

Characteristics of Electrocardiographic Changes with Some Representative Antiarrhythmic Drugs in Adult Rats

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ABSTRACT. The characteristics of ECG changes with representative antiarrhythmic drugs; procainamide (PA) (class Ia), lidocaine (LC) (class Ib), propranolol (PN) (class II), and verapamil (VP) (class IV) were investigated in adult rats. Action potential (AP) was also recorded from myocardial cells during electrical stimuli with frequencies of 1–5 Hz. All the four drugs produced ECG abnormalities which contained AV and SA blocks at middle and high dose levels. Three drugs except VP induced a prolongation of QRS complex and notched QRS at low or middle dose level. As compared such effects with those in dogs and humans, some differences were noted as follows: (1) a dose-dependent prolongation of QT interval by LC and PN, and (2) a shortening of RR interval by VP at the dose of 0.6 mg/kg or less. LC and PN elongated the QT interval in the unipolar precordial chest lead ECGs at right anterior chest positions. These two drugs did not affect the duration of AP (APD₉₀), whereas maximum upstroke velocity (\dot{V}_{max}) decreased. These results suggest that the prolongation of QT interval with LC and PN was due to a delay in local ventricular conduction time, especially on the right ventricle. The shortening of RR interval by VP was clearly blocked by the pretreatment with PN, indicating that this shortening reflected the sympathetic nervous reflex presumably due to the peripheral vasodilation effect of VP.—**KEY WORDS:** antiarrhythmic drug, arrhythmia, electrocardiogram, myocardial cell, rat.

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Antiarrhythmic drugs induce a prolongation of excitation time or a decrease in conduction velocity by their direct electrophysiological action on myocardial cells and conduction system. Such actions result in the suppression of various arrhythmias which are caused by abnormal excitation or conduction [18, 19, 24]. However, the overdose of these categorical drugs can cause adverse reactions to the heart such as sino-atrial (SA) or atrioventricular (AV) block and bradycardia [4, 20]. Since these secondary effects yield serious problems in clinical aspects, it is of importance to clarify their variable physiological actions.

Assessing the therapeutic and toxic effects of antiarrhythmic drugs on electrocardiograms (ECG) has been frequently carried out in the rats as well as in other animal species because of their usefulness as an experimental animal in various screening tests and well documented background data [22]. However, the rat heart has some functional characteristics, e.g., the absence of ST segment in ECG and high frequency of heart beats (300 to 400 bpm) [10, 11, 22, 29] different from the other animal species. Such characteristics are speculated to influence the appearance of the effects of antiarrhythmic drugs on the heart. Nevertheless, less is known about the difference of electrocardiographic changes by anti-

arrhythmic drugs between the rat and other species.

In this study, we investigated the effects of four typical antiarrhythmic drugs, procainamide (class Ia), lidocaine (class Ib), propranolol (class II), and verapamil (class IV) on ECG in adult rats. In addition, action potentials were recorded from myocardial cells during electrical stimuli in order to examine the effects of lidocaine and propranolol on these unitary components.

MATERIALS AND METHODS

Animals and anesthesia: Male Wistar rats aging 10 to 15 weeks were used in this study. All experiments were done under anesthesia with pentobarbital sodium (40 mg/kg, i.p.). Rats were restrained in supine position on an operating table warmed 37°C during experiments.

Drug preparation and dose: Procainamide (PA), lidocaine (LC), propranolol (PN), and verapamil (VP) were selected as antiarrhythmic drugs which are commercially available from Sigma Chemical Company. PA, PN, and VP were dissolved in physiological saline (0.9% NaCl), and LC in solution of mixture of saline and equimolar hydrochloride. Three levels of dose were used for each drug, according to the methods reported previously [4,

18]. The 'low' and 'high' dose levels were adopted at approximately maximum clinical dose and nearly LD₅₀ dose, respectively. Middle dose was between these two doses. In each drug the injection volume was adjusted as 0.1 ml per 100 g of body weight. The individual drug was administered into the femoral vein via a small catheter during 20 sec. In each animal, the injection was performed three times at 10 or 20 min interval with increasing doses (from low to high dose levels).

