The Egyptian Journal of Hospital Medicine Vol., 3 : 126 - 140 June 2001
I.S.S.N: 12084

Some Pharmacological Studies of Ropivacaine in comparison With bupivacaine

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Abstract

The effect of ropivacaine as a recent amino-amide local anaesthetic compared with bupivacaine on analgesic activities, cardiac contractility, blood pressure, heat rate, Electrocardiogram (ECG) and toxicity was studied. The result of our study revealed that ropivacaine Exhibited a less degree of analgesic potency than bupivacain, it increase the reaction time by 20.6 and up to 167.6%while bupivacaine increased it by 37.32 up to 197.1%. On isolated rabbits heart, ropivacaine and bupivacaine induced a significant dose dependent –ve inotropic effect. The cardiodepressant action of ropivacaine was lesser than that of bupivacaine. IV injection of ropivacaine (0.35-2.8mg\kg) produced slight increase in arterial blood pressure but in the last dose produce decrease in arterial blood pressure. Bupivacaine 0.5-1mg\kg produce no significant change in arterial blood pressure but in the subsequent doses it produces hypotension up to death, this hypotension may be the beginning effect of high toxic blood level of the drug. Ropivacaine showed no alterations in ECG apart from significant decrease in heart rate only in high doses, but on the other hand bradycardia started earlier with bupivacaine (1mg\kg) and ECG changes were seen after 5 minutes from injecting 2mg\kg which ended by cardiac arrest. In respect to toxicity, intra peritoneal LD50 of ropivacaine was found to be 115mg\kg compared to 90mg\kg of bupivacaine. We concluded that ropivacaine nearly resembles bupivacaine in its local analgesic effect but has a great margin of safety with less cardiodepressant action.

Introduction

Ropivacaine is the (s) isomer of 1-propyl-2, 6, pipecoloxylidide an amide local anaesthetic with a structure similar to that of mepivacaine and bupivacaine (McClure, 1996). Ropivacaine shows a high degree of sensory motor block separation. At high doses it is an effective anaesthetic, giving profound sensory and motor block. At low doses, it has an effective analgesic, producing almost exclusive sensory block with minimal motor block allowing rapid recovery to full patient mobilization (kalpokas et al, 1994). Subsequent work showed that ropivacaine is well tolerated and can be administered in large doses before early features of both cardiovascular and CNS toxicity are apparent (cederholm, 1997, Scott et al, 1989). In addition, accidental IV injection of the drug did not produce serious adverse effects (Morton et al, 1997). The present study was designed to compare the haemodynamic effects of bupivacaine and ropivacaine on isolated rabbit's heart, BP and ECG of anaesthetized cats after intravenous injection of each drug in different doses levels to clarify which of the drugs is less cardiotoxic.

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Material and Methods

A. Experiment on the central nervous system:-

Analgesic activities was done by hot plate method (Woolfe and McDonald 1994). Nine group of mice, weighting 20-25 gm body weight were used (each group consists of ten mice). Four group of them were given 1.25, 2.5, 5 and 10mg/kg ropivacaine intrapeitoneal respectively. Another four groups of mice received 1.75, 3.5, 7 and 14 mg/kg bupivacaine. The last one was used as a control group and was given normal saline. In all groups, after half an hour from drug injection each mouse was placed separately on a hot plate (55-65^{o}c) and the time needed for jumping and trying to escape from the cylinder was recorded.

B. Experiments on the cardio vascular system:-

In vitro experiment, Twelve adult male rabbits weighting about 1.5Kg were divided into two groups. Both groups were sacrified. The chest was opened to expose the heart and then quickly excised and thoroughly washed it several times in oxygenated reinger's solution. The heart was immersed in langendorffs apparatus (Burns, 1952) which designed to deliver oxygenated mammalian reinger's solution at a constant temperature 37^{O}c and fixed pressure. Drugs were then injected into the perfusion fluid proximal to the heart through a rubber tube as single shot injections. The effect of different doses of ropivacaine (1.5-12ug /ml) on isolated heart was studied. The same procedure was repeated to investigate the effect of different doses of bupivacaine (2-16ug/ml) on the isolated heart.

In vivo experiment, sixteen cats of either sex weighting between 2-3Kg were divided into two groups. The cats were anaesthetized and the left common carotid artery was canulated and connected to a mercury manometer. The drug was injected into the femoral vein and electrodes of the ECG was connected to the limbs of the animal, lead II was recorded by a Siemens cardiostate. The effect of different doses of ropivacaine (0.35- 2.8mg/Kg) and bupivacaine (0.5-4mg/Kg) on arterial blood pressure and ECG (lead II) on anaesthetized cats were recorded.

