Korean J. of Pharmacology
Vol. 22, No. 2, pp. 105-114, 1986

Effects of Cyclobuxine D on the Electrocardiogram (ECG) and Heart Rate in Anesthetized Rats and Isolated Frog Heart

Jong-Hwoa Lee,[1] Young-Hyun Park, Byung-Heon Cho
Yu-Jae Kim, Jong-Bae Kim, Chun-Sook Kim, Young-Dong Cha and Young-Suk Kim

Department of Pharmacology, College of Medicine, Soonchunhyang University, Onyang, Korea

ABSTRACT

This study was undertaken to search for a new antiarrhythmic agent in natural plants. Extracts of *Buxus microphylla var. koreana* Nakai have been used as folk remedies of several diseases, including malaria and venereal disease, but any study on the pharmacological actions of this plant has not yet been carried out and its active ingredients have not been identified. In our laboratory, we isolated buxuletin (nonalkaloid) and cyclobuxine D (steroidal alkaloid) from *Buxus microphylla var. koreana* Nakai and reported their pharmacological actions: diuretic effects of buxuletin in rabbits and hypotensive effect of cyclobuxine D in rats.

In the present study, we investigated the effect of cyclobuxine D on isolated frog heart and heart rate in urethane anesthetized rats. In order to clarify the mechanism of bradycardic effect of cyclobuxine D, we examined the changes of the ECG parameters (PR, QRS and R α T interval) produced by intravenous injection of cyclobuxine D in anesthetized rats.

Cyclobuxine D depressed the contractile force in isolated frog heart and exerted a dose-dependent bradycardic effect in anesthetized rats. Intracerebroventricular injection of cyclobuxine D caused a fall in blood pressure and an increase in heart rate, but those effects were not significant. Cyclobuxine D prolonged the PR interval and R α T interval (α T indicates the apex of T), but was without significant effects on the duration of the QRS complex and PRc in urethane anesthetized rats.

Key Words: Cyclobuxine D, Rat electrocardiogram, Heart rate, Antiarrhythmia, Frog heart contraction.

INTRODUCTION

The clinical management of cardiac arrhythmias has undergone a great deal of change over the last ten years. During this period coronary-care units in many counteries have shown that, by early recognition and prompt treatment of arrhythmia, the mortality rate in acute myocardial infarction can be reduced significantly, the introduction of direct current countershock revolutionized the acute management of most types of paroxysmal arrhythmia. As a method, however, cardioversion is of limited value in the prophylaxis of recurrent arrhythmias and may be hazardous in the control of arrhythmias due to digitalis excess which is becoming an increasingly recognized cause of disturbances of cardiac rhythm and conduction. The emphasis is therefore once again shifting to the use of antiarrhythmic drugs in the elective and prophylactic management of cardiac arrhythmias.

Advances have been made at both levels, basic and clinical in our understanding on the origin of cardiac arrhythmias during the last ten years. There is now general agreement that arrhythmias occur either as a result of disordered impulse formation or disordered impulse conduction or combination of both processes. The actions of antiarrhythmic drugs may thus be interpreted in terms of their net effects on these two fundamental abnormalities in relation

1. Author to whom correspondance should be addressed.

to the changes in ionic permeabilities that occur under the influence of the agents in known therapeutic concentrations (Bleifeld W. 1971).

The electrocardiogram (ECG) has provided to be an indispensable tool toward the characterization of the cardiac action of compounds. In practice it can not be replaced by other methods although the ECG is not sufficient to give a complete picture of cardiac function until now the dog has been the preferred species in the pharmacological or toxicological investigation of cardiovascular drug actions. As far as the ECG is concerned, there are obvious similarities between dog and man. The rat ECG, however, differs considerably from the two other species, particularly in heart rate and configuration. On the other hand, the use of rats in pharmacological and toxicological experiments undoubtedly has adventages over the dog: rats are well standardized, easily handled, and available in large numbers. But the shortage of published data on drug effects on the rat ECG warrants further investigation in order to establish background data for the transferability of rat ECG results to man (Budden *et al.*, 1980).

In screening of new antiarrhythmic compounds it should be desirable to assess their effects on the ECG intervals in small laboratory animals like rats in order to select compounds not only on the basis of their antiarrhythmic activity but also on the basis of their effects on the conduction velocity.

Buxus microphylla var. koreana Nakai is distributed widely in Korea as an ornamental plant. *Buxus microphylla var. koreana* Nakai contained several derivatives (from four to five) of steroidal alkaloids whose structures were identified or not identified.

The present study was undertaken to search for a new antiarrhythmic compound. Cyclobuxine D, steroidal alkaloid, was isolated from *Buxus microphylla var. koreana* Nakai. We investigated the effects of cyclobuxine D on the isolated frog heart, the ECG and heart rate in urethane anesthetized rats.