Recordings of ECGs: Bipolar limb lead ECGs (I, II, and III) were recorded with a bioamplifier (San-ei Sokki: 1205C, time constant = 1.5 sec) and displayed on a visigraph (San-ei Sokki: 5L36ME) or ECG processor (Softtron: FP-1). Fine needle electrodes (25G) were placed in the subcutaneous tissue of forelimbs and hindlimbs bilaterally. ECG recordings were carried out before injections and at 0.5, 1, 2, 3, 5, 7 and 10 min (low dose level), 20 min (middle dose level) or 30 min (high dose level) after injections.

Unipolar precordial chest lead ECGs were recorded especially in LC and PN treatment groups in order to investigate the cause for QT changes obtained in limb lead ECGs. The unipolar precordial chest lead ECGs were recorded simultaneously from 6 positions of anterior chest surface (Fig. 1) using a bioamplifier (San-ei Sokki: 1205C), and recorded on a thermal recorder (Graphtec: WR7700). The other procedures were the same as those mentioned above.

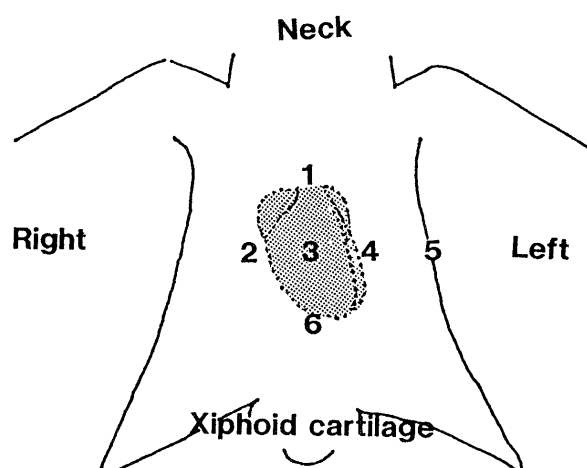


Fig. 1. Recording positions (number 1-6) of unipolar precordial chest lead ECGs.

Determination of drug concentration in plasma:

Concentration of the four drugs in plasma was determined in experiments with low and middle doses. Assay for plasma PA and LC was carried out by an enzyme-multiplied immunoassay method using commercially available enzyme-immunoassay-kits (Syva) [2, 5]. Plasma PN was measured based on a fluorometric assay method developed by Pritchard *et al.* [13, 16], while plasma VP was assayed with a modified fluorometric assay method developed by McAllister and Howell [9, 12].

Recordings of action potentials (APs) from myocardial cells: APs of ventricular muscles were also examined for each of LC and PN to investigate the cause of QT changes in bipolar ECGs occurred by injections of these drugs. For this purpose, right ventricular tissues of adult rats were superfused with oxygenated Tyrode's solution in a temperature-controlled water bath. APs were recorded from central part of the right ventricular endocardium using standard 3M KCl-filled glass micropipettes. These preparations have been precisely described in the previous study [29]. The drug concentration in the Tyrode's solution was 10^{-6} , 10^{-5} and 10^{-4} M for each drug. Electrical stimulation was applied to the split muscle by another bipolar electrode with different stimulus frequencies of 1, 2, and 5 Hz using an electrostimulator (San-ei Instrument: ES-104). The voltage for stimulus was 3V. The APs were displayed on a dual-beam oscilloscope (Iwatu: SS5702) and the signals were photographed by a long oscilloscope (Nihon Kodens: PC-2B).

The effect of autonomic nervous blockades: In order to block the autonomic nervous innervation to the heart [6], PN (1 mg/kg) and atropine (1 mg/kg) were intravenously injected prior to the application of VP (0.2 and 0.6 mg/kg) in three rats (ANB group). ECG (limb lead II) and blood pressure (BP) were recorded in these rats, and their results were compared with those obtained from control rats in the absence of autonomic nervous blocking.

Data analyses: RR, PR, QT intervals and QRS duration were measured in order to evaluate the effects of each drug on ECG. Moreover, the 90%-duration time of action potentials (APD₉₀) recorded from myocardial cells was measured. Statistical analyses were performed on the difference between values before and after injections of each drug, using Student's paired *t*-test. Statistical significant difference was considered if P value less than 0.05.

RESULTS

Bipolar limb lead ECGs: Various ECG changes were caused by intravenous injections of PA, LC, PN and VP. Figure 2 shows typical examples of such ECG changes and the results are summarized in Table 1.