C. Acute toxicity tests:-

The acute toxicity test was performed in both sexes of mice using sixteen groups, each consisting of 10 mice. Ropivacaine (80-150 mg/kg) and bupivacaine (70-105 mg/kg) were injected intraperitoneally (IP) to the different groups of mice then the animals were observed for twenty-four hours after drug administration. Those mice dying during the first hour were deprived. The percent mortality of mice after each dose was calculated and LD**50** of each drug was calculated by the method of lich field and wilcoxon (lichfield and wilcoxon, 1949).

The available data were subjected to paired student's "t" test and chi- square (x^2) test.

RESULTS

The analgesic activity of ropivacaine in relation to control (by using hot plate method) was found statistically signifi - cant in the last 3 doses. Bupivacaine increased significantly in different doses (table 1, Fig. 1& 2).

Table (1): mean reaction time (sec) to the stimulus of hot plate test of mice treated by different doses of ropivacaine and bupivacaine and of control untreated mice.

	Control	***Ropivacaine (mg/kg)***				***Bupivacaine (mg/kg)***			
		1.25	***2.5***	***5***	***10***	***1.75***	***3.5***	***7***	***14***
Mean	10.200	12.300	15.00	19.00	27.300	14.00	17.00	22.400	30.300
+ SEM	1.162	1.789	1.633	2.028	2.625	1.096	1.961	2.363	1.550
P		>0.05	<0.05	<0.01	<0.001	<0.05	<0.01	<0.001	<0.001
% activity	0	20.6	47.1	86.3	167.6	37.3	66.7	119.6	1s97.1

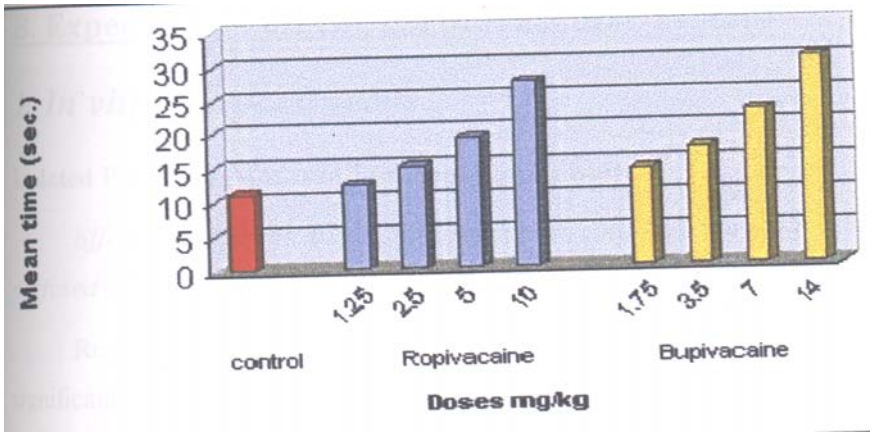

Fig. 1: Analgesic activities of ropivacaine and bupivacaine on the hot plate method

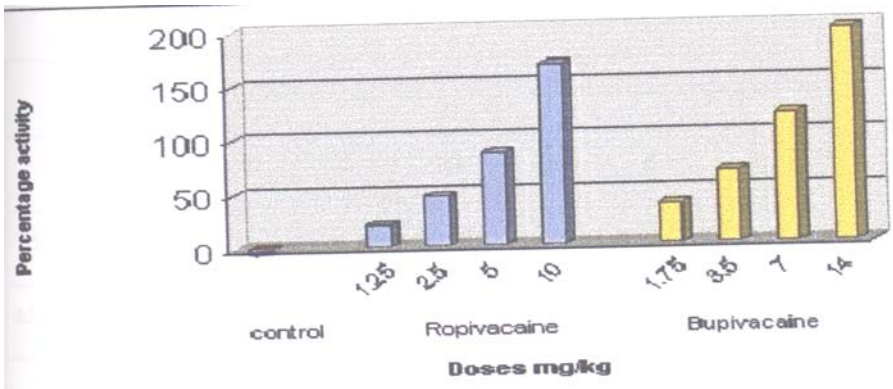

Fig. 2: percentage increase of the reaction time in the hot plate test by ropivacaine and bupivacaine

Ropivacaine (1.5-12 ug/ml) and bupivacaine (2-16 ug/ml) produce a significant reduction in myocardial contractility and cardiodepressant effect of bupivacaine (17.301-83.010 %) was much greater than that of ropivacaine (11.142-49.144%) (Table 2, fig 3 & 4).

