COMPARITIVE STUDY BTWEEN PANTOPRAZOLE AND RANITIDINE ON SOME CARDIOVASCULAR PREPARATIONS

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ABSTRACT

Because of the abundant use of proton pump inhibitors (PPIs) and histamine H_2-receptors antagonists (H_2RAs) and considering the hazards of high intravenous (IV) dosing especially in critically ill intensive care unit (ICU) patients and in view of controversy about the cardiac effects of these drugs. So it was of interest in the present work to investigate and compare the effects of either pantoprazole or ranitidine on some cardiovascular aspects using both isolated and intact experimental animal preparations.

The effect of different increasing doses of pantoprazole or ranitidine on the amplitude of myocardial contraction of isolated perfused rabbit heart and on NE-induced contraction of aortic spiral strips of rabbits were studied. Their effects on the mean arterial blood pressure (MABP), heart rate (HR) and electrocardiogram (ECG) of anaesthetized cats were also investigated.

This stady showed that, pantoprazole caused a significant dose-dependent reduction in the amplitude of myocardial contraction with mean percentage reductions ranged from 2.5 ± 0.55 to 58.4 ± 3.82, while ranitidine had no effect. The cardioinhibitory effect of pantoprazole was proven to be due to a calcium channel blocking effect. On NE-induced contraction of aortic spiral strips, both pantoprazole and ranitidine produced a significant dose dependent reduction. The mean percentage reductions ranged from 3.9 ± 0.59 to 40.3 ± 2.13, and8.3 ± 2.45 to 45.4 ± 5.82 for pantoprazole and ranitidine respectively. Intravenous bolus injection of both drugs produced a significant dose-dependent reduction in MABP. The mean percentage reductions ranged from 0.6 ± 0.23 to 16.1 ± 3.15 and 0.7 ± 0.19 to 42.6 ± 3.21 for pantoprazole and ranitidine respectively and were found to be statistically significant. On the other hand, continuous intravenous infusion of pantoprazole 1.5 mg/kg or ranitidine 2 mg/kg which is equivalent to the human therapeutic dose (HTD), for 2 hours did not produce any change in the MABP, ECG pattern and heart rate of an anaesthetized cat all over the time of infusion.

In conclusion, ranitidine had no cardioinhibitory effect compared to pantoprazole. So, it could be prefered to pantoprazole especially in cardiac patients. On the other hand, the possibility of negative inotropic effect with pantoprazole should be considered carefully especially in patients with myocardial contractility dysfunction.

In the setting where intermittent IV bolus administration of either pantoprazole or ranitidine is needed, pantoprazole seems to be more favourable of the two drugs evident by its less hypotensive effect plus insignificant effect on heart rate and no changes in ECG record even at high doses.

The continuous IV infusion route may be safer and better chosen rather than IV bolus intermittent dosing to avoid any possible cardiovascular side effects of either pantoprazole or ranitidine.

INTRODUCTION

Prophylaxis against the development of stress ulcers and subsequent gastric bleeding is a major therapeutic challenge in intensive care medications in the inpatients and intensive care unit settings. Stress related mucosal damage is an acute, erosive gastritis of unclear pathophysiology, representing conditions ranging from stress-related injury to stress ulcer. It is apparent in 75-100% of critically ill patients within 24 hours of admission to an intensive care unit **(Grube and May, 2007).**

Proton pump inhibitors (PPIs) and histamine H_2-receptor antagonists (H_2RAs) are commonly used in oral and intravenous formulations as prophylaxis against stress-induced gastritis, ulcers, and gastrointestinal bleeding in high-risk patients. Proton pump inhibitors may be also a particularly important intervention after cardiac surgery ***(Hata et al., 2005).*** The advantage of PPIs over H_2RAs is that, there was no tachyphylactic phenomena reported in patients taking PPIs, resulting in more perdictable and sustained PH control than H_2RAs **(Pongprasobchai, 2009).**

They are also commonly prescribed prophylactically to patients with ischemic heart disease including stable angina that have received percutaneous coronary intervention to prevent gastrointestinal bleeding particularly for those patients considered to be at high risk **(Wu *et al.*, 2011).**

In a report, the use of high-dose of ranitidine H_2-blocker was associated with several adverse effects such as bradycardia, sinus arrest, atrio-ventricular conduction disturbances, and cardiac decompensation **(Hinrichsen *et al.*, 1995).** However, another study reported that H_2-blocker could modulate heart-rate variability, and has the possibility to inhibit the increase in the sinus rate and prevent ventricular ectopy **(Ooie *et al.*, 1999).** Moreover the PPI, pantoprazole has been found to depress cardiac contractility at higher concentration in-vitro, although omeprazole administration did not lead to any changes in the cardiac performance of patients with congestive heart disease **(Tanaka *et al.*, 2008).**

MATERIALS AND METHODS

Animal doses corresponding to the human therapeutic doses were calculated according to the method given by **Paget and Barnes, (1964)** who calculated the dose in relation to the animal surface area.

I) In-Vitro studies:

1- Isolated perfused rabbit heart: The effect of different increasing doses of either pantoprazole (1.5-48 µg/ml) or ranitidine (2 - 64 µg/ml) on the amplitude of myocardial contractility of isolated perfused rabbit heart was studied by **(Modified Langendorff preparation**): (Staff of the department of pharmacology. Edinburgh, 1970a) and the site of action was investigated.

2- Isolated aortic spiral strips of rabbit: The effect of different increasing doses of either pantoprazole (1.5-48 µg/ml) or ranitidine (2 - 64 µg/ml) on the NE-induced contraction of isolated rabbit aortic spiral strips was also studied. (***Furchgott and Bhadrakom),*** (Staff of department of pharmacology, Edinburgh, 1970 $_a$).

II) In-vivo studies:

Effect on the mean arterial blood pressure (MABP), **heart rate and ECG of anaesthetized cats.**

The effect of different increasing doses of either pantoprazole (0.37 – 12mg/kg) or ranitidine (0.5-16mg/kg) on MABP, heart rate and ECG pattern and also the effect of IV infusion of either pantoprazole (1.5mg/kg) or ranitidine(2 mg/kg) were studied according to the Staff of department of pharmacology, Edinburgh, 1970 [a]) and the site of action was investigated.

t-test for comparision and of significance **(Steel and Torrie 1960)**.

RESULTS:

I) In-vitro studies:

1) Isolated perfused rabbit heart: the effect on the amplitude of myocardial contraction(cm)

Pantoprazole (1.5 µg/ml - 48 µg/ml) caused a significant dose-dependent reduction in the amplitude of myocardial contractility as shown in (Fig. 1). The mean percentage reductions ranged from 2.5 ± 0.55 to 58.4 ± 3.82 and were found to be statistically significant (Table 1). The cardioinhibitory effect of pantoprazole was persisted after the complete blockade of nicotinic and muscarinic receptors. In addition, it did not affect neither the positive inotropic action of isoprenaline nor histamine. The myocardial depressant effect of pantoprazole was completely abolished by Ca^{+2} channel blocker, indicating that Ca^{+2} could play a role in pantoprazole mediating myocardial depression, as shown in (Fig. 2 a, b,c,d,e&f). Ranitidine at all doses shad no effect in the amplitude of myocardial contractility as shown in (Fig. 3).

2) Effect on NE-induced contraction (cm) of isolated rabbi t aortic strip:

Pantoprazole or ranitidine in small doses produced no effect, while in larger doses 3 µg/ml - 48 µg/ml for pantoprazole and 8 µg/ml - 64 µg/ml for ranitidine they produced a significant dose dependent reduction of NE-induced contractions. The mean percentage reductions ranged from 3.9 ± 0.59 to 40.3 ± 2.13, and8.3 ± 2.45 to 45.4 ± 5.82 for pantoprazole and ranitidine respectively and were found to be statistically significant (Fig. 4 & 5, Table 2 & 3). No significant difference was found on comparing the mean percentage reduction in NE-induced contraction between the two drugs. Ranitidine produced a slightly less relaxant effect than pantoprazole at all doses except at the very large dose as shown in (Table 4 & Fig. 6).

II) In-vivo studies

Effect on the mean arterial blood pressure (MABP), **heart rate and ECG of anaesthetized cats.**

Intravenous bolus injection of small dose of pantoprazole (0.37 mg/kg) elicited no effect, while larger doses 0.75-12mg/kg produced a significant dose-dependent reduction in MABP. The mean percentage reductions ranged from 0.6 ± 0.23 to 16.1 ± 3.15 (Fig. 7 & Table 5).

The blood pressure lowering effect of pantoprazole was persisted after the complete blockade of nicotinic, muscarinic, β-adrenergic and histamine (H_1 &H_2) receptors. However the fall in BP induced by pantoprazole was completely abolished by blocking the Ca^{+2} channel as shown in (Fig. 8 a,b,c ,d, e). On ECG, pantoprazole showed insignificant effect on heart rate and there was no abnormalities in the ECG pattern (Fig. 9). On the other hand, continuous intravenous infusion of pantoprazole 1.5 mg/kg, which is equivalent to the human therapeutic dose (HTD), for 2 hours at a rate of 12µg/min did not produce any change in the MABP, ECG pattern and heart rate of an anaesthetized cat all over the time of infusion (Fig. 10).

The intravenous bolus injection of ranitidine (0.5-16mg/kg) was also found in the present work to exert a dose-dependent reduction in the MABP as shown in (Fig. 11) . The mean

percentage reductions ranged from 0.7 ± 0.19 to 42.6 ± 3.21 and were found to be statistically significant (Table 6). The blood pressure lowering effect of ranitidine was persisted after the complete blockade of nicotinic, muscarinic, β-adrenergic, H_1-receptors and complete blockade of Ca^{+2} channel (Fig. 12 a,b,c,d &e). Ranitidine had no effect on heart rate except for the largest dose in which ranitidine produced a significant increase in the heart rate. No abnormalities in ECG pattern were observed as shown in (Fig. 13). On the other hand, continuous intravenous infusion of ranitidine 2 mg/ml, which is equivalent to the HTD, for 2 hours at a rate of 16.7 µg/min did not produce any change in the MABP or ECG pattern and heart rate of an anaesthetized cat all over the time of infusion (Fig. 14).). Significant difference was found on comparing the mean percentage reduction on MABP of anaesthetized cat (Table 7 & Fig. 15 & 16).