In the PA group, notched QRS was noted in most of animals at low (20 mg/kg) and middle (40 mg/kg) dose levels. One of 6 rats showed SA block after the injection with middle dose. At high dose (80 mg/kg) level, the first or second degree of AV block was recorded in all 6 rats, and three of them died. In the LC group, notched QRS was present in one of 5 rats after injections of 2 and 4 mg/kg. Following the injection of high dose of LC (8 mg/kg), a deep S wave and complete AV block exhibited in one of 5 rats. In the PN group all 5 rats showed a deep S wave after the injection with 5 mg/kg, and one of those showed the second degree of AV block.

In the PA and LC groups, the conduction times, i.e., QRS, PR, QT, and RR intervals were prolonged by each dosage level ($p < 0.05$). Especially, the prolongation of QRS duration, RR and QT intervals in LC group and of RR, PR and QT intervals in PA group showed a dose-dependent increase following the injections (Fig. 3). In the PN group, injections with 5 mg/kg induced a prolongation of all the intervals, whereas injections with 0.2 and 1 mg/kg a prolongation of only PR and QT intervals. In the VP group, RR interval was markedly shortened by injections of 0.2 and 0.6 mg/kg ($p < 0.05$), while PR interval prolonged in all dose levels (Fig. 4).

Drug concentration in plasma: The plasma concentration levels of all four drugs declined bi-exponentially, and therefore the pharmacokinetic parameters were calculated by fitting the two-compartment model (Table 2). Mean $T_{1/2b}$ (elimination phase) in the middle dose of PA, LC, and

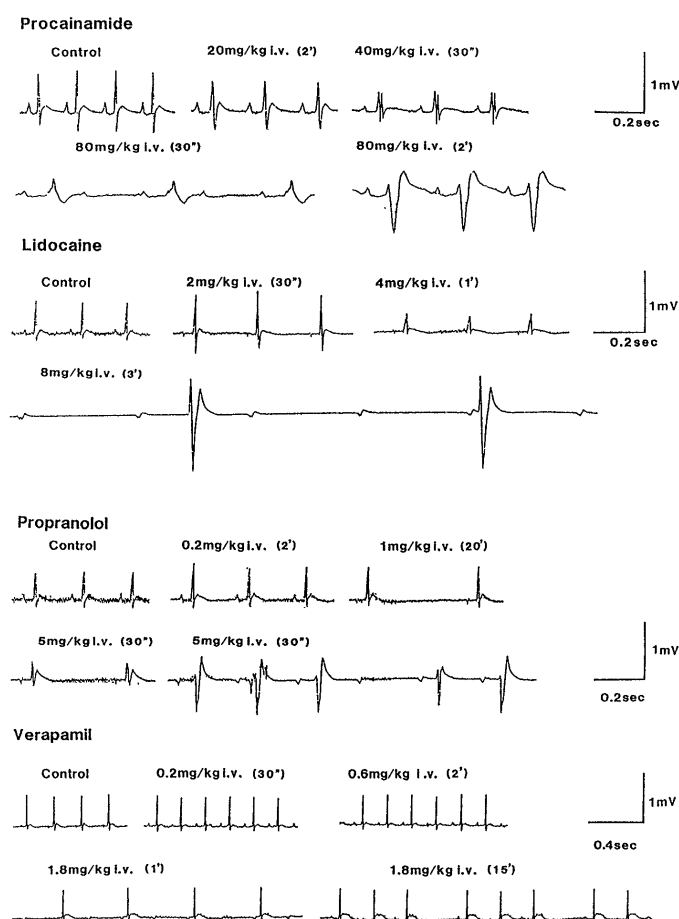


Fig. 2. ECG recordings from rats treated with antiarrhythmic drugs.