Table (2): percentage reduction in the amplitude of contractions (cm) of isolated rabbit's heart in response to different doses of ropivacaine and bupivacaine.

	Ropivacaine (ug/ml)				***Bupivacaine (ug/ml)***			
	1.5	***3***	***6***	***12***	***2***	***4***	***8***	***16***
MEAN	11.142	22.634	34220	49.144	17.301	36.327	52.104	83.010
+ SEM	0.924	1.4	1.464	3.954	0.914	1.769	2.508	3.645
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

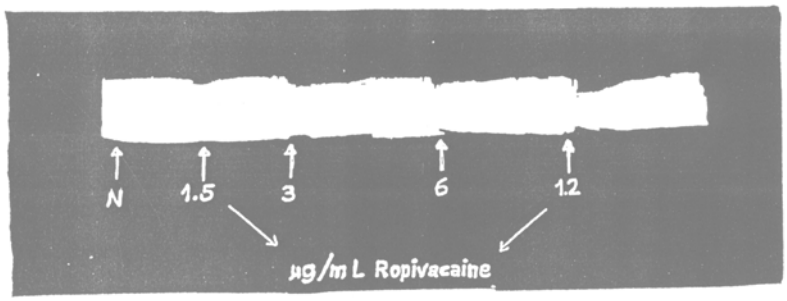

Fig. 3: Effect of ropivacaine on the amplitude of myocardial contractions of isolated rabbit's heart

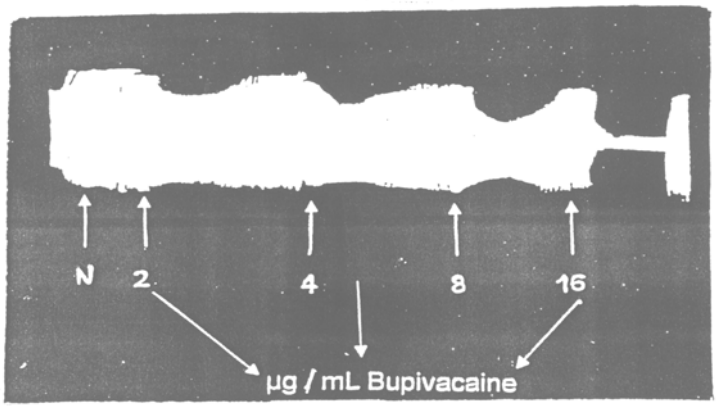

Fig. 4: Effect of bupivacaine on the amplitude of myocardial contractions of isolated rabbit's heart

Ropivacaine (0.35-1.4 mg/kg) produced slight rise in arterial Bp and the mean percent increase of arterial Bp was found to be statistically significant. The last dose of ropivacaine (2.8 mg/kg) showed significant increase of blood pressure in six cats while it produced hypotension in two (table 3, Fig. 5)

Table (3): percentage change in the mean arterial blood pressure (mmHg) of pentobarbitone anaesthetized cats in response to different doses of ropivacaine (mg/kg) and bupivacaine (mg/kg).

	Ropivacaine (mg/kg)				***Bupivacaine (mg/kg)***			
	0.35	***0.7***	***1.4***	***2.8***	***0.5***	***1***	***2***	***4***
	% increase	% increase	% increase	% increase	% increase	% increase	% decrease	
Mean	7.289	8.865	9.732	10.828	2.167	3.319	20.011	
+SEM	0.636	0.807	0.724	0.837	0.919	1.398	0.732	
P	<0.001	<0.001	<0.001	<0.001 *	<0.005	<0.005 **	<0.001 ***	****

* 2 cats out of 8 showed decrease in the mean arterial blood pressure.
** 3 cats out of 8 showed decrease in the mean arterial blood pressure.
*** 3 cats out of 8 (the previous hypotensive cats) died.
**** All remaining 5 cats died.

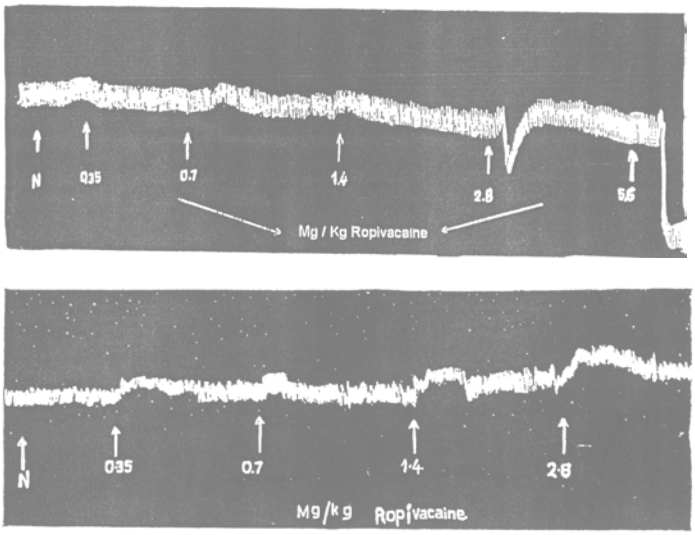

Fig. 5: Effect of ropivacaine on mean arterial blood pressure of normal anaesthetized cats