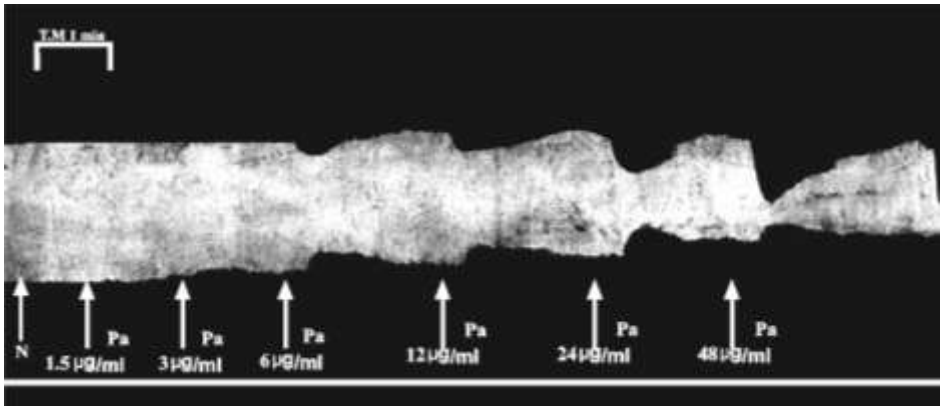


Figure (1): Effect of pantoprazole (1.5-48 µg/ml) on the amplitude of myocardial contraction(cm) of isolated rabbit heart. N:normal Pa :pantoprazol

Table (1): Mean % reductions caused by pantoprazole (1.5-48 µg/ml) on the amplitude of myocardial contraction of isolated rabbit heart.

	Doses (1.5 – 48 µg/ml)					
	1.5	**3**	**6**	**12**	**24**	**48**
Mean	**2.5**	**5.7**	**13.6**	**19.7**	**37.6**	**58.4**
± SEM	**0.55**	**0.67**	**1.40**	**1.61**	**2.63**	**3.82**
P	<0.01*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*

P= Test of significancy between pantoprazole and rantidine

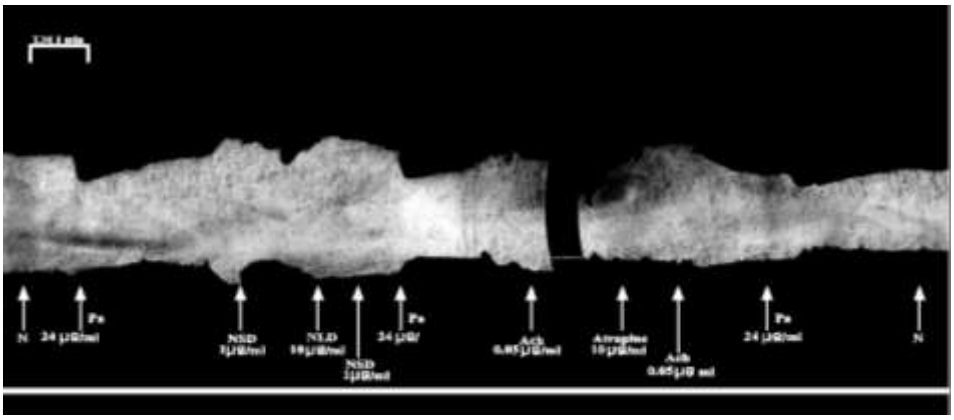


Figure (2a): Effect of pantoprazole (24µg/ml) on the isolated perfused rabbit heart after the complete blockade of nicotinic and muscarinic receptors.

N = Normal contraction Pa = Pantoprazole
NSD = Nicotine small dose NLD = Nicotine large dose
Ach = Acetylcholine

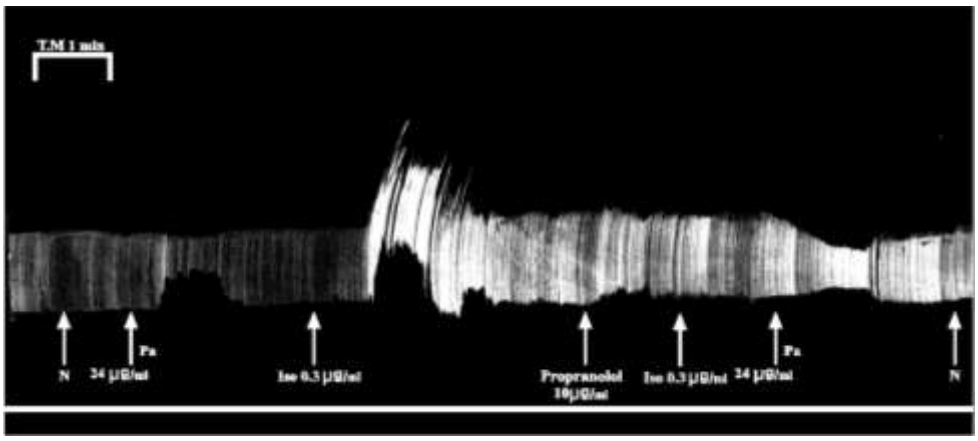


Figure (2b): Effect of pantoprazole (24µg/ml) on isolated perfused rabbit heart after the complete blockade of B-adrenoceptors. N:normal Iso: isoprenaline

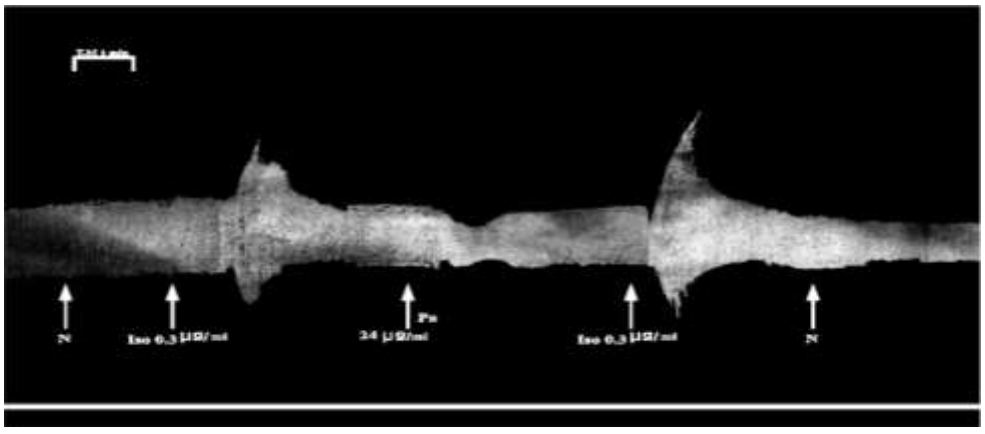


Figure (2c): Effect of pantoprazole (24µg/ml) on isoprenaline-induced positive inotropic effect of isolated perfused rabbit heart.

N= Normal Pa.= Pantoprazole
Iso= Isoprenalin

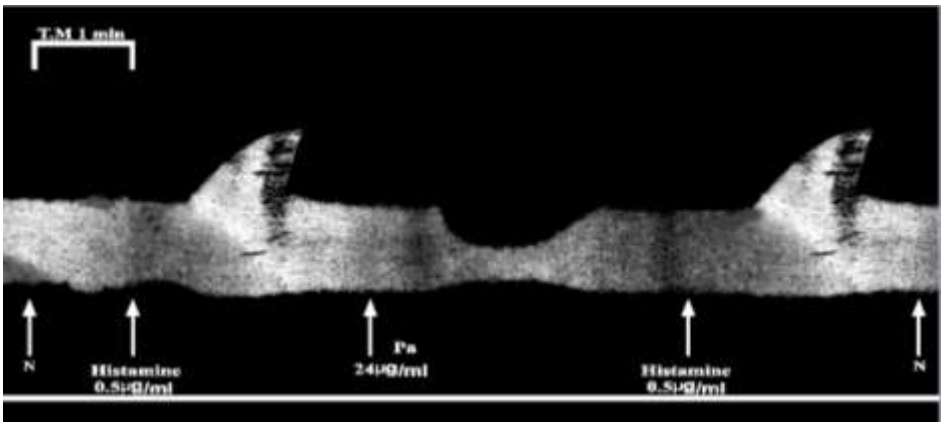


Figure (2d): Effect of pantoprazole (24µg/ml) on histamine-induced positive inotropic effect of isolated perfused rabbit heart.
N= Normal contraction Pa= Pantoprazole

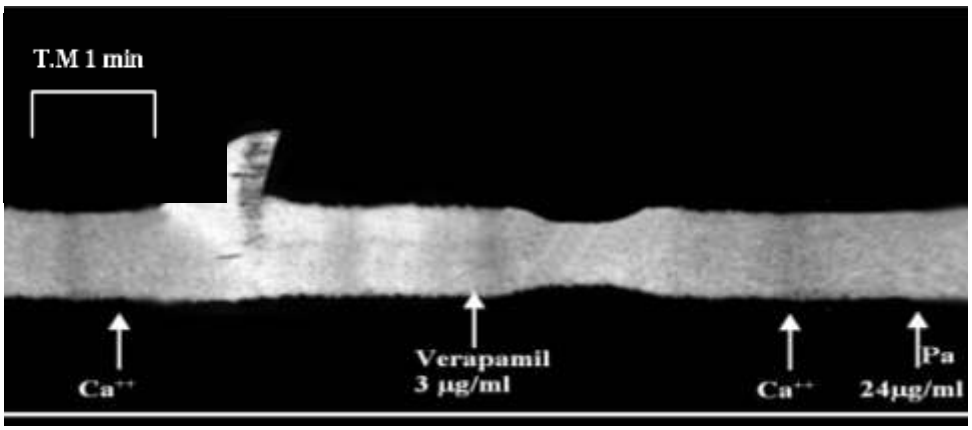


Fig. (2e): Effect of pantoprazole (24µg/ml) on isolated perfused rabbit heart after the complete blockade of calcium channel by verapamil. Ca^{+2} = Calcium gluconate (300µg/ml)