Table 1. Arrhythmias and other ECG changes induced by the four drugs tested

| Drugs | Dose (mg/kg i.v.) | ECG findings |
|----------------------|----------------------|---|
| Procainamide (PA) | 20 40 80 | notched QRS (4/6) notched QRS (6/6) SAb (1/6) 2° AVb (1/6) Cardiac Arrest (3/6) |
| Lidocaine (LC) | 2 4 8 | notched QRS (1/5) notched QRS (1/5) S(a) ↑ (3/5) 3° AVb (1/5) Cardiac Arrest (1/5) |
| Propranolol (PN) | 0.2 1 5 | — — S(a) ↑ (5/5) 2° AVb (1/5) |
| Verapamil (VP) | 0.2 0.6 1.8 | — — 2° AVb or 3° AVb (4/5) |

Note: SAb: Sino-atrial block. AVb: Atrioventricular block.

2° AVb: Second degree of AVb.

3° AVb: Third degree of AVb.

S(a) ↑ : Increase in amplitude of S wave.

Number in parenthesis means number of animals.

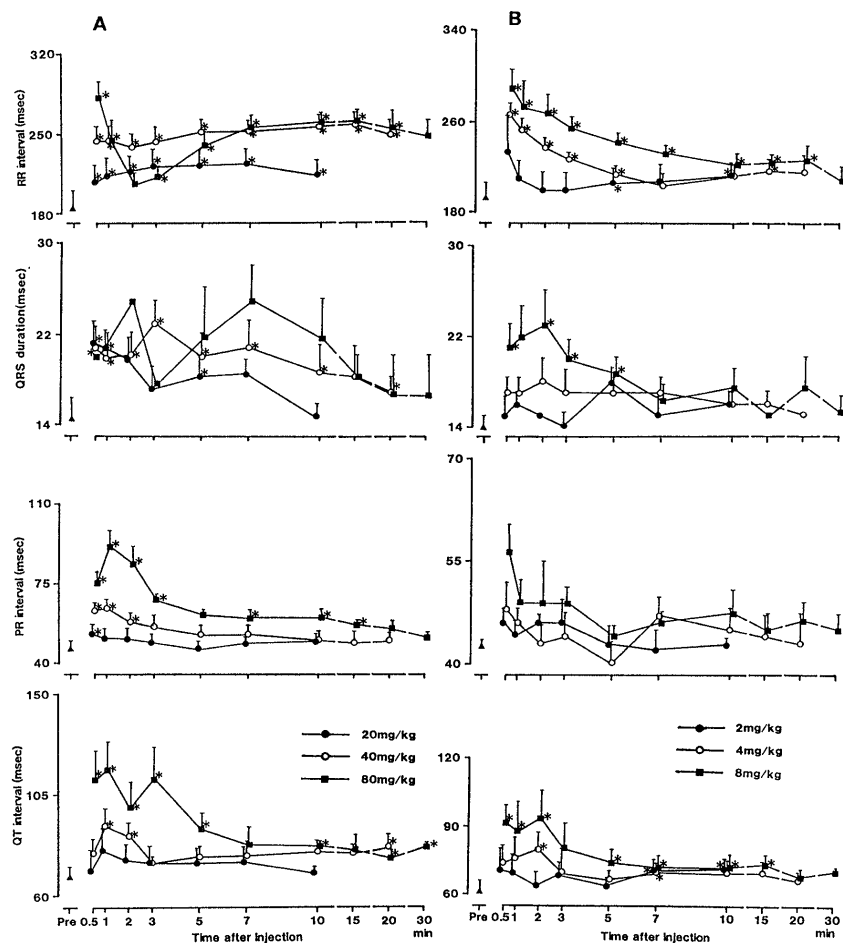


Fig. 3. Time-response curves of RR, QRS, PR and QT intervals after injections of antiarrhythmic drugs. A: Procainamide. B: Lidocaine. Each point and vertical bar represents mean value and SE from 6 rats. *: Significantly different from pre-injection values ($P < 0.05$).