MATERIALS AND METHODS

Effects on Isolated Frog Heart

Frog(25-30g) was collected in group of 6. Heart of frog was perfused according to Yagi's method (Yakagi, K and Ozawa, H. 1969). Each of the compounds was administered directly into the perfusion cannula. Contractile force was recorded on polygraph (San-Ei) 8K21 recorder. Ringer's solution was used as normal medium.

Effects on Blood Pressure and Heart Rate in Anesthetized Rats

Sprague-Dawley male rats were anesthetized by intraperitoneal administration of urethane (1.25 g/kg). The trachea was cannulated with a short polyethylene tube. Intravenous injections were made through a fine polyethylene tube tied into the left femoral vein. A polyethylene tube, filled with 200 u./ml of heparin in saline (0.9% w/v sodium chloride in distilled water) was tied into the right carotid artery and connected to a Consolidated Electrodynamics pressure transducer. The amplitude output and heart rate were recorded with a San-Ei recorder. Drugs were dissolved in saline. Care was taken to ensure that the maximum volume of drug solution and saline follower injected intravenously at one time was 0.2 ml.

Intracerebroventricular injections were performed through a fine polyethylene tube (26 gage) tied into the lateral ventricle. A polyethylene tube was inserted into the lateral ventricle. A polyethylene tube was inserted into a hole drilled in the skull such the tip of the tube would be positioned at a desired area. The coordinates of polyethylene tube were (for lateral venticle) AP, −1.0 mm; L, 1.5 mm; H, −3.5 mm from bregma. To determine the site of cannula placement, 5 μl of 1% methylene blue was injected into the polyethylene tube and the brain was removed, dissected and examined. Only data from rats with correct placement were used.

Effects on the rats ECG

The experiments were performed in male rats (SD, 250-300 g), anesthetized with urethane (1.25 g/kg i.p.). The animals were fixed in the supine position; ECG (lead II) and heart rate were recorded simultaneously on a direct recorder (San-Ei). The definition of the measured ECG interval are given in Fig. 2.

After an equilibration period of at least 10 min, predrug values were taken during a 5-min period immediately before the start of the drug injection. The drugs were administered by acute intravenous injection and continuous intravenous infusion into the femoral vein. Infusion rate was increased x-fold every 10 min, without changing the infusion volume (0.1 ml/min).

Statistics

Statistical analysis of the data was performed in each case according to Student's t-test. Significance was taken as $p<0.05$.

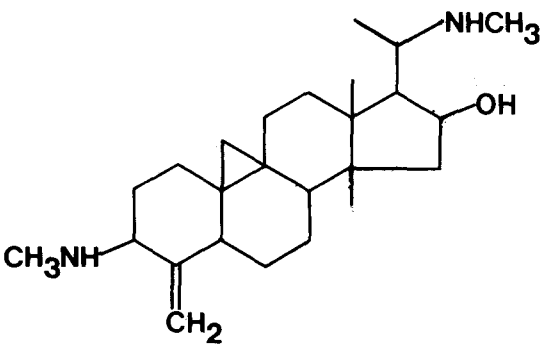

Fig. 1. The structure of cyclobuxine D.

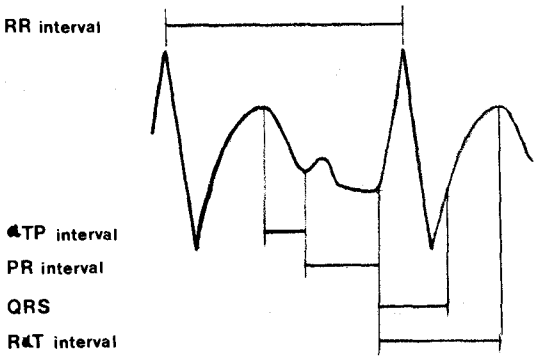

Fig. 2. Definition of the measured ECG intervals in rats.

