Med. J. Cairo Univ., Vol. 62, No. 2 June : 337-349, 1994

Experimental Study of the Effects of Pipecuronium, Atracurium and Pancuronium on Cardiovascular System

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Abstract

The present work was undertaken to study the effects of pipecuronium, atracurium and pancuronium on isolated perfused rabbit heart, isolated rabbit atrium and on carotid arterial blood pressure as well as ECG changes with each drug administration. The results demonstrated that pipecuronium in a dose of 100 μg/kg B.W. had no significant effect on heart rate and carotid arterial blood pressure of anaesthetized cat. Atracurium (150 μg/kg B.W.) produced 7.5% increase in basal heart rate and short lasting drop of arterial blood pressure lasting for approximately 1- 1.5 min. followed by rapid recovery. Pancuronium (100 μg/kg B. W.) increased heart rate by about 15.5% ($p < 0.05$) and long lasting hypotension lasted for approximately 4-5 min. with gradual recovery to the pre-injection level. Pipecuronium and pancuronium produced no change in isometric contraction of rabbit atria in concentration range (5-20 μg/ml). However, atracurium in concentrations of 30, 60, 120 μg/ml produced dose-dependent increase in contraction of rabbit atria without any effect on heart rate. When the chronotropic effects of three drugs were investigated using acetylcholine as an agonist on isolated perfused rabbit heart, it was found that pancuronium but not pipecuronium and atracurium, produced a significant degree of antagonism to the bradycardia produced by acetylcholine. We concluded that pipecuronium appears to be a suitable replacement for pancuronium for the production of muscular relaxation of relatively long duration in patients in whom elevation of heart rate has to be avoided. Also, the vagolytic effects of pancuronium is desirable, especially when counter acting the bradycardic tendency of large doses of fentanyl. And that the transient haemodynamic effect of atracurium is probably of little clinical significance in the healthy patient. The effect may be more important in the haemodynamically unstable patient who is hypovolaemic or has cardiovascular disease.

Introduction

THE selection of which muscle relaxant to be used for surgical anaesthesia depends primarily on six factors: Cardiovascular effects, duration of action, pharmacokinetic profile, class of muscle relaxant (depolarizing s. non depolarizing), onset time and reversal of neuro-muscular blockade [1].

As the cardiovascular effects of relaxants have diminished with the introduction of new agents, this subject becomes more and more a matter of historical value. Nevertheless, it is worthwhile to note the increasing safety ratios of the newer agents for the two prominent side effects vagal block and histamine release [2].

Pipecuronium bromide is a new long acting neuromuscular blocking drug reportdely devoid of cardiovascular side effects [3].

It is a steroidal molecule similar in structure to pancuronium but it has a longer duration [4].

The present work was undertaken to study the effects of pipecuronium, atracurium and pancuronium on myocardial contractility, heart rate, ECG recording and arterial blood pressure.

Material and Methods

Drugs used are:

* Pipecuronium bromide (Arduan) (Richter).
* Pancuronium bromide (Pauvlon) (Organon Oss, Holland).
* Atracurium (Tracrium) Wellcome, England).

I- In-vitro Experiments :

1. Isolated perfused Rabbit Heart:

Modified Langendorff's coronary perfusion method [5].

The perfusate comprised oxygenated Ringer-Lock solution maintained at 37°C and constant pH. Each preparation was allowed to equilibrate and stabilize for 20 min. Following the equilibration period, a control injection of acetylcholine 1 μg [6] and the resulting bradycardia recorded. Pipecuronium 2 mg litre^{-1} or atracurium 6 mg litre^{-1} or pancuronium 3 mg litre^{-1} or was added to the Ringer Lock solution. These doses are assumed to be equipotent concentration and thought to represent the peak plasma concentration that could be found in man, after a normal intubating dose of the drug [7], and are consistent with concentrations used by other workers [6, 8]. The solutions were perfused for 20 min. before injection of Ach 1 μg and the resulting bradycardia was recorded.