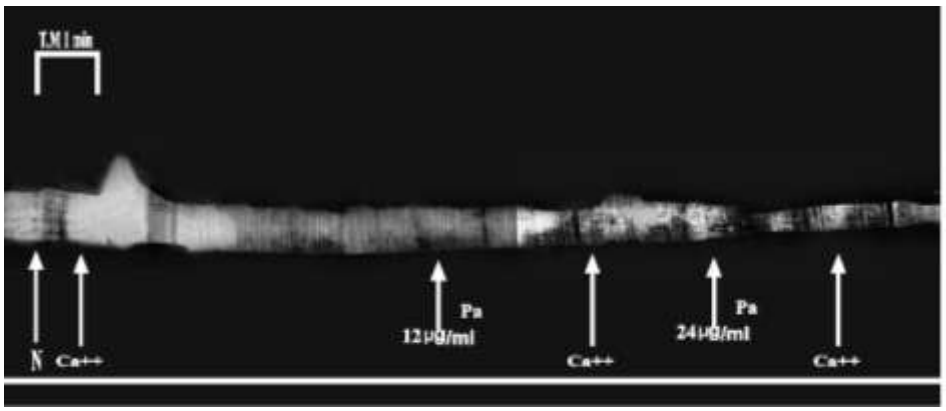


Figure (2f): Effect of pantoprazole on calcium induced-positive inotropic effect of isolated perfused rabbit heart.
N = Normal Pa = Pantoprazole
Ca^{+2} = Calcium gluconate (300µg/ml)

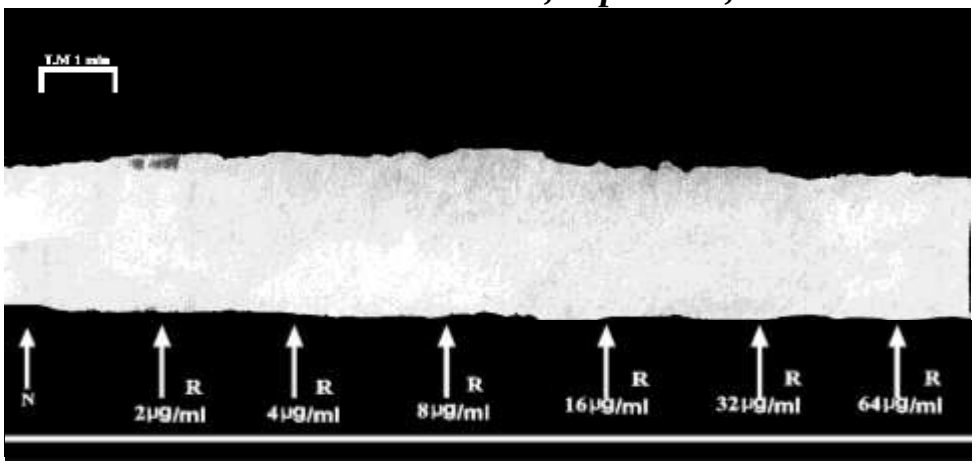


Figure (3): Effect of ranitidine (2 - 64 µg/ml) on the amplitude of myocardial contraction (cm) of isolated rabbit heart. N:normal R: ranitidine

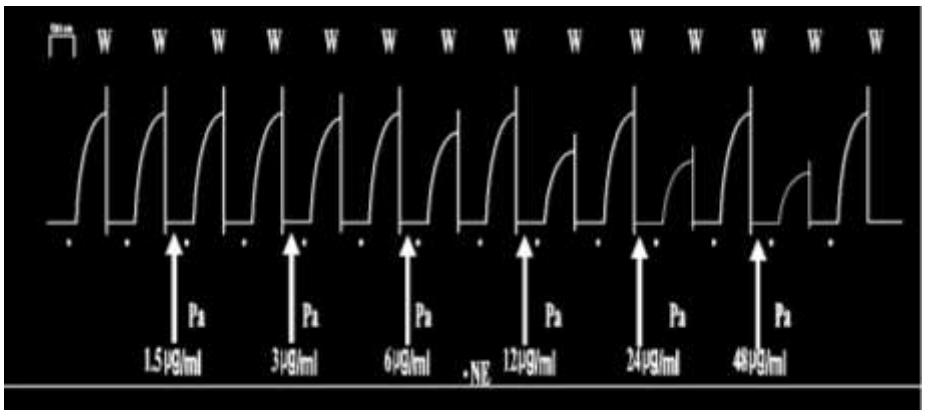


Figure (4): Effect of pantoprazole (1.5 - 48 µg/ml) on norepinephrine-induced contraction(cm) of rabbit aortic spiral strip.
Pa = Pantoprazole W = Wash
NE = Norepinephrine (0.5µg/ml) R: ranitidine

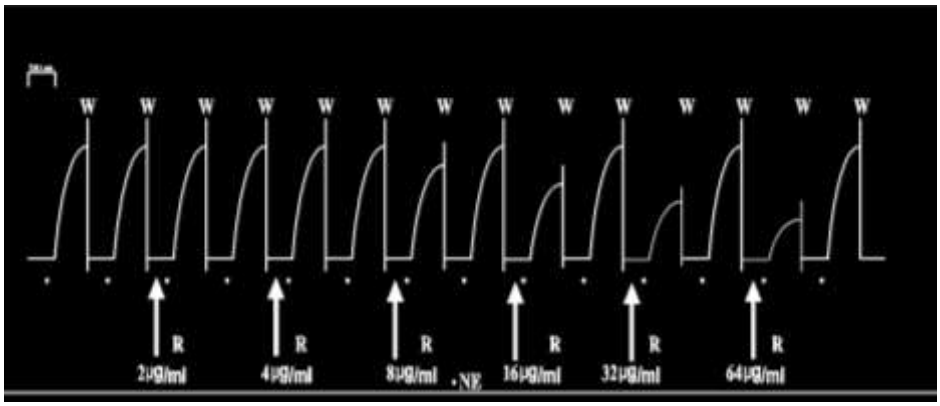


Figure (5): Effect of ranitidine (2 - 64 µg/ml) on norepinephrine-induced contraction of rabbit aortic spiral strip.

Table (2): Mean % reductions caused by pantoprazole (1.5-48 µg/ml) on norepinephrine-induced contraction (cm) of isolated rabbit aortic spiral strip.

	Doses (1.5 – 48 µg/ml)					
	1.5	**3**	**6**	**12**	**24**	**48**
Mean	**0**	**3.9**	**12.7**	**20.9**	**27.8**	**40.3**
± SEM	**--------**	**0.59**	**0.93**	**1.25**	**1.61**	**2.13**
P		<0.05*	<0.05*	<0.05*	<0.05*	<0.05*

* = significant P<0.05

Table (3): Mean % reductions caused by ranitidine (2-64 µg/ml) on norepinephrine- induced contraction (cm) of isolated rabbit aortic spiral strip.

	Doses (2 – 64 µg/ml)					
	2	**4**	**8**	**16**	**32**	**64**
Mean	0.0	0.0	**8.3**	**15.8**	**26.1**	**45.4**
± SEM	0.0	0.0	**2.45**	**2.85**	**3.82**	**5.82**
P			<0.05*	<0.05*	<0.05*	<0.05*

* = significant P<0.05

Table (4): Comparison between mean % reductions in norepinephrine-induced contraction(cm) of isolated rabbit aortic spiral strip caused by either pantoprazole (1.5-48µg/ml) or ranitidine (2-64µg/ml).

	Pa 3	**R 4**	**Pa 6**	**R 8**	**Pa 12**	**R 16**	**Pa 24**	**R 32**	**Pa 48**	**Ra 64**
Mean	**3.9**	**0.0**	**12.7**	**8.3**	**20.9**	**15.8**	**27.8**	**26.1**	**40.3**	**45.4**
±SEM	**0.59**	**0.0**	**0.93**	**2.45**	**1.25**	**2.85**	**1.61**	**3.82**	**2.13**	**5.82**
p•	>0.05		>0.05		>0.05		>0.05		>0.05	

Pa= Pantoprazole R=Ranitidine

p• = Test of significance between pantoprazole and ranitidine.

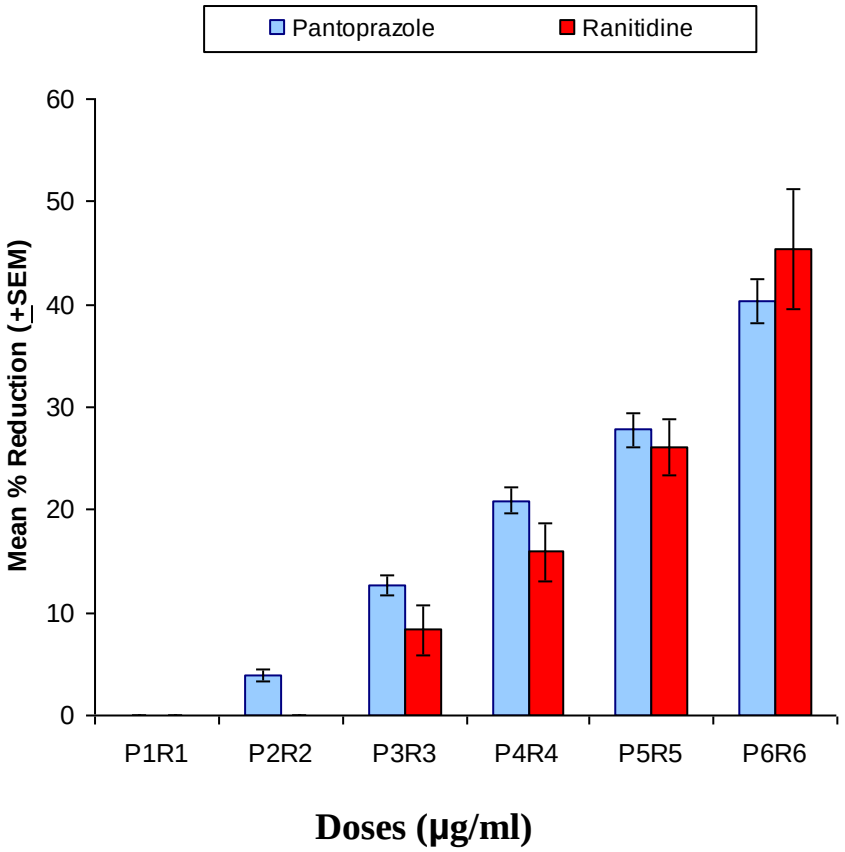


Figure (6): Bar chart showing the comparison between the mean % reduction (± SEM) of pantoprazole and ranitidine on norepinephrine-induced contraction of isolated rabbit aortic spiral strip.