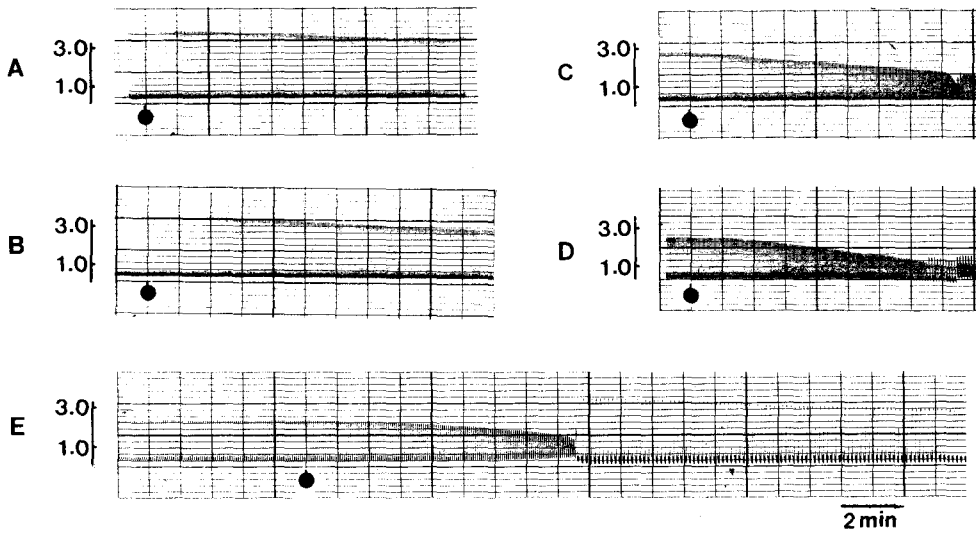

Fig. 3. Effects of cyclobuxine D on the contractile force of isolated frog heart. Each panel is contractile force in gm. A, 0.81×10^{-6}M; B, 1.62×10^{-6}M; C, 3.23×10^{-6}M; D, 6.46×10^{-6}M; E, 8.07×10^{-6}M of cyclobuxine D

Table 1. Effects of cyclobuxine D on the contractile force of isolated frog heart

Treatment	Dose ($\times 10^{-6}$M)	n	Contractile force (gm)
Ringer solution	—	12	3.14 ± 0.32
Cyclobuxine D	1.62	5	2.85 ± 0.16
	3.23	7	2.23 ± 0.21^{b}
	6.46	5	1.25 ± 0.23^{b}
	8.07	5	two to one A-V blocking

Mean ± SD., n: Number of experiments in each group
Significance of difference (^{a} $p<0.05$, ^{b} $p<0.01$) compared with the corresponding control values.

RESULTS

Effects of cyclobuxine D on isolated frog heart

In control experiments, infusion of Ringer's solution did not change contractile force. Effects of cyclobuxine D are shown in Fig. 3 and Table 1. Perfusion of cyclobuxine D (final concentration $0.81\text{-}6.46 \times 10^{-6}$M) resulted in a decreased in contractile force. A concentrtion of 8.07×10^{-6}M caused an arrhythmia (a ratio of two to one A-V blocking), which returned to normal state after the solution was exchanged for drug-free Ringer's solution.

Cyclobuxine D abolished significantly the positive

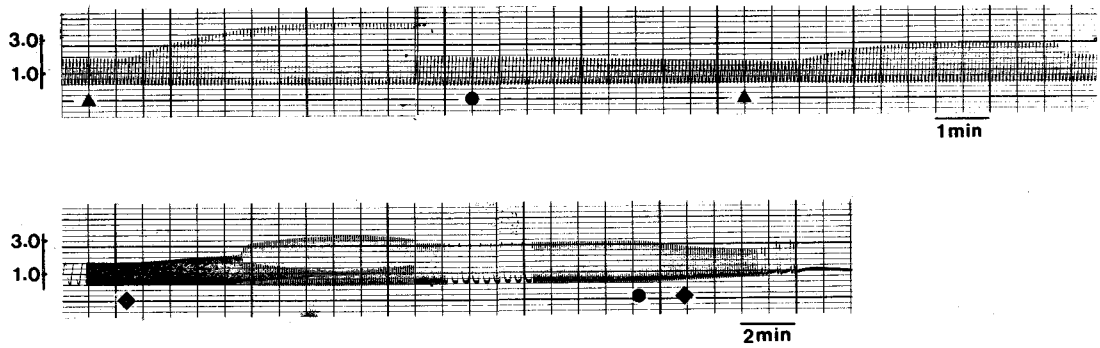

Fig. 4. Effects of cyclobuxine D on the positive inotropic effects of isoproterenol and ouabain in isolated frog heart. Each panel is contractile force in gram. ▲, isoproterenol (final concentration, 4.73×10^{-6}M); ◆, ouabain (final concentration, 3.56×10^{-5}M); ●, 8.07×10^{-6}M of cyclobuxine D.