2. Isolated Rabbit Atrium:

Daws technique [9] using Ringer-Lock solution with the following composition:

NaCl 9.0, KCl 0.42, $CaCl_2.6$, H_2O 0.24, $MgCl_2$ 0.21, $NaHCo_3$ 0.20 and glucose 2.0 g/L.

The experimental work was designed to demonstrate the effects of 3 drugs in increasing concentrations. Pancuronium or pipecuronium were introduced into the bath in concentration range 5-20 μg ml^{-1} [10]. Atracurium in concentration of 30, 60, 120 μg/ml. The effect on heart rate was measured at each concentration.

II - In Vivo Experiments :

Recording of the carotid arterial blood pressure of anaesthetized intact cats as well as E. C. G. changes with each drug administration.

Each experiment was repeated at least 6 times on six different preparations. Statistical analysis of data was performed using the paired student's test [11].

Results

1. Effect on Isolated Perfused Rabbit Heart:

Pipecuronium perfusion in a dose of 2 mg/Litre for 20 min., was found, after 5 min. from infusion, to produce increase in both amplitude of cardiac contraction and heart rate by 20% and 6% respectively. At the end of 20 min. infusion, it has no effect on heart rate and insignificant reduction of cardiac contraction (Table 1, Fig. 1).

Also the results demonstrated that A ch. in a dose of 1 μg produced reduction of amplitude of cardiac contractions by -35% and slowing of heart rate by -36%/min. (33.33%). Pipecuronium infusion for 20 min. not antagonised bradycardia produced by acetylcholine (Table 2, Fig. 1).

When atracurium was perfused in a dose of 5 mg/L for 20 min., we noticed that after 5 min. from infusion, atracurium produced an increase in amplitude of cardiac contraction (+ve inotropic effect) by +20% without any effect on heart rate. At the end of 20 min. infusion no effect on amplitude of contraction was detected. Meanwhile the heart rate was reduced by -12/min. (Table 1, fig. 2).

Ach. in a dose of 1 μg produced reduction in amplitude of cardiac contraction by 38.09% and reduced rate by 31.5%. Atracurium infusion for 20 min. not antagonized bradycardia produced by acetylcholine (Table 2, Fig. 2).

Pancuronium perfusion in a dose of 3 mg/L. for 20 min. produced increase in amplitude of cardiac contraction and heart rate by +13.8% and +12/min. (11.5%) respectively after 5 min. infusion. While after 20 min. infusion pancuronium produced -20% reduction of cardiac contraction and 12/min. increase in heart rate (Table 1, Fig. 3).

Also results demonstrated that Ach. in a dose of 1μg reduced amplitude of cardiac contraction by -33.8% and slowing of heart rate by -30% (27.7%). pancuronium infusion for 20 min. produced complete antagonism to the bradycardia produced by acetylcholine (Table 2, Fig. 3).

Table (1): Comparative Influence of Slow Continuous Infusions of Specified Test Concentrations of Three Non-Depolarizer Skeletal Muscle Relaxants Comparable to Lapine Equivalents of In-Vivo Human Plasma Circulating Levels on the Force (Inotropic) and Rate (Chronotropic) of Cardiac Contractions of In-Vitro Isolated Coronary Perfused Rabbit Heart.

Non depolarizer skeletal muscle relaxants and in vivo clinically effective human dose	Adopted test concentrations of drug solutions in perfusion fluid	Duration of slow continuous infusion of drug solutions (minutes)	Drug-induced alterations in specified items	
			Heart rate / minute counts (Chronotropism)	Amplitude of cardiac contractions (Inotropism)
1) Pipecuronium bromide 0.05 mg / kg	2 mg Litre $^{-1}$	a.5 Min.	Acceleration ↑+ 6/ Min (108 → 114 / min)	Increase↑ + 20%
		b.20 Min.	No effect (108 → 108 / min)	Red.↓ - 8.6%
2) Atracurium 0.25 mg / kg	6 mg Litre $^{-1}$	a.5 Min.	No effect (114 → 114 / min)	Increase↑ + 20%
		b.20 Min.	Slowing↓ - 18 / Min. (114→ 96 / min)	No Effect
3) Pancuronium bromide 0.06 mg / kg	3 mg Litre $^{-1}$	a.5 Min.	Increase↑ + 12 / min (108→ 120 / min)	Increase↑ + 13.8%
		b.20 Min.	Increase↑ + 12 / min (108→ 120 / min)	Red.↓ - 50%