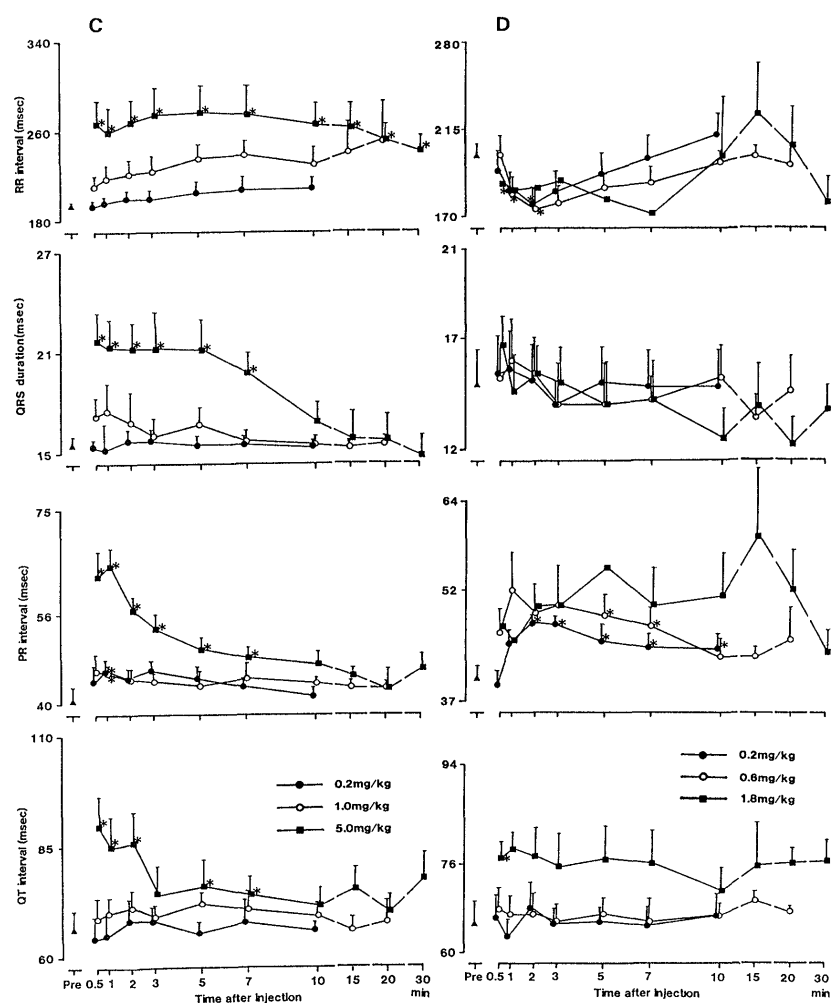


Fig. 4. Time-response curves of RR, QRS, PR and QT intervals after injections of antiarrhythmic drugs. C: Propranolol. D: Verapamil. Each point and vertical bar represents mean value and SE from 6 rats. *: Significantly different from pre-injection values ($P<0.05$).

Table 2. Intravenous pharmacokinetic parameters of the four drugs tested

| Drugs | Dose (mg/kg) | A ($\mu\text{g/ml}$) | B ($\mu\text{g/ml}$) | a (min^{-1}) | b (min^{-1}) | T1/2b (min) | AUC ($\mu\text{g}\cdot\text{min/ml}$) | Vss (l/kg) | Cl (ml/min) |
|-------------------|--------------|------------------------|------------------------|-------------------------|-------------------------|-------------|---|------------|-------------|
| Procainamide (PA) | 20 | 82.37 | 19.43 | 2.09 | 0.14 | 4.85 | 122.62 | 0.63 | 0.16 |
| | 40 | 86.40 | 52.23 | 0.71 | 0.06 | 11.21 | 852.96 | 0.59 | 0.05 |
| Lidocaine (LC) | 2 | 1.15 | 1.62 | 1.12 | 0.28 | 2.46 | 4.68 | 0.93 | 0.43 |
| | 4 | 4.22 | 1.02 | 0.71 | 0.05 | 12.97 | 20.96 | 2.34 | 0.19 |
| Propranolol (PN) | 0.2 | 0.29 | 0.09 | 1.56 | 0.03 | 22.03 | 2.81 | 1.96 | 0.07 |
| | 1.0 | 12.31 | 0.39 | 7.50 | 0.05 | 13.37 | 7.16 | 1.73 | 0.14 |
| Verapamil (VP) | 0.2 | 0.53 | 0.15 | 2.87 | 0.08 | 9.11 | 1.89 | 1.09 | 0.11 |
| | 0.6 | 4.34 | 0.31 | 3.67 | 0.05 | 15.37 | 6.66 | 1.40 | 0.09 |

Kinetic parameters: $C_p = A \cdot e^{-at} + B \cdot e^{-bt}$ (C_p : concentration of central compartment).

T1/2b: terminal phase half-life.