Doses of pantoprazole (P_1: P_6) are 1.5, 3, 6, 12, 24 & 48 µg/ml.

Doses of ranitidine (R_1: R_6) are 2, 4, 8, 16, 32 & 64 µg/ml.

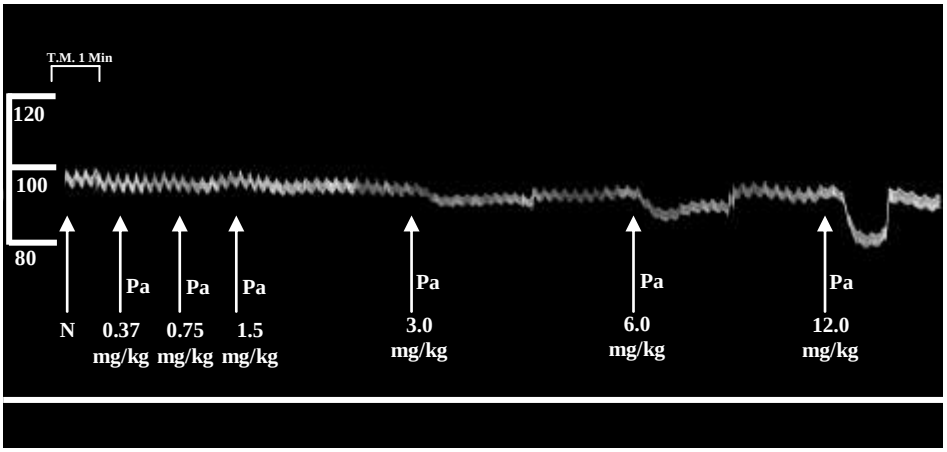


Figure (7): Effect of pantoprazole (0.37-12 mg/kg) on the mean arterial blood pressure of anaesthetized cat.

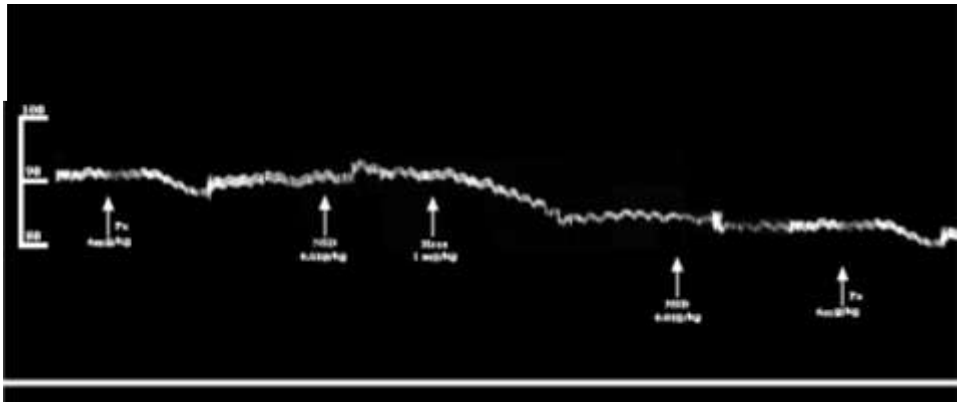
N=Normal Pa = Pantoprazole

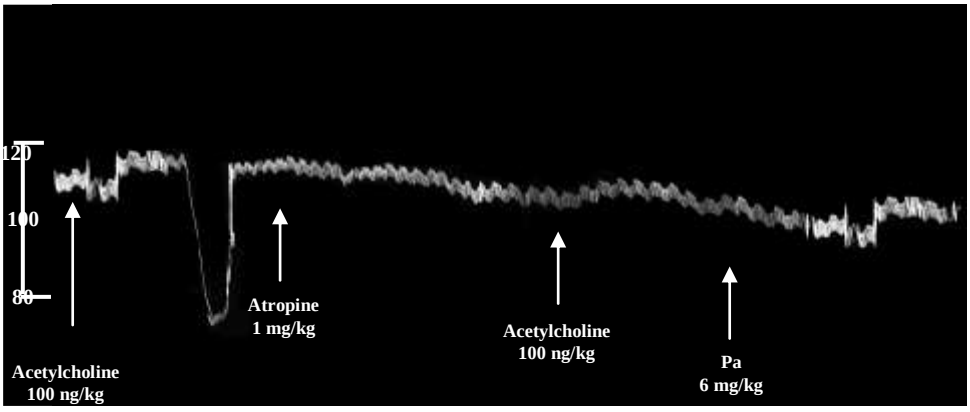
Table (5): Mean % reductions caused by pantoprazole (0.37-12mg/kg) in the mean arterial blood pressure of anaesthetized cat.

	Doses (0.37 – 12 mg/kg)					
	0.37	**0.75**	**1.5**	**3**	**6**	**12**
Mean	**0.0**	**0.6**	**2.0**	**4.1**	**8.4**	**16.1**
± SEM	**0.0**	**0.23**	**0.37**	**0.65**	**2.18**	**3.15**
P		< 0.05*	< 0.01*	<0.001*	<0.001*	<0.001*

*= Significant P < 0.05

a



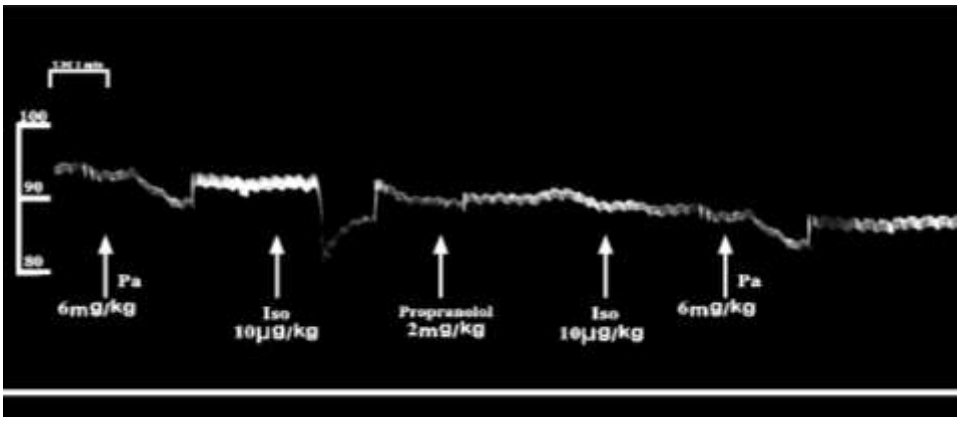


b

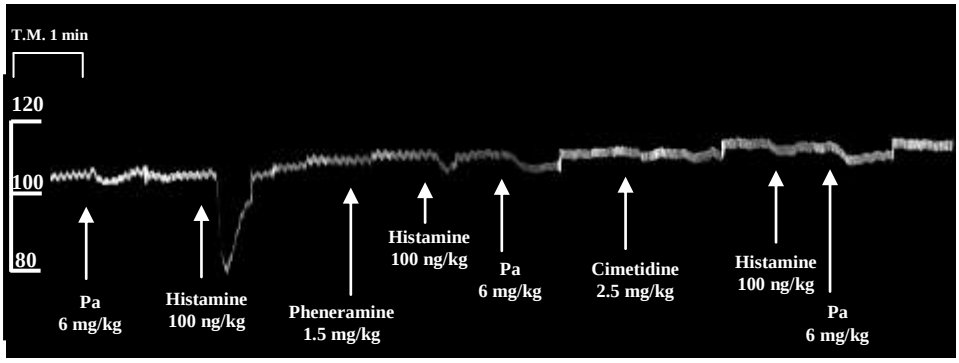
Figure (8 a&b): Effect of pantoprazole after complete blockade of nicotinic (a) and muscarinic receptors (b)

Pa = Pantoprazole Hexa = Hexamethonium bromide

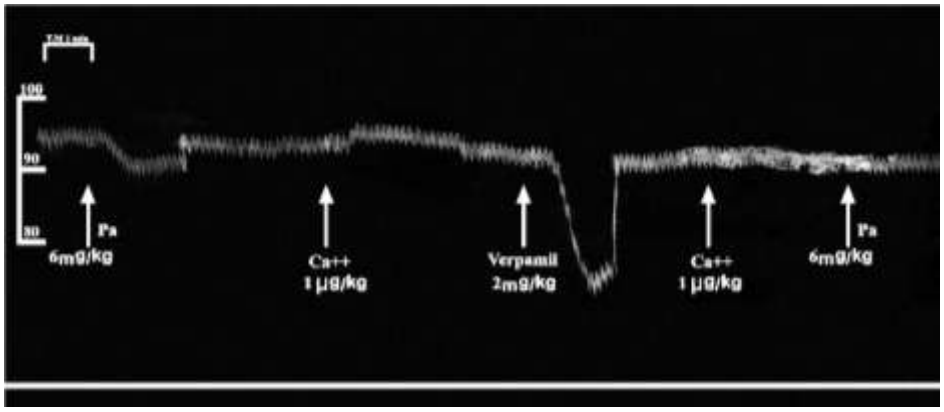
NSD = Nicotin small dose



c



d



e

Figure (8 c, d & e): Effect of pantoprazole (6mg/kg) after complete blockade of β-adrenergic receptors (c), histamine H_1& H_2 (d) and calcium channel (e).
P:pantoprazole , Iso: isoprenaline, Ca^{+2} = Calcium