Table (2): Patterns of Interactions of Slow Continuous Infusion Over 20 Minutes Period of Specified test Concentrations of Three Diverse Non-Depolarizer Skeletal Muscle Relaxants Comparable to Lapine Equivalents of In-vivo Human Plasma Circulating Levels with the Negative Cardiac Inotropic and Chronotropic Activities of 1μg Fixed Dose Acetylcholine (Ach.) Adminstered by Rapid Injection Technique into The Cannula of In-Vitro Isolated Coronary Perfused Rabbit Heart (Langendorff's Procedure)

Types of experimental Trials	Concentrations of test drugs in perfusion fluid	Drug-induced Alterations in Specified Items		Remarks
		Amplitude of cardiac contractions expressed as percentage (Inotropism)	Heart rate / minute counts (Chronotropism)	
a) Ach. (1μg Dose)	0.20μg/ ml	Red. ↓ - 35%	Slowing↓ - 36 / Min. (108→ 72 / min)	Pipecuronium infusion for 20min. Not antagonised brady cardia produced by acetyacetylcoline.
b) Pipecoronium Bromide	2 mg / litre (20 minutes)	Red. ↓ - 8.6%	No effect (108→ 108 / min)	
Effect of Ach. (1μg Dose) after Pipecuronium Bromide Infusion:	0.20μg / ml A ch. after 2 mg / liter pipecuronium	Red. ↓ - 30%	Slowing↓ - 42 / Min. (108→ 66 / min)	
a) Ach. (1μg Dose)	0.20 μg / ml	Red. ↓ - 38%	Slowing↓ - 36 / Min. (114→ 78 / min)	Atracurium also could not antagonised brady-cardia produced by acetylcholine
b) Atracurium	6 mg / litre (20 minutes)	Increase.↑ + 20%	Slowing↓ - 18 / Min. (114→ 96 / min)	
Ach. (1μg Dose) after Atracuium Infusion:	0.20 μg / ml 6 mg / liter Atracurium	Red. ↓ - 30.76%	Slowing↓ - 36 / Min. (114→ 78 / min)	
a) Ach. (1μg Dose)	0.20 ug / ml	Red. ↓ - 33.8%	Slowing↓ - 30 / Min. (108→ 78 / min)	Pancuronium perfusion in a dose of 3 mg / 1 for 20 min.Completely antagonised brad cardia produced by acetylcholine (1 μg).
b) Pancuronium Bromide	3 mg / liter (20 minutes)	Red. ↓ - 50%	Increase↑ + 12 / Min. (108→ 120 / min)	
Ach. (1μg Dose) after pancoroniom Infusion	0.20 ug / ml Ach. after 3 mg / litre Pancuronium	No Effect	No Effect (108→ 108 / min)	

- Rapid injection of 1μg A.ch dose yields final concentration of 0.2μg/ml in the perfusion fluid reaching the heart

2. Isolated Rabbit Atrium:

We found no statistical difference in the effect of pipecuronium and pancuronium in both force or rate of contraction of isolated rabbit atrium in the concentration range used (5-20 μ/mo) (Figs. 4,5). However atracurium in concentrations of 30, 60, 120, μg/ml produced dose dependent +ve inotropic effect without any effect on heart rate (Fig. 6).

3. Effect on Carotid Arterial Blood Pressure of Anaesthetized Cat:

I.V. injection of pipecuronium in a dose of 100 μg/kg B. W. produced transient blood pressure rise +10 mm Hg about 2 minutes duration (Table 3, Fig. 7).