Bupivacaine in a dose of 0.5 mg/kg produced no significant change in the mean arterial blood pressure while 1 mg/kg produced no change in the mean arterial blood pressure of five cats only and hypotension in the remaining three animals. As regards 2 mg/kg of bupivacaine, it developed hypotension in five cats and death of the rest. The survivors died after being injected with the last dose of bupivacaine (4 mg/kg) (table 3, Fig.6).

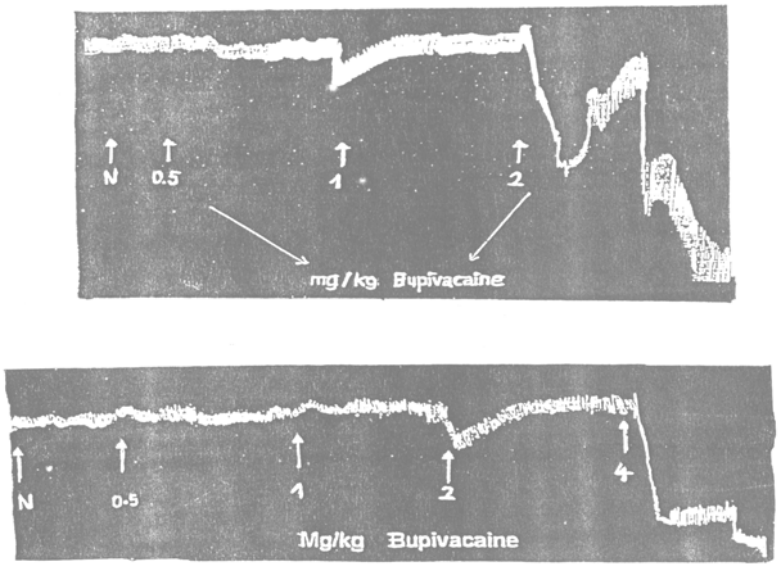

Fig. 6: Effect of bupivacaine on mean arterial blood pressure of normal anaesthetized cats

No abnormality in the ECG pattern was observed with ropivacaine apart from the decrease in heart rate occurring with the last doses of the drug (1.4-2.8 mg/kg). Concerning the effect of bupivacaine on the ECG, bradycardia occurred with 1 and 2 mg/kg of the drug and ECG changes were seen after a period of five minutes from injecting 2 mg/kg of bupivacaine. These changes included depression of ST segment, widening of QRS complex, decreased QRS voltage, prolongation of PR interval and finally ended by cardic arrest and death of three cats. The last dose of bupivacaine was fatal to the remaining survivors (table 5, Fig 7 & 8).

Table (5): percentage reduction in heart rate (beats/minutes) of pentobarbitone anaesthetized cats in response to different doses of ropivacaine (mg/kg) and bupivacaine (mg/kg)

	Ropivacaine (mg/kg)				***Bupivacaine (mg/kg)***			
	0.35	***0.7***	***1.4***	***2.8***	***0.5***	***1***	***2***	***4***
Mean	4.022	5.123	8.926	12.676	4.894	9.481	13.822	
+SEM	1.964	2.214	2.35	2.151	2.084	1.628	1.731	
P	<0.05	<0.05	<0.01	<0.001	<0.05	<0.001	<0.001 *	**

*3 cats out of 8 developed cardiac arrest and died.
** All remaining 5 animals died.