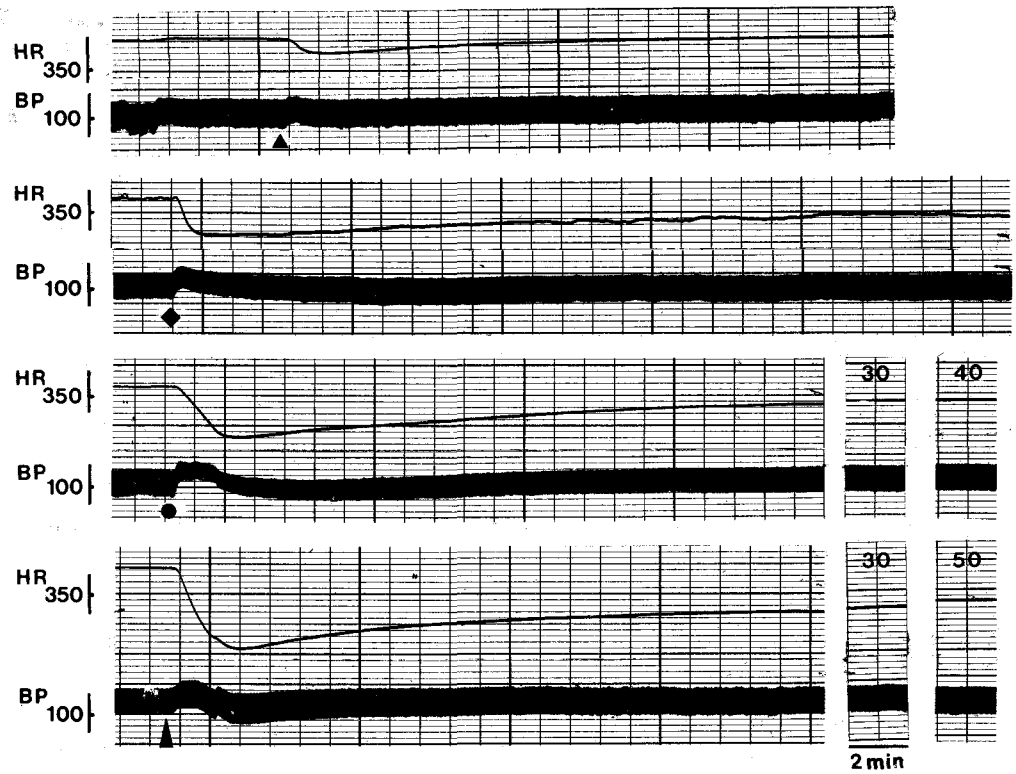

Fig. 5. Effects of cyclobuxine D on blood pressure and heart rate in urethane anesthetized rats. In each panel, the upper recording is heart rate (HR) in beats/min and the lower panel is blood pressure (BP) in mmHg. Drug was given by intravenous injection. ▲, 1mg/kg; ◆, 2mg/kg; ●, 4mg/kg; ▲, 8mg/kg of cyclobuxine D.

inotropic effects of isoproterenol and ouabain (Fig. 4).

Bradycardic effects of cyclobuxine D in anesthetized rats

Effects of cyclobuxine D on blood pressure and heart rate in anesthetized rats were shown in Fig. 5. Cyclobuxine D exerted a dose-dependent bradycardiac effects but did not affect significantly blood pressure. The bradycardiac effect of cyclobuxine D (8 mg/kg) was of long duration, a period of 50-70 min being reguired for the heart rate to return to

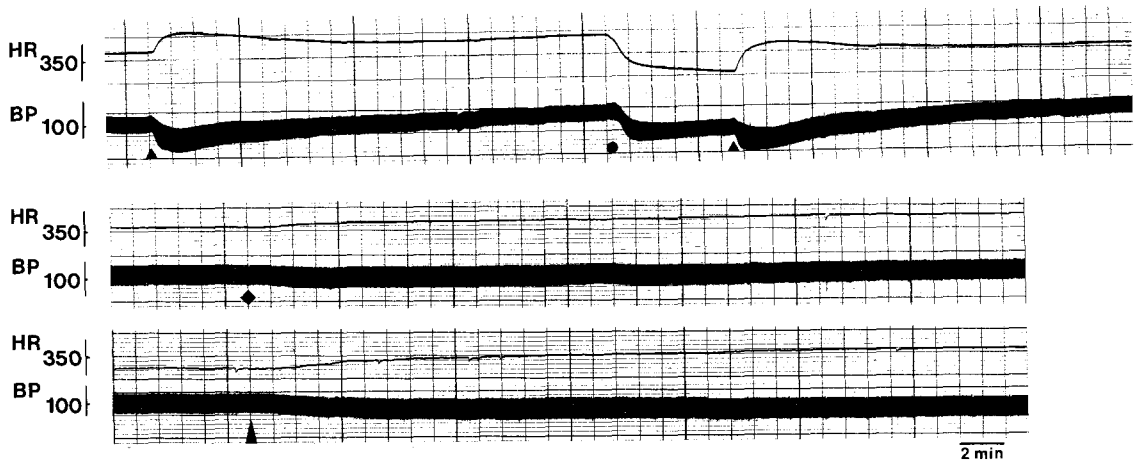

Fig. 6. Effects of cyclobuxine D on the positive chronotropic effect of isoproterenol after intravenous injection and on blood pressure and heart rate after intracerebroventricular (icv) injection in urethane anesthetized rats. In each panel, the upper panel is heart rate (HR) in beats/min and the lower panel is blood pressure (BP) in mmHg. ▲, 8μg/kg of isoproterenol (iv); ●, 4mg/kg of cyclobuxine D (iv); ◆, 25μg/kg of cyclobuxine D (icv); ▲, 50μg/kg of cyclobuxine D (icv)