Atracurium in a dose of 150 μg/kg B.W. produced temporary short lasting drop of blood pressure -30 mmHg (-30%). The onset of hypotension was rapid occurring within 30 seconds to 1 min. of drug injection lasted for approximately 1-1.5 minutes followed by rapid recovery of the arterial pressure to the pre-injection level (Table 3, Fig. 8).

Pancuronium bromide in a dose of 100 μg/kg B.W. produced biphasic vasodepressor response, comprising brief initial abrupt B.P. fall, partially recoverable followed by secondary longer lasting hypotension lasted for approximately 4-5 min. with gradual recovery of arterial pressure to the pre-injection level (Table 3, Fig. 9).

4. Effect of ECG Tracing of Anaesthetized Cats:

I.V. injection of pipecuronium in a dose of 100 μg/kg B.W. produced insignificant increase of the basal heart rate from 200 beat/min. to 205/min. with 2.5% increase (Fig. 10a).

Atracurium (150 μg/kg B. W.) produced increase of basal heart rate from 200 beat/min. to 215/min. The mean percentage increase from the basal level was approximately 7.5% (Fig. 10b).

Pancuronium (100 μg/kg) produced increase of basal heart rate from 200/min. to 230/min. The mean percentage increase from the basal level was 15.5% (fig. 10c).

The comparative electrocardiographic alterations elicited by single I. V. dosing with three skeletal muscle relaxants are summarized in table (4).

Discussion

The present experimental work demonstrated that intravenous bolus injection of pipecuronium in anaesthetized cat in a dose of 100 μg/g B.W. produced 2.5% increase in basal heart rate and transient insignificant rise in B.P. Atracurium (150 μg/kg B. W.) produced 7.5% increase in basal heart rate and temporary short lasting drop of arterial B. P. lasting for approximately 1.5 min.followed by rapid recovery. Pancuronium 100 μg/kg B. W. produced long lasting hypotension lasted for

Table (3): Comparative Carotid Arterial Blood Pressure Reactivity to Single i.v. Dosing with Three Chemically Divrse and Clinically Useful Muscle Relaxants Administered in Feline Equivalents of their Respective Effective Doses in Adult Male Chloralosed Cat under Controlled Respiration in Air.

Skeletal muscle relaxants and clinically effective human i.v. dose	Feline equivalents of clinically effective human i.v. dose	Carotid arterial B.P. (mm Hg) as determined		Peak drug induced B.P. alterations and duration of changes (minutes)
		Per-Dosing	Post-Dosing	
1)Pipecuronium (0.05 mg / kg)	100 μ g kg B.W.	120 / 100	130 / 100	Transient B.P. rise ↑ + 10 mm Hg 2 minutes duration
2)Atracurium 0.25 mg / kg	150 μ g / kg B.W.	120 / 100	120 / 70	Temporary short lasting drop of B.P. ↓ - 30 mm Hg 1-1.5 minutes duration
3)Pipecuronium bromide 0.06 mg / kg	100 μ g / kg B.W.	120 / 105	120 / 70	Biphasic vasodepressor response comprising brief initial ABR UPT B.P fall partially recoverable followed by secondary longer lasting hypotension ↓ - 35 mm Hg 4-5 minutes duration

60 minutes time intervals between successive i.v. dosing.

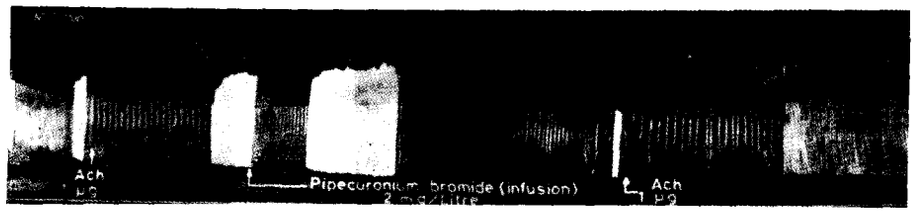

Fig. 1. Effect of pipecuronium perfusion on isolated perfused rabbit heart and its effect on bradycardia produced by 1 µg acetylcholine.