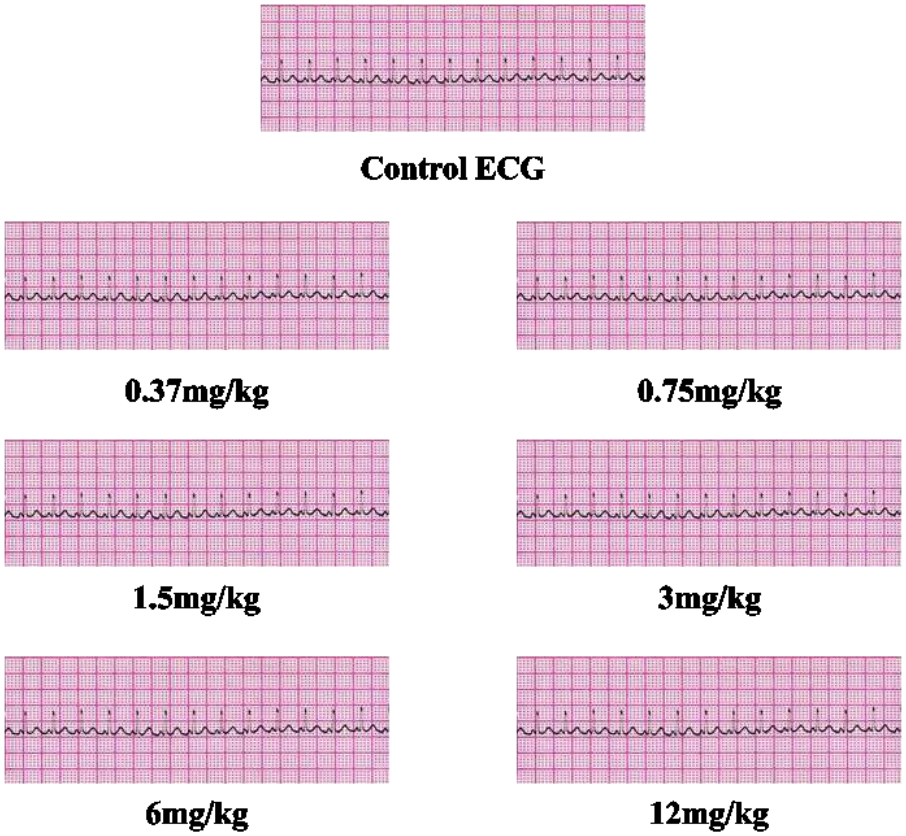


Figure (9): Effect of pantoprazole (0.37-12mg/kg) on ECG records and HR of normal anaesthetized cat.

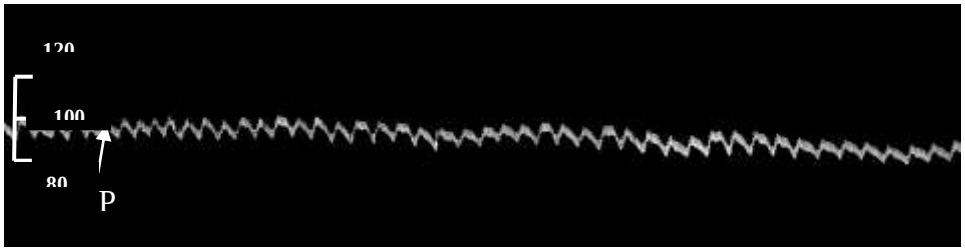


Figure (10): Effect of intravenous infusion of pantoprazole (1.5mg/kg) for 2 hours on the mean arterial blood pressure of anaesthetized cat

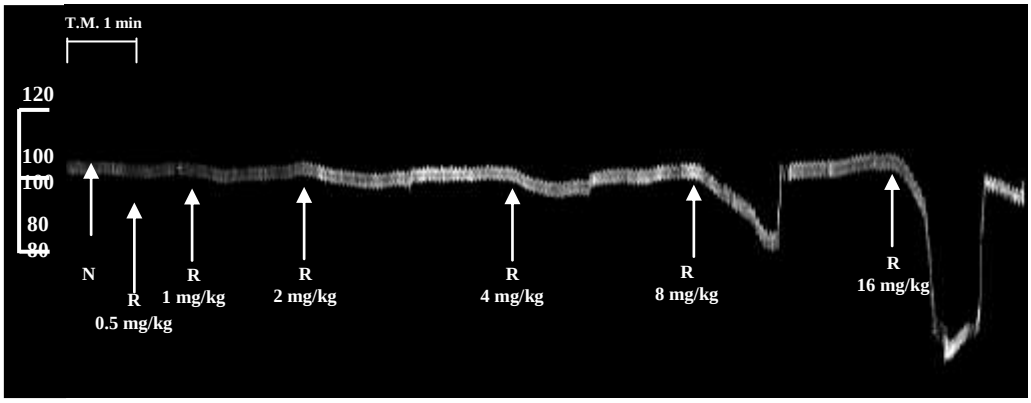
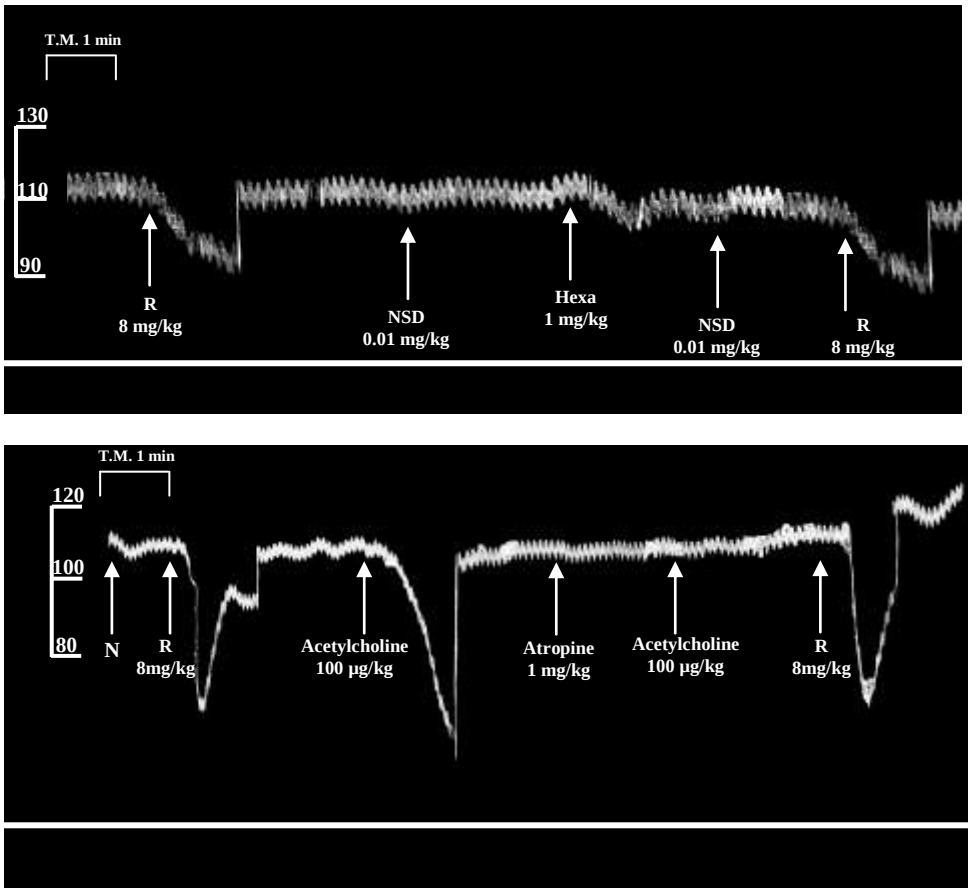


Figure (11): Effect of ranitidine (0.5-16 mg/kg) on the mean arterial blood pressure of normal anaesthetized cat. N :normal , R: ranitidine

Table (6): Mean % reductions caused by ranitidine (0.5-16mg/kg) in the mean arterial blood pressure of anaesthetized cat.

	Doses (0.5 – 16 mg/kg)					
	0.5	**1**	**2**	**4**	**8**	**16**
Mean	**0.7**	**1.6**	**3.8**	**9.4**	**23.6**	**42.8**
± SEM	**0.19**	**0.37**	**0.45**	**1.29**	**1.77**	**3.21**
P	< 0.05*	< 0.05*	< 0.05*	< 0.05*	< 0.05*	< 0.001*

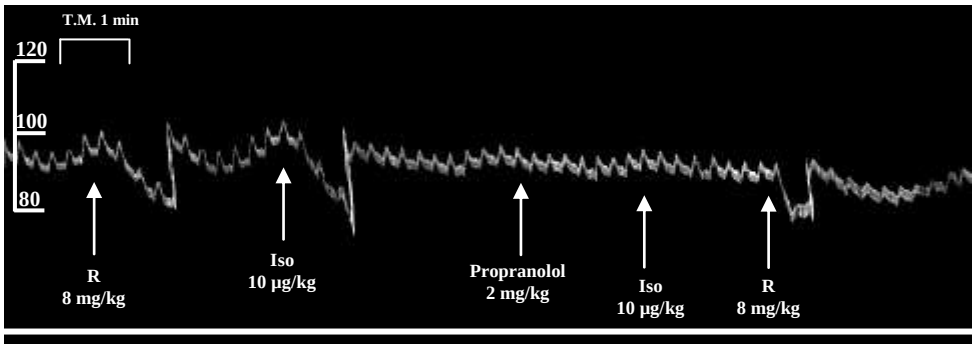
* = Significant (P< 0.05).



b

Figure (12 a&b): Effect of ranitidine (8mg/kg) after complete blockade of nicotinic (a) and muscarinic receptors (b).