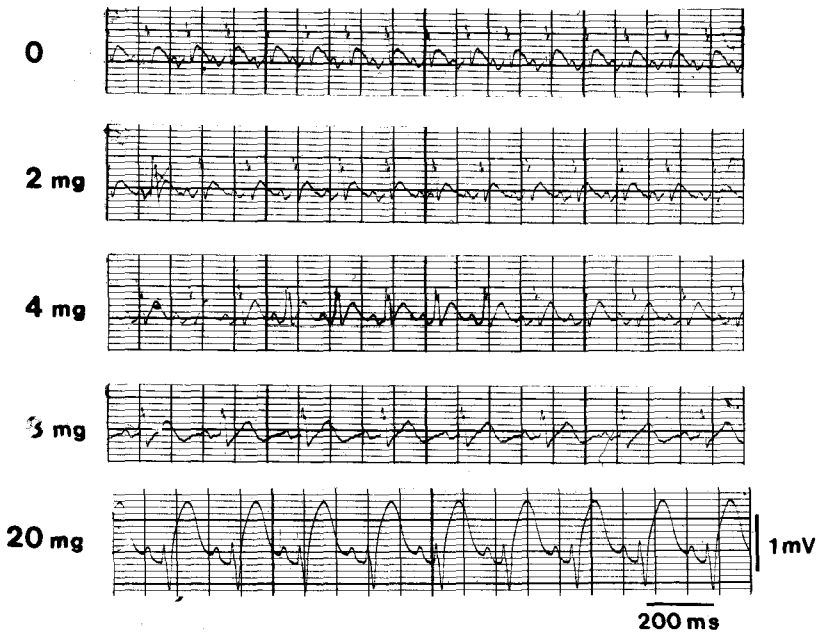

Fig. 7. ECG changes (lead II) induced by intravenous injection of cyclobuxine D in urethane anesthetized rats.

normal. Cyclobuxine D failed to antagonized the positive chronotropic effect of isoproterenol in rats (Fig. 6).

In anesthetized rats, intracerebroventricular injection of cyclobuxine D caused a prolonged fall in arterial blood pressure and an increase in heart rate, but those effects were not significant (Fig. 6).

Effects on the ECG in anesthetized rats

Cyclobuxine D exerted a significant negative chronotropic action, the fall in heart rate progressing with increase doses. At the high dose cyclobuxine D caused A-V blocking and ventricular bradycardia

Table 2. Effects of an intravenous injection of cyclobuxine D on heart rate and ECG parameters in anesthetized male rats (1.25g urethane /kg intraperitoneally)

Concentration (mg/kg)	n	Heart rate	PR interval (ms)	PRc interval (ms)	QRS (ms)	R α T interval (ms)
0	8	439 ± 51	43.1 ± 4.3	43.1 ± 4.3	23.2 ± 2.3	34.3 ± 3.6
2	4	391 ± 23	47.0 ± 3.2	43.2 ± 3.2	25.4 ± 2.1	38.3 ± 4.1
4	4	359 ± 11[a]	48.7 ± 2.8[a]	42.9 ± 2.6	25.6 ± 1.5	50.3 ± 3.1[b]
6	4	333 ± 16[b]	54.0 ± 3.3[b]	41.8 ± 3.7	25.1 ± 2.1	59.7 ± 3.9[b]
8	4	288 ± 28[b]	60.0 ± 3.8[b]	41.0 ± 3.2	36.8 ± 8.7	85.5 ± 7.1[b]

Mean ± SD. Injection rates were 0.1 ml/min.
ECG lead: lead II.
[a]$p<0.05$ and [b]$p<0.01$ to predrug value (Student's t-test for paired observations)

Table 3. Effects of a long intravenous infusion of cyclobuxine D on heart rate and ECG parameters in anesthetized male rats (1.25g urethane /kg intraperitoneally).

Experimental time (min)	Cumulated dose (mg/kg)	n	Heart rate (beats/min)	PR interval (ms)	PRc interval (ms)	QRS (ms)	R α T interval (ms)	MBP (mmHg)
0	0	4	401 ± 15	43.2 ± 3.1	43.2 ± 3.1	23.1 ± 1.2	35.4 ± 1.6	92 ± 9
10	0.059	4	392 ± 11	45.5 ± 3.1	45.3 ± 3.1	23.4 ± 0.9	36.5 ± 1.5	91 ± 12
20	0.649	4	377 ± 17	48.0 ± 3.0	46.4 ± 2.7	24.1 ± 1.2	36.8 ± 1.7	92 ± 9
24	3.000	4	340 ± 29[a]	47.7 ± 2.1	42.5 ± 2.5	23.5 ± 1.1	47.9 ± 2.3[b]	94 ± 11
30	6.530	4	302 ± 25[b]	54.0 ± 2.9[b]	44.2 ± 2.9	25.1 ± 1.4	69.7 ± 2.9[b]	90 ± 7
34	11.232	4	270 ± 37[b]	56.0 ± 4.1[b]	41.8 ± 4.1	25.1 ± 1.9	80.0 ± 7.1[b]	81 ± 15

Mean ± SD. Infusion rates were 0.0059, 0.059, 0.59, 1.18 mg/kg, min; they were increased at 10, 20 and 30 min after the start of the lowest infusion rats.
ECG lead: lead II
MBP: Mean Blood Pressure
[a]$p<0.05$ and [b]$p<0.01$ to predurg value (Student's t-test for paired observations)

Table 4. Effects of an intravenous administration of quinidine sulfate on heart rate and ECG parameters in anesthetized male rates.