AUC: area under curve.

Vss: volume of distribution at steady-state.

Cl: total systemic plasma clearance.

Table 3. QT interval in unipolar precordial chest lead ECGs obtained from rats treated with lidocaine

| Dose | Time after injection | Limb lead II | Unipolar precordial chest lead positions | | | | | |
|---------------|----------------------|-------------------------|--|-------------------------|-------------------------|-----------|------------------------|-------------------------|
| | | | 1 | 2 | 3 | 4 | 5 | 6 |
| Pre-injection | | 71.8±4.18 | 80.4±8.9 | 83.0±4.5 | 76.4±7.6 | 75.2±4.1 | 74.6±5.3 | 84.8±3.1 |
| 2 mg/kg | 0.5 min | 80.6±6.8 | 80.4±7.9 | 82.4±3.6 | 90.2±4.3 ^{b)} | 84.0±5.2 | 75.2±6.6 | 99.6±3.2 |
| | 1 min | 76.8±4.7 ^{a)} | 80.0±7.0 | 83.6±5.5 | 81.6±7.8 | 79.0±5.2 | 77.0±4.5 | 93.4±1.3 |
| 4 mg/kg | 0.5 min | 85.0±4.4 ^{a)} | 89.8±8.6 ^{a)} | 97.2±4.5 ^{b)} | 92.4±4.0 | 89.2±7.1 | 80.0±5.6 | 108.0±2.2 ^{b)} |
| | 1 min | 83.4±6.5 ^{a)} | 80.8±7.5 | 98.3±3.0 | 92.6±3.0 ^{a)} | 84.0±6.8 | 81.0±7.1 | 105.0±4.8 ^{a)} |
| 8 mg/kg | 0.5 min | 103.0±6.9 ^{a)} | 112.0±10.2 ^{b)} | 113.0±6.7 ^{b)} | 116.0±2.5 | 90.0±11.3 | 94.5±5.1 ^{b)} | 123.0±3.7 ^{b)} |
| | 1 min | 95.3±7.7 ^{b)} | 108.0±8.2 | 120.0±8.6 ^{b)} | 123.0±3.7 ^{a)} | 100.0±8.4 | 98.0±10.4 | 123.0±6.6 ^{a)} |

Each value represents mean ± S.E. (msec).

1 to 6 Corresponding to chest lead positions in Fig. 1.

a), b) Significantly different from pre-injection values at $P < 0.05$ and $P < 0.01$.

Table 4. QT interval in unipolar precordial chest lead ECGs obtained from rats treated with propranolol

| Dose | Time after injection | Limb lead II | Unipolar precordial chest lead positions | | | | | |
|---------------|----------------------|------------------------|--|------------------------|----------|-----------|----------|------------------------|
| | | | 1 | 2 | 3 | 4 | 5 | 6 |
| Pre-injection | | 52.0±3.0 | 76.0±9.7 | 79.4±3.1 | 84.0±2.4 | 64.0±4.8 | 63.4±7.4 | 78.4±4.4 |
| 0.2 mg/kg | 0.5 min | 53.0±3.4 | 77.0±8.2 | 86.6±2.1 ^{a)} | 86.0±4.0 | 62.0±4.5 | 57.6±2.1 | 86.6±1.9 |
| | 1 min | 58.6±3.8 ^{a)} | 86.4±3.9 | 82.6±1.7 | 86.8±1.1 | 62.5±5.2 | 55.2±2.1 | 84.4±2.5 |
| 1 mg/kg | 0.5 min | 56.8±3.6 | 85.8±5.2 | 81.6±4.0 | 89.0±2.5 | 67.3±5.2 | 52.2±1.0 | 87.2±1.9 |
| | 1 min | 58.6±3.8 ^{a)} | 87.6±3.5 | 85.6±3.0 ^{a)} | 86.6±2.9 | 63.7±6.7 | 52.2±2.4 | 85.0±2.8 |
| 5 mg/kg | 0.5 min | 65.0±2.8 ^{a)} | 103.2±2.1 ^{b)} | 90.2±8.9 | 95.2±3.3 | 73.5±10.8 | 59.2±3.1 | 94.0±5.4 ^{a)} |
| | 1 min | 63.0±1.8 ^{a)} | 101.6±2.8 ^{a)} | 92.4±6.0 | 98.0±6.6 | 71.8±8.7 | 59.0±2.6 | 97.2±3.6 ^{b)} |

Each value represents mean ± S.E. (msec).