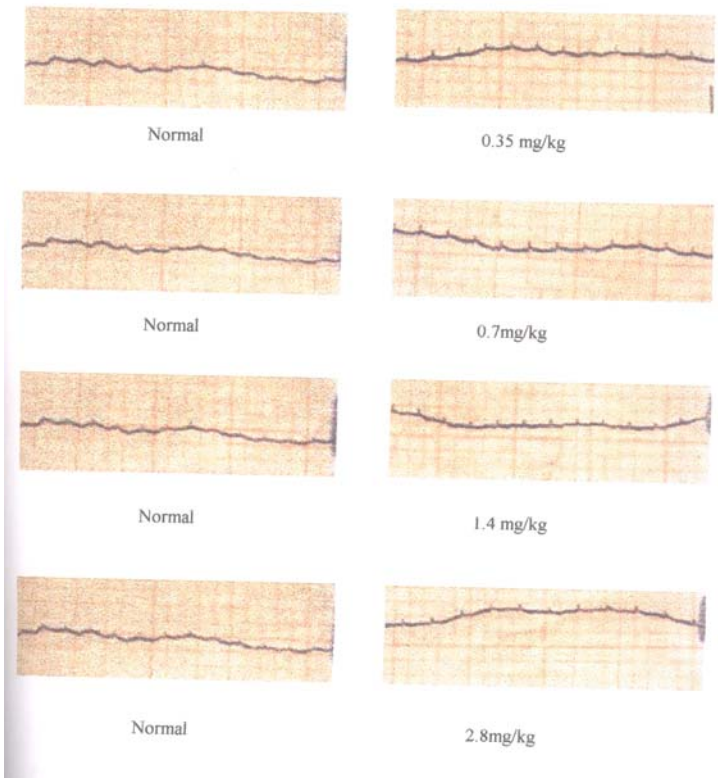

Fig. 7: Effect of ropivacaine on ECG rate and pattern on anaesthetized cats

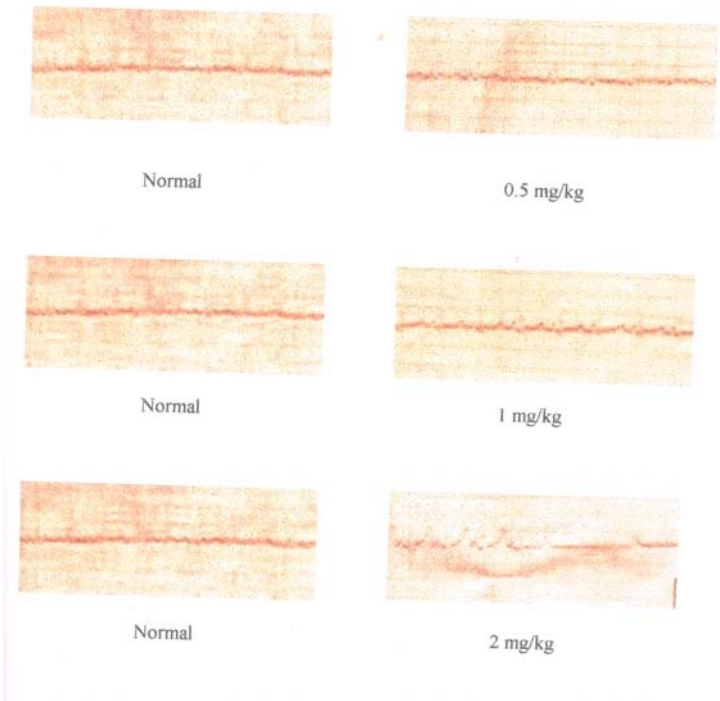

Fig. 8: Effect of bupivacaine on ECG rate and pattern of anaesthetized cats

The results of intraperitoneal (IP) acute toxicity of ropivacaine and bupivacaine in mice. The LD50 of ropivacaine was found to be 115 mg/kg compared to 90 mg/kg of bupivacaine. (Table 6 & 7)

Table (6): Acute intraperitoneal toxicity of ropivacaine in adult mice.

Group number	*IP test doses of ropivacaine (mg/kg)*	*24 hours observed mortality data*		*Expected % mortality*	*Observed minus expected*	*Nomograph N0.1 contribution to (chi) .*
		Dead/tested	*Observed % mortality*			
1	*80*	*0/10*	*0*	*1.2*	*1.2*	*0.012*
2	*90*	*1/10*	*10*	*7*	*3*	*0.015*
3	*100*	*2/10*	*20*	*20*	*0*	
4	*110*	*4/10*	*40*	*40*	*0*	
5	*120*	*6/10*	*60*	*60*	*0*	
6	*130*	*8/10*	*80*	*80*	*0*	
7	*140*	*9/10*	*90*	*90*	*0*	
8	*150*	*10/10*	*100*	*95.5*	*4.5*	*0.046*

Total animals =80 Total = 0.073
No. Of dose level (k) = 8 (chi) = 0.073 * 10 = 0.73
Degree of freedom = k – 2 = 6
(Chi) from table 2 for (n) of 6 = 12.6
Since 0.73 is less than 12.6 therefore the data are not significantly heterogeneous and the line is a good fit.