Concentration (mg/kg)	n	Heart rate	PR interval (ms)	PRc interval (ms)	QRS (ms)	R α T interval (ms)
0	8	363 ± 30	50.7 ± 1.6	50.7 ± 1.6	23.1 ± 1.8	42.7 ± 6.1
4	4	349 ± 11	54.5 ± 4.9	54.4 ± 5.9	25.1 ± 2.3	51.9 ± 7.1[a]
8	4	338 ± 21	59.6 ± 3.2[b]	58.7 ± 8.7[a]	36.2 ± 2.4[a]	60.4 ± 5.9[b]
16	4	320 ± 27[a]	65.8 ± 7.1[b]	65.7 ± 9.1[b]	36.4 ± 2.5[a]	72.1 ± 6.6[b]

The results are mean ± SD, n: Number of experiments in each group.Injection rates were 0.1 ml/min. ECG lead: lead II
[a]$p<0.05$ and [b]$p<0.01$ to predrug value (Student's t-test for paired observations)

(Fig. 7). Cyclobuxine D produced a prolongation of the PR interval and a marked prolongation of the R α T interval. Cyclobuxine D was without significant effect on the duration of the QRS complex and PRc, which was a derived value supplying information about the extent of a change in the duration of the PR interval at a constant heart rate (Table 2 and 3).

Quinidine sulfate produced a marked prolongation of A-V conduction (Table 4, Fig 8). Quinidine sulfate exerted a dose-dependent prolongation in R α T interval but did not affect

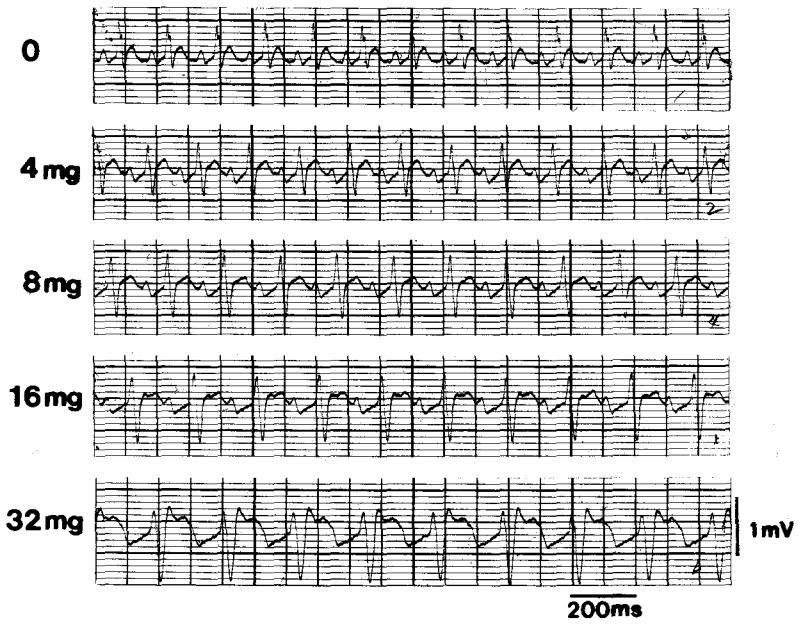

Fig. 8. ECG changes (lead II) induced by intravenous injection of quinidine sulfate in urethane anesthetized rats.

Table 5.

Class*	Mode of Action	Drugs	Expected ECG Changes			
			RR	RR	QRS	R α T
1a	membrane stabilization and reduced conduction velocity	quinidine, ajmaline	▲	▲	▲	▲
1b	membrane stabilization and unchanged conduction velocity	lidocaine	▲	0	0	0
2′	anti-sympathetic	propranolol	▲	0	0	0
3	uniform prolongation of action potential duration	amiodarone	0	0	0	▲
4	calcium antagonistic	verapamil	▲	0	0	0

▲ increase 0 unchanged

* classification according to Vaughan Williams 1970, 1979 and Singh and Hauswirth 1974

significantly the QRS duration. PRc (PR interval corrected for intra-individual heart rate changes) was lengthened by quinidine sulfate, this parameter was not changed by cyclobuxine D (Table 2, Table 4). As can be seen from Fig. 8, the decrease in heart rate by quinidine sulfate was mainly due to an increase in the PR intrerval and R α T interval.

DISCUSSION

Cyclobuxine D produced a significant negative chronotropic effect in anesthetized rats but was without significant effect on blood pressure. In isolated frog heart, which was used to give some complementary result to the evidence for the experiment in rats, cyclobuxine D caused a decrease of contractile force. In high dose, cyclobuxine D

produced partial A-V blocking (generally 2 or 3:1). The positive inotropic effects of isoproterenol and ouabain were significantly blocked by the pretreatment with cyclobuxine D in isolated frog heart. Pretreatment with cyclobuxine D did not abolish the positive chronotropic effect of isoproterenol in anesthetized rats. Cyclobuxine D (25 and 50μg/kg icv) exerted a fall in arterial blood pressure and an increase in heart rate, but these effects were not significant. These results excluded apparently the possibility of beta cardiovascular receptor and mediation of central nervous system participation in the negative chronotropic effect of cyclobuxine D in anesthetized rats.