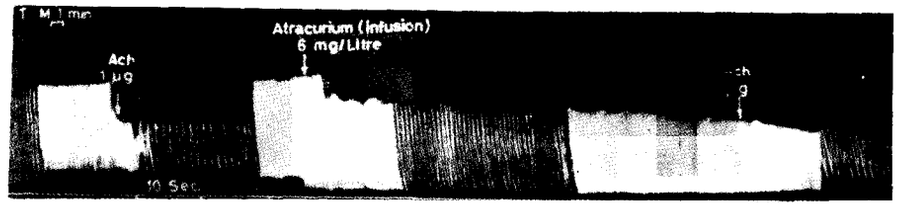

Fig. 2. Effect of atracurium perfusion on isolated perfused rabbit heart and its effect on bradycardia produced by 1 µg acetylcholine.

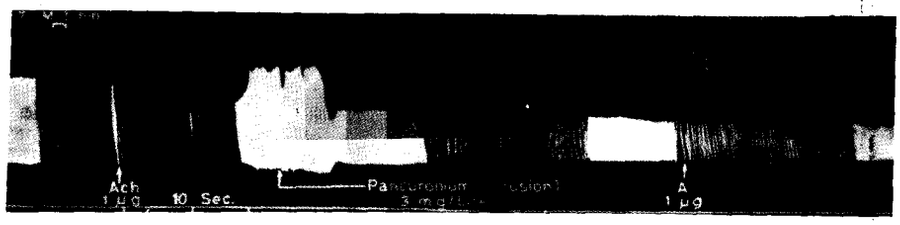

Fig. 3. Effect of pancuronium perfusion on isolated perfused rabbit heart and its effect on bradycardia produced by 1 µg acetylcholine.

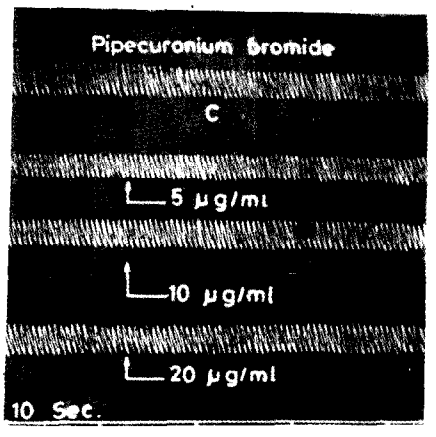

Fig. 4. Effect of pipecuronium increasing concentrations on isolated rabbit atrium.

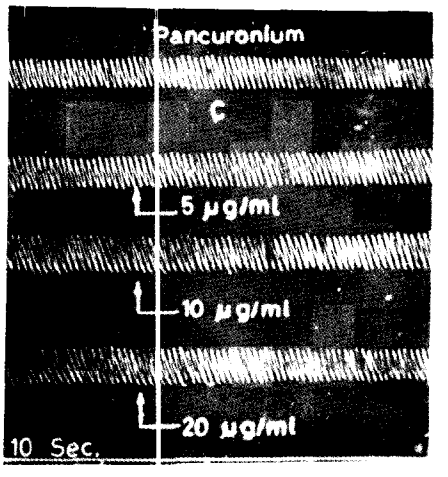

Fig. 5. Effect of pancuronium increasing concentrations on isolated rabbit atrium.

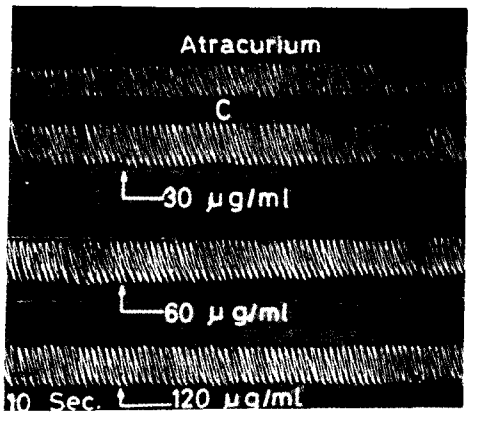

Fig. 6. Effect of atracurium increasing concentrations on isolated rabbit atrium.

