985): Use of esmolol in hypertension after cardiac surgery. Am. J. Cardiol., 56 (11), 49-56.

6 . Kirshenbaum, J.M.; Kloner, R.A.; Antman, E.M. and Braunwald, E. (1985): Use of an ultra short-acting beta-blocker in patients with acute myocardial ischemia. Circulation, 72 (4), 873-880.

7 . Liu, P.L., Gatt, S.; Gugino, L.D., Mallampati , S.R. and Covino, B.G. (1986): Esmolol for control of increases in heart rate and blood pressure during tracheal intubation after thiopentone and succinylcholine. Can. Anaesth. Soc. J., 33 (5). 556-562.

8 . Robella, S.; Gomes, S.F. and Rico, J.J. (1928): Actions of certain anthelmentics on cestodes, ascaris and ankylostomes. Sc. D. Biol., 89, 955-999.

9 . Sheppard, D.; Ditefano, S.; Byrd, R.C.; Eschenbacher, W.L.; Bell. V.; Steck , J. and Laddu, A. (1986): Effects of esmolol on airway function in patients with asthma. J. Clin. Pharmacol., 26 (3), 169-174.

10. Sochynsky, R. and Hardcastle, J. (1986): "Therapeutic Categories Main volume", 7, 225-227.

11. Sum, C.Y., Yacobi, A.; Kartzinel, R.; Stampfli, H.; Davis, C.S. and Lai, C.M. (1983): Kinetics of esmolol, an ultra-short acting beta blocker and its of majer metabolite. Clin . Pharmacol. Ther., 34 (4), 427-734.