Table (7): Acute intraperitoneal (IP) toxicity of bupivacaine in adult mice.

Group number	***IP test doses of bupivacaine (mg/kg)***	***24 hours observed mortality data***		***Expected % mortality***	***Observed minus expected***	***Nomograph N0.1 contribution to (chi) .***
		Dead/tested	***Observed % mortality***			
1	70	0/10	0	3	3	0.030
2	75	1/10	10	10	0	
3	80	2/10	20	20	0	
4	85	3/10	30	37	7	0.022
5	90	5/10	50	50	0	
6	95	7/10	70	70	0	
7	100	9/10	90	80	10	0.52
8	105	10/10	100	89	11	0.130

Total animals = 80 Total = 0.234
No. Of dose level (k) = 8 (chi) = 0.234 * 10 = 2.34
Degree of freedom = k – 2 = 6
(chi) from table 2 for (n) of 6 = 12.6
Since 2.34 is less than 12.6 therefore the data are not significantly heterogeneous and the line is a good fit.

Discussion

Most serious toxicities of local anesthetics represent extension of the therapeutic effect on the brain and circulatory system. This is clearly related to the blood level of these agents **(Miller; 1997).** High plasma concentration can occur by accidental intravascular injection of the drug or the administration of an excessive dose **(Covino and Wildsmith 1998).** A large number of local anesthetics are available commercially and they differ markedly in both clinical profiles and potential for toxicity. Knowledge of the clinical pharmacology of these various drugs is essential, if the appropriate agent is to be selected for a specific clinical situation **(Covino and Wildsmith 1998).** In the present study ropivacaine, a new local anesthetic is compared with bupivacaine, which had become relatively popular for regional anesthesia.

By screening the analgesic activity of ropivacaine and bupivacaine, Ropivacaine prolonged the reaction time to the stimulus of mouse hot plate test less than did bupivacaine. **Zaric et al; 1996** reported that 0.1 % of ropivacaine produced limited analgesia compared to 0.2 and 0.3 % of the drug, which showed extensive analgesia. **Feldman et al, 1996** also stated that ropivacaine produced shorter duration of sensory and motor block than corresponding concentrations of bupivacaine. **Markham and Faulds, 1996** suggested that ropivacaine blocked nerve fibers responsible for transmission of pain (A delta and C fibers) more completely than those that control motor function (A beta fibers) However comparative study has shown ropivacaine and bupivacaine to have similar efficiency, but ropivacaine has a greater degree of separation between motor and sensory blockade than bupivacaine **(Cederholm., 1997).**

In the cardiovascular experim - ents of this work, ropivacaine and bupivacaine in all concentrations, exer - ted a significant -ve inotropic effect on the isolated perfused rabbit's heart. The myocardial depressant action of bupivacaine was found greater than that of ropivacaine and the last dose of bupivacaine (4mg/kg) caused 83.01 $^{+}$/- 3.645 % reduction. Such finding was in agreement with Feldman et al 1990 who reported that ropivacaine is less potent in decreasing myocardial contractility than bupivacaine. MoIIer and Covino., 1992 also stated that ropivacaine was 3-5 times less potent in depressing cardiac Electrophysiologic parameters than bupivacaine. The outcome of this response might also be explained by Josephson.,1988 who reported that local anesthetics, in addition to their effects on voltage dependent sodium (Na+) channels, they are likely to produce similar inhibition at other chemically gated ion channels. Inhibition of calcium (Ca++) and potassium (K+) currents in myocardial tissues have been demonstrated and an external site for local anesthetics binding in myocardial tissue has been identified (Karon et al., 1995). Minakuchi and Itoh., 1991 attributed the potent cardiodepressant activity of bupivacaine compared to that of ropivacaine in terms of its slow release from Na+ channel binding sites as well as Ca++ channel binding. Likewise, Hirota et al., 1997 suggested that binding of bupivacaine more than ropivacaine with dihydropyridine binding sites on neuronal L type of Ca++ channels might be involved in the cardiotoxicity of these agents. The greater lipophilicity and protein binding of bupivacaine favors enhanced uptake

and binding in myocardial tissue (Covino and Wildsmith 1998).