In order to clearify in detail the mechanism of negative chronotropic effect of cyclobuxine D, we examined the effects of cyclobuxine D on the rat ECG parameters (PR interval, QRS complex and R α T interval) and compared the results of cyclobuxine D with those of existing antiarrhythmic agents.

The electrophysiologic properties of the rat heart were contrasted with those of the dog and man. The atrioventricular mode and specialized ventricular conduction system of the rat transmitted the cardiac impulse from atrium to ventricle more rapidly than in the dog heart and the effective refractory period of the atrioventricular node was briefer than in the dog. The total activation time of the ventricle in the rat was about one-third that of the dog. This is accounted for by the smaller heart of the rat and result in a brief QRS duration. In the adult rat, the T wave follows upon the QRS without an isoelectric segment. This is due to the brief duration and lack of plateau phase of the rat ventricular myocardial action potential.

Osborne (1974) has stated that anesthetics are precluded in ECG studies because of (a) possible synergism between the anesthetics used and the compound being tested, and (b) possible changes being produced in the ECG by the anesthetic agent itself. Aviado (1970) Driscoll (1979), Beinfield and Legr (1980) have stated the problem of using anesthetics, pentobarbital and ether. Although Heering (1970) and Zbinden *et al.*, (1980) have demonstrated a urethane-induced bradycardia, mediated through a lengthening of the PQ and QT interval, as well as temporary deformation of the P wave caused by that substance, the fewest problems have seemed to be encountered with urethane.

With cyclobuxine D, the negative chronotropic effect was accompanied by a slowing of A-V conduction as evidence by the prolongation of the PR interval. Cyclobuxine D caused a significant prolongation of the R α T interval suggesting some delay in ventricular repolarization. The lack of a significant effect of cyclobuxine D on the duration of the QRS complex is in agreement with the well known absence of a significant action on conduction in the ventricular muscle. PR interval corrected for intra-individual heart rate changes (PRc) were also considered in the assessment of a drug action (PRc = PRi + (RRO − RRi) × 0.2; cf. Schumacher *et al.*, 1980). Cyclobuxine D was without a significant effect on PRc.

The refractory period relative to the duration of the action potential is uniformly lengthened by all antiarrhythmic drugs although the absolute changes are different for the various substances (John Witting *et al.*, 1973; Graham HB *et al.*, 1986). Most of the drug achieve their main effect on the ventricular part of the myocardium, only quinidine and the β-blocking agents affect the atrium, ventricle and specialized conduction system likewise (Edward C *et al.*, 1982; Thomas Bigger Jr *et al.*, 1970). Antiarrhythmic drugs-quinidine, procainamide, ajmarine, isoprenaline-exert their main effect on the heart by lengthening the refractory period and slowing down the diastolic slope of the membrane potential. The decrease in automaticity and the depression of electromechanical coupling resulting in a negative inotropic effect produce the principal cardiac side reactions.

According to the classification of Vaughan Williams (1970, 1979) and Singh and Hauswirth (1974) four classes of antiarrhythmic action may be defined (Table 5). Quinidine, a representive of class 1 action, prolonged the PR interval, the R α T interval and the duration of QRS complex (Vaughon Williams 1970, 1979, W. Bleifield). The effects of quinidine sulfate on the rat ECG in our laboratory were in good agreement with published data. Lidocaine, representing the group of membrane stabilizing drugs without a marked effect on conduction velocity, did not change any of the measured ECG parameters except for a moderate decrease in heart rate (Kühl UG *et al.*, 1980). But Valle *et al.* (1975) found a significant increase in the PR interval in rats, whereas QRS and QT remained unchanged. Propranolol, representing the group of anti-sympathetic drug, prolonged the PR interval and did not affect significantly the duration of QRS complex. The R α T interval was slightly shortened by propranolol (Buschmann G *et al.*, 1980). With verapamil, a representative of class 4 action, no changes in the measured ECG parameters were observed except for a marked reduction in heart rate (Kühl UG *et al.*, 1980). Bleifield (1971) reported also

the lack of an effect of verapamil on A-V conduction.

With cyclobuxine D, the bradycardic effect in urethane anesthetized rats was accompanied by a slowing of A-V conduction. Cyclobuxine D after an acute intravenous injection and a long intravenous infusion produced a significant prolongation of the R α T interval which suggested slowing down the diastolic slope of the membrane potential. Cyclobuxine D except high dose was without a significant effect on the duration of the QRS complex. These effects of cyclobuxine D on the rat ECG parameters is similar to those of quinidine. As the investigated results in this study might not offer the full information about the effects of cyclobuxine D on cardiovascular system, more detailed examination should be undertaken.