1 to 6 Corresponding to chest lead positions in Fig. 1.

a), b) Significantly different from pre-injection values at $P < 0.05$ and $P < 0.01$.

VP was longer than that in the low dose but the PN data were reverted. In mean AUC, there were dose-dependent increases in all the four drugs.

Unipolar precordial chest lead ECGs: In the LC group, a significant QT prolongation at least at the middle dose level (4 mg/kg) was noted at the point 1, 2, 3 and 6 as well as in bipolar limb lead II ($p < 0.05$) (Table 3). In the PN group, the QT prolongation at the point 1, 2 and 6, and its shortening at point 5 were observed (Table 4).

Myocardial action potentials: Figure 5 shows changes in 90% duration time (APD_{90}) and maximum upstroke velocity (\dot{V}_{max}) of myocardial action potential when exposed to solutions of LC and PN. In PN, APD_{90} and \dot{V}_{max} could not be recorded at $10^{-4}M$ because this concentration markedly inhibited the APs in response to electrical stimuli. There were no effects on APD_{90} in any concentration tested for LC and PN, even if compared the data of preexposure in 5 Hz stimulation rate with those of postexposure in 1 Hz

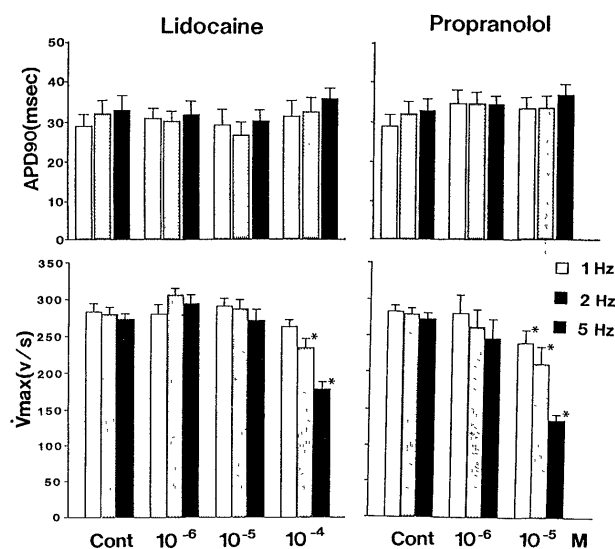


Fig. 5. Effects of lidocaine and propranolol on components of action potential in ventricular myocardium. APD_{90} : Time of duration in action potential measured at the level of 90% from peak. \dot{V}_{max} : maximum upstroke velocity. *: Significantly different from control ($P < 0.05$).

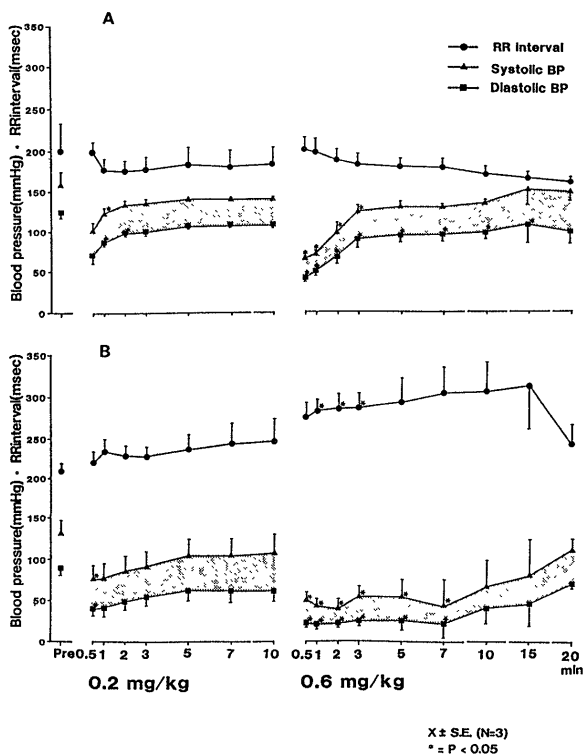


Fig. 6. Effects of verapamil on RR interval and blood pressure. A: Non-treatment with propranolol and atropine. B: Pretreated with propranolol (1 mg/kg, i.v.) and atropine (1 mg/kg, i.v.). *: Significantly different from pre-injection values ($P < 0.05$).

stimulation rate. 10^{-4} M LC caused a significant decrease in \dot{V}_{\max} in parallel with an increase in stimulation rate ($p < 0.05$). PN at concentration of 10^{-5} M caused a significant decrease in \dot{V}_{\max} in all stimulation rates ($p < 0.05$).