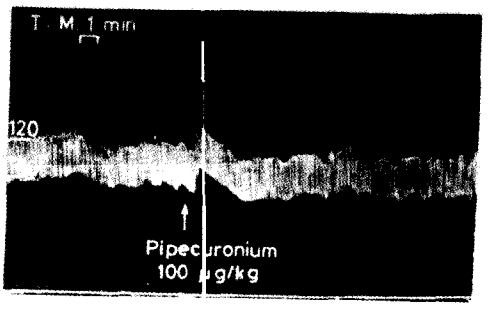

Fig. 7. Effect of pipecuronium on carotid arterial blood pressure anaesthetized cat.

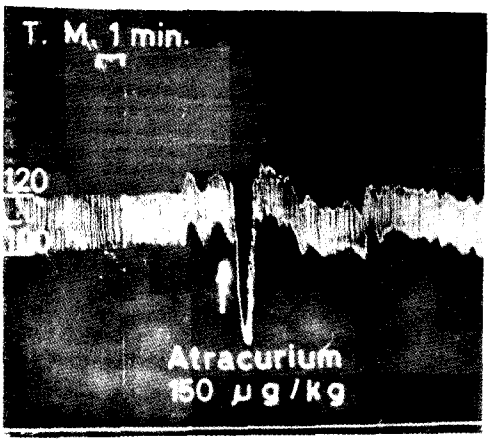

Fig. 8. Effect of atracurium on carotid arterial blood pressure of anaesthetized cat..

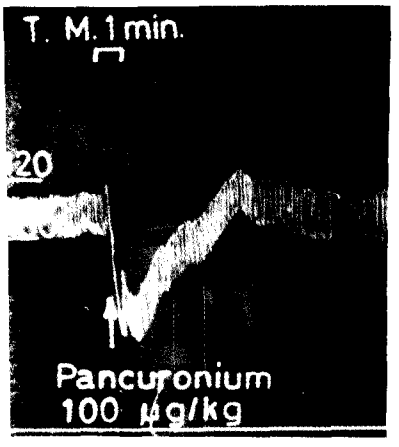

Fig. 9. Effect of pancuronium on carotid arterial blood pressure of anaesthetized cat.

approximately 4.5 min. with gradual recovery to the pre-injection level and 15.5% increase in basal heart rate.

Miller [1] demonstrated that in human, pancuronium causes an increase in heart rate due to primarily vagolytic effect, although the sympathetic nervous system has also been implicated. Pipecuronium appears to have little or no cardiovascular effect [12, 13]. Although there have been occasional reports of mild bradycardia [14, 15]. Atracurium is a mild histamine releaser and, on occasion, can cause a significant decrease in arterial blood pressure.

Foldes et al. [15] demonstrated that pipecuronium had insignificant effect on heart rate or blood pressure and pancuronium significantly increased heart rate by about 20 percent ($p < 0.01$) and caused a moderate, not significant increase of systolic blood pressure. They explained the difference in the cardiovascular effects between pipecuronium and pancuronium by differences observed in their effect on the evoked release of norepinephrine from the isolated right atrium of the guinea pig and on the force of contraction of the electrically stimulated atria.

Foldes et al. [17] found that, pancuronium, produced acceleration of heart rate and elevation of blood pressure. This is due to its inhibitory effect on muscarinic receptors located on the noradrenergic nerve terminals and the pacemaker cells of