REFERENCES

Beinfield WH and Lehr D: *QRS-T variations in the rat electrocardiogram. Am J Physiol 214:197-204, 1968*

Bleifeld W: *Side effects of antiarrhythmic drugs. Naunyn-Schmiedeberg's Arch Pharmacol 296:282-297, 1971*

Budden R, Buschmann G and Kühl UG: *The rat ECG in pharmacology and toxicology (eds Budden R, Detweiler DK and Zbinden G) Pergamon Press pp 41-81, 1980*

Driscoll P: *The electrocardiogram of Roman high-and low-avoidance rats under pentobarbital sodium anesthesia. Arzneim Forsch/Drug Res 29:897-900 (1979)*

Edward C and Tetsunori S: *Shortening of the action potential and reduction of pacemaker activity by lidocaine, quinidine and procainamide in sheep cardiac purkinje fibers. Circul Res 50:257-272, 1982*

Graham HB, James EL and Neil DB: *Comparative electropharmacology of mexiletine, lidocaine and quinidine in a canine purkinje fiber model. J Pharmacol Exp Ther 237:232-236, 1986*

Herring H: *Das elektrokardiogram der wachen und narkotisierten Ratte. Arch Int Pharmacodyn. 185:308-328, 1970*

John W, Lura AH, Andrew GW and Durham NC: *Electrophysiological effects of lidocaine on distal purkinje fibers of canine heart. Am Heart J 86:69-78, 1973*

JR Thomas Bigger J and Mandel WJ: *Effects of lidocaine on the electrophysiological properties of ventricular muscle and purkinje fibers. J Clin Invest 49:63-77, 1970*

Osborne BE: *Uses and applications of electrocardiography in toxicology. Experimental model systems in toxicology and their significance in man. Excerpta Medica Amsterdam XV:85-97, 1974*

Schumacher W, Budden R, Buschmann G and Kühl UG: *A new method for the evaluation of ECG and blood pressure parameters in anesthetized rats by on-line biosignal processing. The rat ECG in pharmacology and toxicology. Pergamon Press pp 171-178, 1980*

Singh BN and Hauswirth O: *Comparative mechanism of action of antiarrhythmic drugs. Am Heart J 87:367-382, 1974*

Takagi K and Ozawa H: *"Yakubutsugaku Jinkken" 5th ed., Nanzando, Tokyo pp 118-121, 1969*

Valle LBS, Oliveira-Filho RM, Armonia PL, Nassif M and Saraceni GJ: *Sensibilisation de la bradycardie pendant l' hypotension finale déclenchée par la sérotonin chez le rat: Effect de la lidocaine. Arch Int Physiol Biochem 83:647-657, 1975.*

Vanghan Williams EM: *Classification of antiarrhythmic drugs. Symposium on Cardiac Arrhythmias (eds. Sandoe E, Flenstedt-Jensen E and Olesen KH). A B Astra Sodertalje Sweden, 1970*

Vaughan Williams EM: *Characterisation of new antiarrhythmic drug. Prog Pharmacol 2:13-23, 1979*

Zbinden G, Kleinert R and Rageth B: *Assessment of emetine cardiotoxicity in a subacute toxicity experiment in rats. J Cardiovasc Pharmacol 2:155-164, 1980*

= 국문초록 =

Cyclobuxine D의 흰쥐에 있어서 ECG와 심박동수에 대한 작용과 적출 개구리 심장에 대한 작용

순천향대학 의학부 약리학교실

이종화, 박영현, 조병헌, 김유재, 김종배, 김천숙, 차영덕, 김영석

본 실험실에서는 민간요법으로 말라리아와 성병등의 치료제로 사용되어온 회양목(*Buxus microphylla var. koreana* Nakai)에서 steroid성 alkaloid인 cyclobuxine D와 nonalkaloid인 buxuletin을 분리하였다. Buxuletin의 가토에 있어서 이뇨작용에 대해서는 본 실험실에서 보고한 바 있으며 cyclobuxine D의 약리작용에 대한 보고는 지금까지 전무한 상태이다.

본 실험에서는 새로운 항부정맥 약물의 발견의 일환으로 cyclobuxine D의 적출 개구리 심장에 대한 작용과 마취시킨 흰쥐의 ECG와 심박동수에 대한 작용을 관찰하였다. Cyclobuxine D는 적출 개구리 심장에 대해 용량의존적 심근 수축력 감소를 나타냈으며 흰쥐에 있어서 현저한 심박동수 감소를 나타냈다. Cyclobuxine D는 흰쥐의 ECG에 있어서 PR interval과 R αT interval을 연장시키며, QRS complex와 PR interval의 심박동수에 대한 보상치인 PRc에 대해서는 고용량에서는 연장시키나 그 작용이 현저하지 않다. 이 결과로 보아 cyclobuxine D는 흰쥐의 ECG에서 A-V conduction과 ventricular depolarization에 주로 관여하는 것으로 사료되며 이는 기존의 antiarrhythmic drugs과 비교해 볼 때 quinidine sulfate와 유사성이 있다고 추정된다.