R= Ranitidine Hexa = Hexamethonium bromide NSD: nicotine small dose



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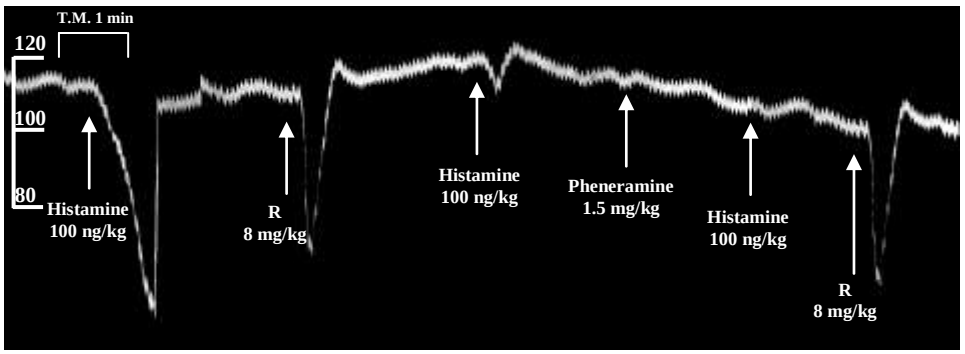

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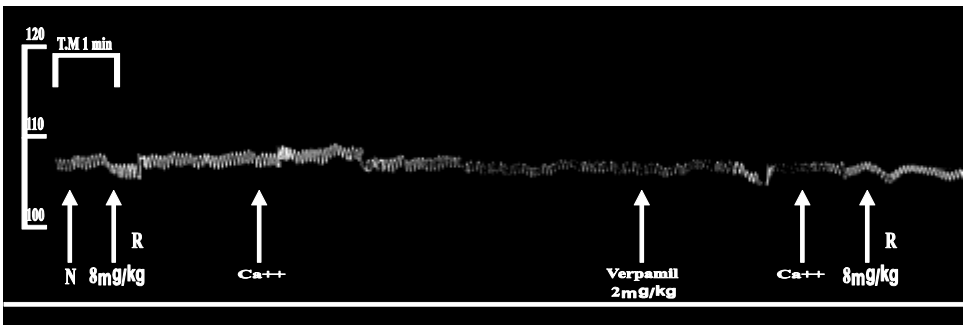

e

Figure (12 c, d & e): Site of action of ranitidine (8mg/kg) after complete blockade of β-adrenergic receptors (c), histamine H_1 -receptors (d) and calcium channel (e). , Iso: isoprenaline R= Ranitidine, N:normal

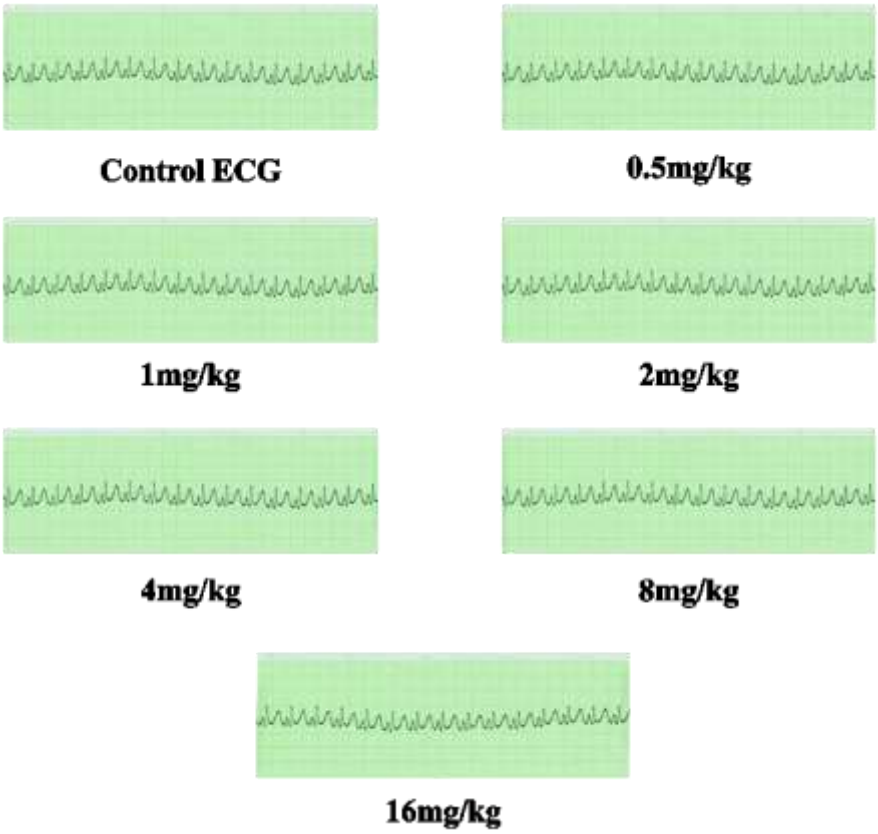

Figure (13): Effect of ranitidine (0.5-16mg/kg) on ECG records of anaesthetized cat.

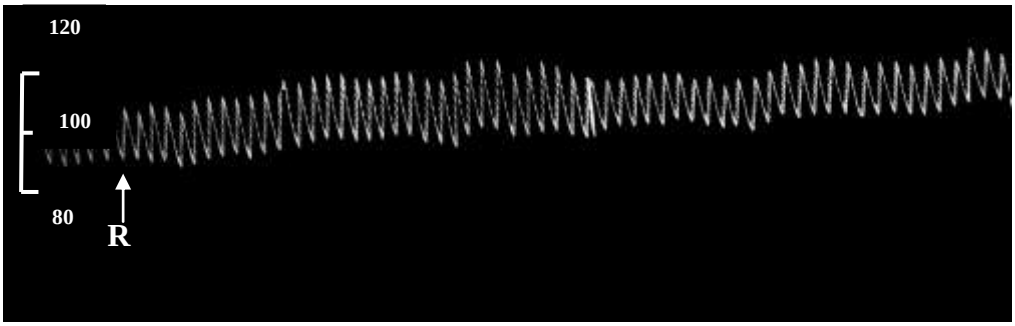

Figure (14): Effect of intravenous infusion of ranitidine (2mg/kg) for 2 hours on arterial blood pressure of anaesthetized cat.

Table (7): Comparison between mean % reductions in the mean arterial blood pressure caused by either pantoprazole (0.37-12mg/kg) or ranitidine (0.5-12mg/kg).

	Pa 0.37	R 0.5	Pa 0.75	R 1	Pa 1.5	R 2	Pa 3	R 4	Pa 6	R 8	Pa 12	R 16
Mean	**0.0**	**0.7**	**0.6**	**1.6**	**2.0**	**3.8**	**4.1**	**9.4**	**8.4**	**23.6**	**16.1**	**42.8**
±SEM	---	**0.19**	**0.23**	**0.37**	**0.37**	**0.45**	**0.65**	**1.29**	**2.18**	**1.77**	**3.15**	**3.21**
P•	< 0.02*		<0.05*		< 0.05*		< 0.05*		< 0.05*		< 0.05*	

Pa = Pantoprazole R = Ranitidine

p• = Test of significance between pantoprazole and ranitidine

***= Significant**

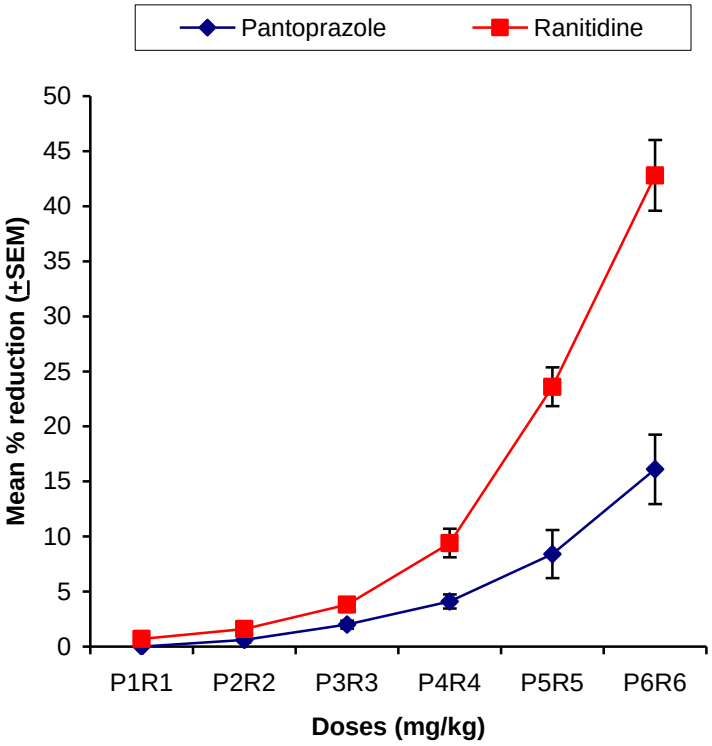

Figure (15): Comparison between the mean % reduction (± SEM) of pantoprazole and ranitidine on the mean arterial blood pressure (MABP) of anaesthetized cat.
Doses of pantoprazole (P_1: P_6) are 0.37, 0.75, 1.5, 3, 6, 12 mg/kg.
Doses of Ranitidine (R_1: R_6) are 0.5, 1, 2, 4, 8, 16 mg/kg.