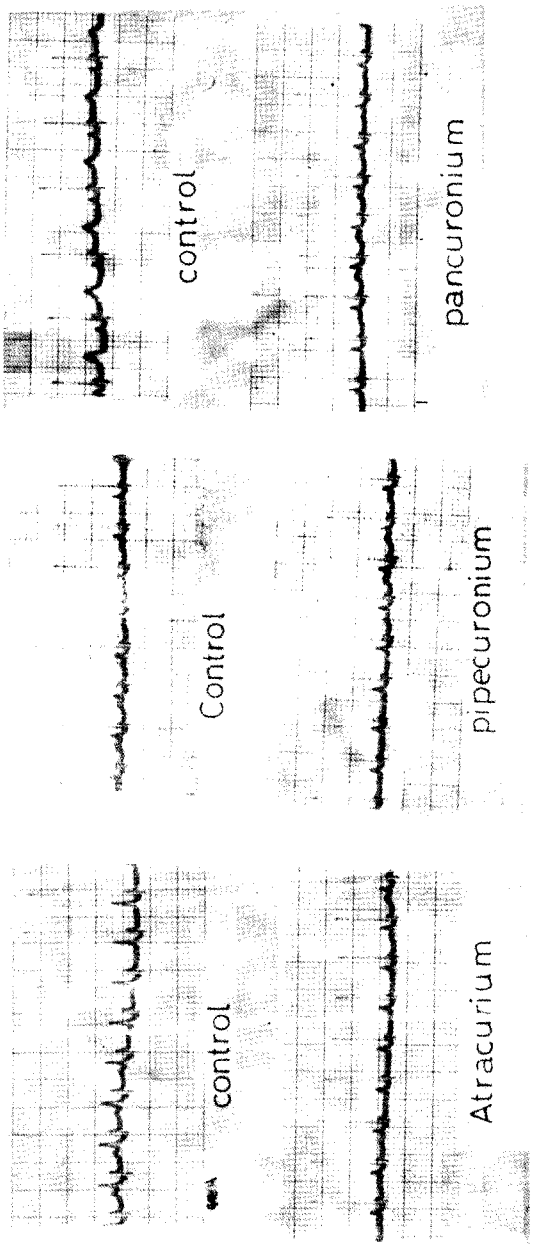

Fig. 10. ECG tracing showing:
a - Effect of pipecuronium bromide
b - Effect of atracurium.
c - Effect of pancuronium bromide

the right atria increases the evoked release of norepinephrine and the force of contraction of the electrically stimulated right atria. While pipecuronium has little or no inhibitory effect on these muscarinic receptor and consequently causes no elevation of heart rate [18]. In our present study, we found that pancuronium produced hypotension effect. This may be explained on basis that the majority of nondepolarizing neuromuscular blocking cation [15].

Scott et al. [19] demonstrated that, the rapid (5c) bolus dose of atracurium I. V. resulted in a significant increase in plasma histamine concentration ($p < 0.05$) and was associated with a decrease in mean arterial pressure and increase in heart rate. Hasking et al. [20]. found that large doses of atracurium cause hypotensive effect.

The present study demonstrated that pipecuronium and pancuronium produced no changes in force and rate of contraction of rabbit atria. And that pancuronium but not pipecuronium or atracurium produced complete antagonism to the bradycardia produced by acetylcholine.

Duke et al. [21] reported that pancuronium in concentrations from 10^{-5} to 10^{-2} g/litre did not alter the force of contraction in isolated rabbit atrial strips and this was inconsistent with the findings in this study. However. Iwatsaki et al. [10] reported that pancuronium increased that force of contraction in the ventricular muscle of healthy dogs.

Goat and Feldman [8] reported that pancuronium perfusate in a concentration of 2 mf/L. completely antagonised acetylcholine bradycardia. But in the study carried by Baden [6], pancuronium perfusate 2 mg/L. resulted in a 20% decrease in the heart rate acetylcholine injected as a bolus dose to the heart. In the present study pancuronium 3 mg/L in perfusate completely antagonised bradycardia produced by acetylcholine.

We concluded that, pipecuronium appears to be a suitable replacement for pancuronium for the production of muscular relaxation of relatively long duration in patients in whom elevation of heart rate has to be avoided. The vagolytic effects of pancuronium is desirable, especially when counteracting the bradycardic tendency of large doses of fentanyl. But pancuronium should not be given to patients with myocardial ischemia because of the tachycardia may augment the chances of ischemia and/or infarction. And that the transient haemodynamic effect of atracurium is probably of little clinical significance in the healthy patient. The effect may be more important in the haemodynamically unstable patient who is hypovolaemic or has cardiovascular disease.

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