In experiments on the arterial blood pressure and ECG of Pentobarbitone - anaesthetized cats, ropivacaine (0.35 — 2.8 mg/kg) exerted a slight rise of arterial blood pressure. In two cats out of eight, the last dose of the drug produced a drop of arterial blood pressure. ECG records, in the present investigation, showed decrease in heart rate of anesthetized cats that received only large doses of ropivacaine (1.4— 2.8 mg/kg). No abnormalities in the ECG pattern were observed. In conformity with the fore-mentioned results were the findings of Ishiyama et al., 1997, who indicated that IV ropivacaine (4 mg/kg) caused canine pial vascular constriction associated with decrease in heart rate. Studies on isolated rings of human arteries revealed that ropivacaine has a biphasic effect on vascular smooth muscle with contraction at low concentrations and relaxation at high ones. Removal of the endothelium did not affect contractile activity of the drug (Gherardini et at, 1995). McClure., 1996 also added that the vasoconstrictor action of ropivacaine is present at clinically used concentrations; thus it is unlikely to be marketed in preparations containing epinephrine. Hypotension that occurred in two cats injected with 2.8 mg/kg of ropivacaine in the present study might be explained by achievement of high blood level of the drug in these animals leading to myocardial depression and vasodilatation. Animal variability, as regards rate of absorption, metabolism and excretion of the injected drug, as well as the way of injection may influence the blood level and accordingly toxicity of the drug. The rate of injection and rapidity with which a particular blood level is achieved will influence the toxicity of local anesthetics (Scott, 1989). If the blood level of local anesthetic is excessively elevated, cardiovascular depression occurs that is related to its depressant effect on myocardial contractility, heart rate and conductivity as well as the peripheral vasodilator action of this agent (Covino and Wildsmith 1998).

In contrast to the vasopressor effect of ropivacaine in this study, bupivacaine elicited varied pattern of arterial blood pressure. 0.5 and I mg/kg of the drug had no significant effect on the mean arterial blood pressure; in only three cats out of eight 1 mg/kg produced drop of arterial blood pressure. On the other hand, 2 mg/kg of bupivacaine exerted hypotension in five cats and resulted in death of the remaining animals. All survivors died after being injected with the last dose of the drug (4 mg/kg). The ECG studies of the present thesis revealed that the first dose of bupivacaine only (0.5 mg/kg) had no significant —ve chronotropic effect while all other doses (1-4 mg/kg) showed decrease in heart rate. ECG changes in the form of prolongation of PR interval, widening of QRS complex, decrease of QRS voltage, flattening of ST segment and hyperacute T wave appeared after five minutes from injecting the animals with 2 and 4 mg/kg. These changes ended by heart block, cardiac arrest and death in three cats out of eight received 2 mg/kg of bupivacaine and in all remaining animals received 4 mg/kg. The variation in the effect of bupivacaine in this study might be explained by the occurrence of cardiovascular toxicity in some animals receiving IV bupivacaine as a result of elevated peak blood concentration. Non-toxic blood level of the drug produced bradycardia and slight vasoconstriction with no significant change in arterial blood pressure. This result is in accordance with Akerman et

al.,1988, who stated that bupivacaine is less vasoconstrictor than ropivacaine. On examining direct effect of bupivacaine and ropivacaine on femoral artery and vein of dogs, bupivacaine was found to induce lesser constriction in vascular rings under basal tension than ropivacaine (Nakamura et al., 1993). However, Scott etal., 1989 reported that IV infusion of 150mg of ropivacaine and bupivacaine to volunteers increased heart rate and arterial blood pressure.