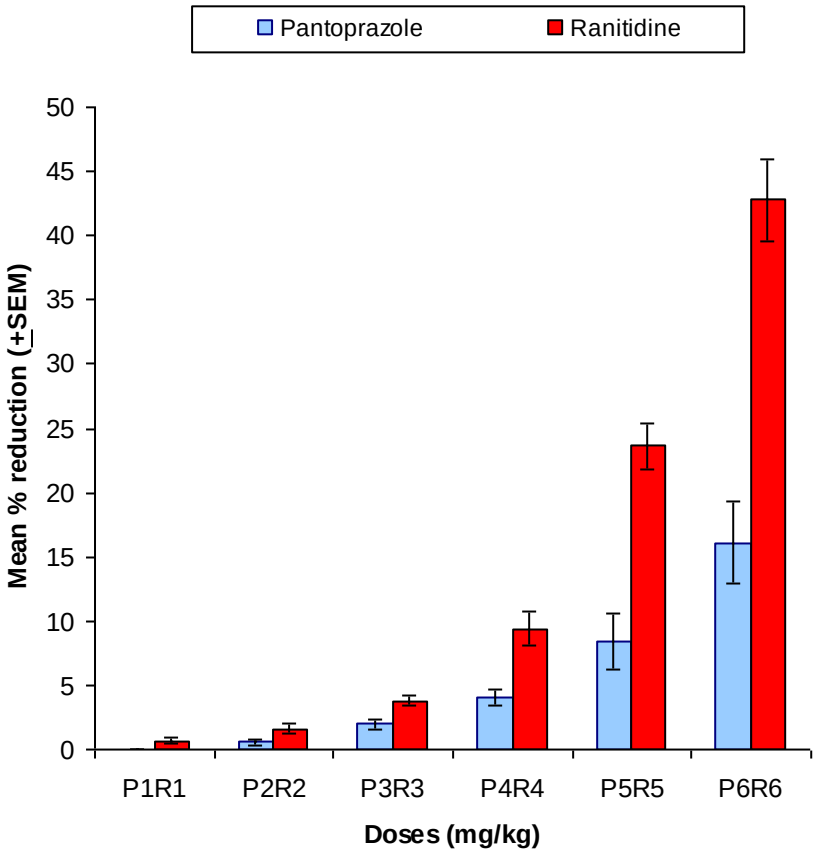

Figure (16): Bar chart showing the comparison between the mean % reduction ± SEM of pantoprazole and ranitidine on the mean arterial blood pressure of anaesthetized cat.

Doses of pantoprazole (P_1: P_6) are 0.37, 0.75, 1.5, 3, 6, 12 mg/kg.
Doses of ranitidine (R_1: R_6) are 0.5, 1, 2, 4, 8, 16 mg/kg.

DISCUSSION

In-vitro studies:

In the present work, the reduction of myocardial contractility with different doses of pantoprazole is consistent with the study carried out by **Schillinger *et al.* (2007),** who reported that, the negative inotropic effect of pantoprazole was present in myocardium from different species (human and rabbit) and in myocardium from different origins (atrial and ventricular), and in different myocardial preparations (multicellular and single cells).

The cardioinhibitory effect of pantoprazole in the present work was completely abolished by the Ca^{+2} channel blocker verapamil, also calcium evoked positive inotropic effect is completely disappeared by pantoprazole, indicating that Ca^{+2} could play a role in pantoprazole mediating myocardial depressant effect.

These findings are in agreement with other studies which showed that, the mechanism underlying the negative inotropic effect of pantoprazole in the myocardium may be completely different from the mechanism of the drug in gastric parietal cells and probably do not involve inhibition of H^+/K^+ ATPase **(Schillinger *et al.*, 2007).** In myocardial tissue, the H^+/K^+ ATPase enzyme may regulate homeostasis of H^+ and K^+; so its suppression could cause

cellular acidosis which interfere with Ca^{+2} responsiveness in the muscle cell, and thereby depress myocardial contractility at the level of myofilament **(Bers, 2001).**

Pantoprazole-induced negative inotropism was found to be based on its effect on Ca^{+2} homeostasis and myofilmant Ca^{+2} responsiveness and two underlying mechanisms have been proposed: (1) reduction in the amplitude of Ca^{+2} transients as a consequence of impaired Ca^{+2} uptake and reduced Ca^{+2} influx, (2) reduced Ca^{+2} responsiveness of the myofilaments as a result of reduced maximal active tension and a slightly lower sensitivity **(Schillinger *et al.*, 2007).**

On the contrary, clinical studies mentioned that, administration of the PPI (omeprazole) did not lead to any changes in the cardiac performance in healthy volunteers after one week oral treatment with therapeutic doses **(Halabi and Kirch, 1992).** In addition, a common high-dose regimen of pantoprazole usually applied for reducing rebleeding after endoscopic treatment of bleeding peptic ulcer did not result in clinically relevant impairment of left ventricular function and hemodynamics in healthy volunteers **(Schillinger *et al.*, 2009).**

However, patients with heart failure are much more susceptible to PPI-negative inotropic effect because of blunted contractile reserve subsequent to decreased sympathetic sensitivity or negative force-frequency relationship. In addition, the dependence of H^+ elimination from H^+/K^+-ATPase may be increased in heart failure because of the impaired function of the Na^+/H^+ exchanger subsequent to increased Na^+ **(Pieske *et al.*, 2002).** Morever a study carried out by **Sossalla *et al.* (2011)** showed that, PPIs; Pantoprazole, esomeprazole, and omeprazole produced a significant and reversible negative inotropic effects on isolated human failing myocardium

In the present work and in contrast to pantoprazole, ranitidine did not cause any change in the amplitude of myocardial contraction of isolated rabbit heart. This finding is simillar to that of **Coruzzi *et al.* (1983)** who reported that, ranitidine was virtually ineffective up to the maximum concentration tested on electrically stimulated human and rabbit isolated myocardium.

In the present study, small dose of either pantoprazole or ranitidine had no effect, while at higher doses a significant dose-dependent reduction in norepinephrine-induced contraction of isolated aortic spiral strips of rabbit was found. . Similar results were obtained by using the PPIs (leminoprazole) on the rat aortic rings precontracted with phenylephrine **(Okabe *et al.*, 1996)**. Also **Kelicen *et al.* (2002)** reported that, omeprazole caused a concentration-dependent relaxation of the rat aortic rings precontracted with phenylephrine. Furthermore, omeprazole and lansoprazole were found to induce relaxation of phenylephrine-induced contractions, of isolated human arteries **(Naseri and Yeniserhirli, 2006).**

The mechanism of the vasorelaxant effect of PPIs is suggested to be unrelated to the inhibition of H^+/K^+ ATPase in vascular smooth muscle; since the concentration of PPIs required to cause maximal inhibition of H^+/K^+ pump is much less than the cocentration required for maximal inhibition of the contractile responses of isolated arteries **(Rhoden, 2000).**

The inhibitory effect of different H^+/K^+ ATPase inhibitors on calcium channels was also suggested in many studies carried out on rat aortic rings **(Okabe *et al.*, 1996),** rabbit corpus cavernosum, and isolated human arteries **(Sarioglu *et al.*, 2000).** In these studies, calcium channel blockade was proposed to be at least partially responsible for the relaxant effect of H^+/K^+ATPase inhibitors on smooth muscle contractility. This is because the intracellular free Ca^{+2} concentration regulates the tension of vascular smooth muscle and a decrease in intracellular Ca^{+2} will lead to vascular smooth muscle relaxation **(Naseri and Yenisehirli, 2006).**

As regard the vasorelaxant effect of ranitidine, this result was in agreement with that mentioned by **Bertaccini *et al.* (1984),** who reported that, the H_2-receptors antagonists, oxmetidine, caused relaxation of agonist-induced contractions of isolated rabbit aorta.

In-vivo studies

In the present study, bolus i.v injection of pantoprazole (0.75 – 12 mg/kg) produced a significant dose-dependent reduction in the mean arterial blood pressure of anaesthetized cat. The same doses caused insignificant change in heart rate and no abnormalities in the ECG pattern (rhythm & waves).

The hypotensive effect of pantoprazole disagrees with results reported by **Booher *et al.* (2010)** who mentioned that, intravenous injection of 40mg of pantoprazole in critically ill patients in the coronary and cardiothoracic intensive care units did not immediately impact important hemodynamic parameters. They also reported no significant change in the systemic blood pressure, cardiac index or heart rate in the hours following pantoprazole administration. Difference in species and pharmacokinetic parameters, could explain the discripancy in this results and ours.

The IV infusion of pantoprazole at a dose of 1.5 mg/kg which is equivalent to the corresponding HTD did not produce any change in the MABP, heart rate or ECG pattern throughout the time of infusion (2 hrs). These findings agrees with that mentioned by **Yenisehirli and Naseri (2008)** who reported that, intravenous infusion of pantoprazole, lansoprazole and omeprazole did not produce any change on blood pressure or heart rate of anaesthetized cat at doses of 7.2, 7.7 and 9mg/kg. In addition, no alteration or rhythm disorder was observed even after the 60-90 min follow-up period with all proton pump inhibitors. **Schillinger *et al.* (2009)** stated that, findings which were seen directly on isolated organs may be masked in-vivo by physiological effects such as preload, afterload, and neurohumoral activation.

In the present study the IV bolus injection of ranitidine (0.5-16 mg/kg) also exerted a significant dose-dependent reduction in MABP, no effect on heart rate except of a significant increase in the heart rate at 16 mg/kg and no abnormalities in ECG pattern. On the other hand, it was found that in the present work, continuous IV infusion of ranitidine (2 mg/kg the dose equivalent to the corresponding HTD) in anaesthetized cat did not produce any change in mean arterial blood pressure, heart rate or ECG pattern throughout the time of infusion (2 hrs). This finding agrees with that reported by **Goelzer *et al.* (1988)** who mentioned that, IV infusion of ranitidine did not produce clinically significant hemodynamic effects in stable patients in intensive care units

In addition it was found that, the intravenous bolus injection of ranitidine or cimitidine to critically ill patients in intensive care unit caused a transient but significant reduction of MABP secondary to peripheral vasodilation without a compensatory increase in cardiac output **(Smith *et al.*, 1987).** In another study it has been reported that, the heart rate did not increase with the decrease in blood pressure following IV administration of these drugs, as might be anticipated, which could represent a relative negative chronotropic effect or a decrease in baroreceptor activity **(Coursin *et al.*, 1988).**

Cardiovascular complications such as severe hypotension, bradycardia, cardiac arrest, and ventricular tachyarrhythmias were observed after large intravenous bolus doses of ranitidine in severely ill patients by **Hu *et al.* (1997).** The mechanism behind ranitidine-induced hypotension was not clear. H_2-receptors blocker-induced hypotension after autonomic denervation appears to be neither associated with stimulation of vasodilatory cholinergic receptors in smooth muscle of certain blood vessels **(Vyas and Verma, 1981),** nor due to its H_2-receptor blocking property,

scince stimulation of vascular H_2-receptors is known to induce hypotension and vasodilation in humans **(Boyce, 1982).** Therefore, it is likely that ranitidine is capable of relaxing the resistance vessels via unspecific mechanism.

In Comparison the hypotensive effect of either pantoprazole or ranitidine on mean arterial blood pressure of anaesthetized cat, both drugs produced a significant dose-dependent decrease in blood pressure, but the mean percentage reductions with ranitidine (0.5-16mg/kg) were higher than with pantoprazole (0.75-12mg/kg) especially at higher doses with a mean percentage reduction ranged from 0.7 ± 0.19 42.8 ± 3.21 for ranitidine and 0.6 ± 0.23 16.1 ± 3.15 for pantoprazole.

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دراسة المقارنة بين دواء الباتتوبرازول ودواء الرانتدين على بعض أعضاء الجهاز الدورى

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ينقسم هدا البحث إلى قسمين :

أ- التجارب على الأعضاء المعزولة: وهى تشمل دراسة تأثير الجرعات المختلفة ومكان عمل كل من دواء بنتوبرازول و دواء رانيتدين على قوة انقباض القلب المعزول من الأرنب البلدى وعلى معدل السريان فى الشريان التاجى. وأيضا دراسة تأثيرهما على التقلصات الناتجة عن النورإبينفرين فى الشرائط الحلزونية المعزولة من الشريان الأورطى للأرنب البلدى.

ب-التجارب على الحيوانات الصحيحة: وهى تشمل التجارب على القطط المخدرة بالفينوباربيتون لدراسة تأثير الجرعات المختلفة ومكان عمل كل من دواء بانتوبرازول و دواء رانيتدين على قياس معدل ضغط الدم الشريانى، ضربات القلب و على تسجيلات رسم القلب الكهربائى بعد كلا من الحقن أو التقطير الوريدى.

أ-التجارب على الأعضاء المعزولة:

- وجد أن دواء بانتوبرازول (١,٥ – ٤٨ ميكروجرام/ميلليتر) قد سبب انخفاضا ذى دلالة احصائية على قوة انقباض القلب المعزول من الأرنب البلدى (مقاسا بالسنتيميتر)، وأن هذا الانخفاض ليس من خلال تأثير الدواء على المستقبلات الكولينيرجية أو بيتا الأدرينالية. كما وجد أن دواء بانتوبرازول (٦ ميكروجرام/ميلليتر) ليس له تأثير مضاد على مستقبلات الهستامين فى عضلة القلب، حيث لم يختفى تأثير الهستامين المنشط لعضلة القلب بعد إعطاء دواء بانتوبرازول. كما لوحظ إختفاء تأثير دواء بانتوبرازول المثبط لعضلة القلب بعد غلق قنوات دخول الكالسيوم، مما يدل على إحتمالية أن يكون للكالسيوم دورا فى تأثير بانتوبرازول المثبط لعضلة القلب.
- وجد أيضا أن دواء بانتوبرازول عند الجرعات (١,٥ – ٢٤ ميكروجرام/ميلليتر) ليس له تأثيرعلى معدل السريان فى الشريان التاجى، بينما فى الجرعات العلاجية الكبيرة (٤٨ ميكروجرام/ميلليتر) وجد أن دواء بانتوبرازول يزيد من سريان الدم فى الشريان التاجى و أن هذه الزيادة ذات دلالة إحصائية.
- فى المقابل لم تؤدى إضافة الرانيتدين فى الجرعات المختلفة (٢– ٦٤ ميكروجرام/ميلليتر) إلى أى تأثير على قوة انقباض عضلة القلب المعزول من الأرنب البلدى. ولكن وجد أن له تأثير مضاد على مستقبلات الهستامين فى عضلة القلب، حيث أختفى تأثير الهستامين المنشط لعضلة القلب بعد إعطاء دواء رانيتدين.
- وجد أيضا أن إضافة الرانيتدين فى الجرعات المختلفة (٢– ٦٤ ميكروجرام/ميلليتر) ليس له تأثير على معدل سريان الدم فى الشريان التاجى.
- عند دراسة تأثير كلا من الدوائين على الشرائط الحلزونية المعزولة من الشريان الأورطى للأرنب البلدى فقد وجد أن الجرعات الصغيرة لكل من دواء بانتوبرازول (١,٥ ميكروجرام/ ميلليتر) ورانيتدين (٢-٤ ميكروجرام/ ميلليتر) ليس لهما تأثير على التقلصات الناتجة عن النورإبينفرين، بينما فى الجرعات من ٣ إلى ٢٤ ميكروجرام/ميلليتر للبنتوبرازول و ٨ إلى ٦٤ ميكروجرام/ميلليتر للرانيتدين فقد وجد أنهما قد تسببا فى تثبيط التقلصات الناتجة عن النورإبينفرين بطريقة متدرجة حسب الجرعة وكان هذا التأثير ذى دلالة إحصائية.
- بمقارنة تأثير كلا من الدوائين على التقلصات الناتجة عن النورإبينفرين فقد وجد أن كلا من الدوائين قد تسببا فى تثبيط هذه التقلصات ولكن كانت النسبة أقل فى الرانيتيدين عنه فى البنتوبرازول فى جميع الجرعات ما عدا الجرعات الكبيرة.

ب-التجارب على الحيوانات الصحيحة:

تأثير دواء بانتوبرازول:

- بالنسبة للتجارب التى أجريت لقياس معدل ضغط الدم الشريانى فى القطط المخدرة، وجد أن دواء بنتوبرازول فى الجرعة الصغيرة (٠,٣٧ميللجرام/كيلوجرام) لم يكن له تأثير على قياس معدل ضغط الدم بينما فى الجرعات من (٠,٧٥ – ١٢ ميللجرام/كيلوجرام) فقد سبب انخفاضا ذى دلالة إحصائية فى ضغط الدم الشريانى، وأن هذا الانخفاض لم يكن من خلال تأثير الدواء على المستقبلات الكولينيرجية أو بيتا الأدرينالية أو مستقبلات الهيستامين بينما لوحظ إختفاء هذا الانخفاض بعد غلق قنوات دخول الكالسيوم ، مما يدل على إحتمالية أن يكون للكالسيوم دورا فى تأثير بانتوبرازول الخافض لضغط الدم.
- بالنسبة للتجارب التى أجريت على تسجيلات رسم القلب الكهربائى للقطط المخدرة فقد وجد أن دواء بانتوبرازول فى الجرعات المختلفة (٠,٣٧ -١٢ ميللجرام/كيلوجرام) ليس له تأثير على ضربات القلب ولا على رسم القلب الكهربائى.
- **تأثير دواء رانيتيدين:**
  - بالنسبة للتجارب التى أجريت لقياس معدل ضغط الدم الشريانى فى القطط المخدرة، وجد أن دواء رانيتيدين فى الجرعات العلاجية المختلفة (٠,٥ -١٦ ميللجرام/كيلوجرام) قد سبب انخفاضا ذو دلالة احصائية فى ضغط الدم، وأن هذا الانخفاض ليس من خلال تأثير الدواء على المستقبلات الكولينيرجية أو بيتا الأدرينالية أو مستقبلات الهيستامين أو قنوات دخول الكالسيوم.
  - بالنسبة للتجارب التى أجريت على تسجيلات رسم القلب الكهربائى للقطط المخدرة فقد وجد أن دواء رانيتيدين فى الجرعات العلاجية (٠,٥ - ٨ ميللجرام/كيلوجرام) لم يكن له تأثير على سرعة ضربات القلب أو على تسجيلات رسم القلب الكهربائى للقطط المخدرة ، بينما فى الجرعة الأخيرة ١٦ ميللجرام/كيلوجرام قد سبب ارتفاعا ذى دلالة إحصائية فى عدد ضربات القلب.

  - بمقارنة تأثير كلا من الدوائين على معدل قياس ضغط الدم للقطط المخدرة وجد أن كلا الدوائين قد سبب إنخفاضا فى معدل قياس ضغط الدم ولكن كان الإنخفاض بنسبة أعلى فى الرانيتيدين عنه فى البنتوبرازول وخاصة فى الجرعات الكبيرة.

<u>من خلال التجارب التى أجريت نستنتج أن</u>:

١ - بالرغم من أن نقل النتائج الإستقرائية من الحيوان إلى الإنسان غير مؤكدة ، وفى ضوء نتائج البحث الحالى نستخلص منه أن دواء رانيتيدين ليس له تأثير مثبط لعضلة القلب بالمقارنة بالبنتوبرازول ولذلك فإنه يفضل عن البنتوبرازول وخاصة فى مرضى القلب. وعلى الجانب الآخر يجب الأخذ فى الإعتبار التأثير المثبط لقوة إنقباض عضلة القلب لدواء البنتوبرازول وخاصة فى مرضى الإختلال الوظيفى فى إنقباض عضلة القلب.

٢- فى المواضع التى نحتاج فيها إلى الحقن الوريدى السريع والمتقطع فإنه يفضل إختيار البنتوبرازول حيث أنه لم يحدث اى تغيرات فى رسم القلب وكان الإ نخفاض فى ضغط الدم بنسبة اقل من الرانيتيدين حتى فى الجرعات الكبيرة.