When the blood level rose to the toxic level in certain cats of this study, bupivacaine produced ECG changes and hypotension. This ended with cardiac arrest and circulatory collapse in some animals when the dose of the drug was furtherly increased. These results can also be explained by the data of Covino and Wildsmith., 1998, which indicated that at relatively non toxic blood levels of local anesthetics, either no change in blood pressure or a slight increase may be observed. Concentrations of these agents, that produce convulsions, may result in marked increase in heart rate, blood pressure and cardiac output. A further increase in blood level of local anesthetics leads to cardiovascular depression. The initial fall in blood pressure is related to a decrease in cardiac output and is spontaneously reversed in most patients. If the blood level excessively rises, a profound state of cardiovascular depression occurs and lastly cardiac arrest and circulatory collapse occur.**Tuman and McCarthy., 1997** postulated that cardiovascular toxicity of local anesthetics is inversely related to potency, and the enhanced protein binding of potent agents facilitates high circulating blood levels as well as increased myocardial tissue binding. The greater lipophilicity and protein binding of bupivacaine in myocardial tissue makes cardiac resuscitation more difficult following bupivacaine induced cardiovascular collapse **(Feldman et al., 1991). Hondeghem., 1987,** noted that bupivacaine can produce fatal ventricular arrhythmia after rapid intravascular administration. Its arrhythmogenicity is likely related to its longer dissociation time from cardiac Na+ channels and production of tonic conduction block. Coupled with blockade of slow Ca++ channels, bupivacaine may lead to reentry type arrhythmias **(Coyle and Sperelakis., 1987).** Elevated blood concentrations are associated with prolonged conduction through various cardiac impulse pathways including prolonged PR interval, QRS width and QT interval, as well as a decrease in automaticity that may result in bradycardia **(Thomas et al., 1986).** Comparing bupivacaine with ropivacaine, **Pitkanen et al., 1992,** pointed out that bupivacaine is more cardiodepressant and arrhythmogenic than ropivacaine. The cardiodepressant ratio of bupivacaine to ropivacaine was 4:3 and the electrophysiological toxicity ratio was 15:6.7 respectively. Furthermore two of the eight pigs died after the highest dose of bupivacaine whereas ropivacaine didn't prove fatal **(Reiz et al., 1989).** The reduced arrhythmogenicity and decreased cardiotoxicity of ropivacaine compared to bupivacaine have been postulated to be at least partially to the drug's availability as a pure S-enantiomer compared to the racemic bupivacaine. Evidence indicated stereospecificity of the cardiac Na+ channel **(Tucker and Lennard., 1990).** S isomers is less cardiotoxic than the R isomer **(Vanhoutte etal.,1991).**

Concerning the acute toxicity test in this study, intraperitoneal lethal dose (LD50) of ropivacaine and bupivacaine

in mice was found to be 115mg/kg and 90mg/kg respectively. **Nancarrow et al, 1998** estimated the mean fatal dose of lidocaine, ropivacaine and bupivacaine in the sheep. They reported that the ratio between the three drugs was approximately 9:2:1 respectively. **Kohane et al., 1998** also compared the systemic toxicity of ropivacaine and bupivacaine in adult rats and pointed out that ropivacaine has a greater margin of safety; the LD**50** of ropivacaine was 54 mg/kg compared to 30 mg/kg of bupivacaine.

Finally, based on these views, although ropivacaine exhibited less analgesic effect than bupivacaine, yet its wide margin of safety, less cardio-depressant activity and ability to produce vasoconstriction offer advantages over either of the currently used long acting agents.

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بعض الدراسات الفارماكولوجية على الروبيفاكين بالمقارنة بالبيوبيفاكين

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تمت دراسة تأثير الروبيفاكين – مخدر موضعي امينو اميدى و مقارنته بدواء البيوبيفاكين على الجهاز العصبى للفئران البيضاء و الجهاز الدورى و تاثيرهما السمى الحاد.
و قد تمت مقارنة نتائج هذا الدواء مع نتائج البيوبيفاكين على نفس المعايير و باربع جرعات مختلفة من الدوائين.
و قد وجد ان عقار الروبيفاكين يمتاز بسرعة التاثير ولكن بدرجة اقل من التاثير المسكن للالم بالمقارنة بعقار البيوبيفاكين.
اما عن تاثير العقاريين على الجهاز الدورى فقد تسبب عقارى الروبيفاكين و البيوبيفاكين فى احداث هبوط فى قوة انقباض عضلة قلب الارنب البلدى المعزول ولكن عقار الروبيفاكين كان اقل تاثيرا.
و قد تسبب الحقن الوريدى لعقار الروبيفاكين فى القطط المخدرة تخديرا كليا الى ارتفاع طفيف فى ضغط الدم و لكن ادت الجرعة الاخيرة الى حدوث هبوطه ويرجع هذا الانخفاض الى ارتفاع نسبة الدواء فى الدم و زيادة سميته. اما بالنسبة للبيوبيفاكين فان الجرعتين 0.5-11مجم/كجم لم يحدث تغيير فى ضغط الدم ولكن الجرعات التالية ادت الى انجفاض فى ضغط الدم حتى الوفاه.
تبين من دراسة رسم القلب ان عقار الروبيفاكين لم يسبب اى تغيير فى عدد نبضات القلب الا فى الجرعات العالية فقد سبب نقصا فى عدد نبضات القلب، اما البيوبيفاكين فقد سبب انخفاضا فى عدد النبضات فى الجرعات (0.5-1مجم/كجم) و الجرعات التالية سببت توقف تام فى عضلة القلب حتى الموت.
قد تبين من دراسة سمية الدواء ان الجرعة التى تؤدى الى نفق نصف الفئران بعد الحقن فى الغشاء البريتونى 115 و 90 مجم/ كجم لعقارى الروبيفاكين و البيوبيفاكين على التوالى.