Effects of VP on blood pressure and RR interval after autonomic nervous blockades (ANB): Injections of 0.2 and 0.6 mg/kg of VP induced a significant prolongation of mean RR interval in ANB group ($p < 0.05$), while this interval shortened in the control group. BP in ANB group fell following the injection of VP and its recovery tended to delay compared with that in the control group (Fig. 6). One of 3 rats in ANB group died by injection with 0.6 mg/kg.

DISCUSSION

In general, PA, LC and PN inhibit fast inward current (sodium channel) of myocardial cells, and also LC and PN inhibit slow sodium inward current. PA elongates APD_{90} accompanied by decrease of

the V_{\max} , while LC and PN shorten APD_{90} accompanied by decrease of the slow sodium inward current. And PN delays the recovery time in phase 4. All these electrophysiological changes result in slowing the conduction velocity in the heart. VP inhibits slow inward current (calcium channel), which results in suppression of conduction time in SA and AV nodes and also cardiac contractility [4, 8, 18, 20, 21, 23–25].

In this study, all the four antiarrhythmic drugs induced arrhythmias such as AV and SA blocks, and the three drugs, except VP, induced a prolongation of QRS duration and changes in configuration of QRS complex. Moreover, these four drugs caused ECG abnormalities which were more frequent at middle and high dosage levels. These findings are consistent with clinical toxic evidences previously reported [4, 15].

The facts obtained were considered to be caused by pharmacological effects that these drugs delayed the conduction velocity [4, 19, 20, 24] and that VP did not affect the AP configuration of ventricular myocytes in the adult rat [29]. In some cases of human, it is said that PA causes paroxysmal tachycardia due to the excess prolongation of QT interval [18, 20]. However, in this study heart rate in rats was decreased consistently by any doses of this drug, though the QT interval prolonged. It was not clear whether such difference in generation of paroxysmal tachycardia was associated with some difference in extent of QT prolongation.

In Table 5, the qualitative changes in conduction times after injections of the four drugs were summarized and compared with those in dogs and humans from many references [4, 14, 15, 19, 21, 23], some differences were noted as follows; 1) A dose-dependent prolongation of QT interval by LC and PN treatments, and 2) a shortening of RR interval by injection with the low and middle doses (0.2 and 0.6 mg/kg) of VP.

Ventricular AP configuration and total epicardial activation time were reported as the main factors of ECG composition, especially for QT interval [22, 29]. Therefore, the investigation for the effects of LC and PN on myocardial AP was performed in this study. Substantially, there were no differences in APD_{90} between preexposure and postexposure of LC and PN, even if the data of preexposure in 5 Hz stimulation (high frequency) were compared with those of postexposure in 1 Hz stimulation (low frequency). This is not consistent with generally

Table 5. Changes in conduction time with the treatment of antiarrhythmic drugs

| Drugs | Class | Qualitative changes in conduction time | | | | | | | |
|-------------------|-------|--|----------|-----|----------|----|----------|----|----------|
| | | RR | interval | QRS | duration | PR | interval | QT | interval |
| Procainamide (PA) | Ia | ▲ | ◊ ◊ | ▲ | ◊ | ▲ | 0/◊ | ▲ | ◊ |
| Lidocaine (LC) | Ib | ▲ | 0/◊ | ▲ | 0 | 0 | 0 | ▲ | 0/◊ |
| Propranolol (PN) | II | ▲ | ◊ | ▲ | 0 | ▲ | 0/◊ | ▲ | ◊ |
| Verapamil (VP) | IV | ▼ | 0/◊ | 0 | 0 | ▲ | ◊ | ▲ | 0 |

Black arrows represent changes in the rat ECG.

White arrows represent changes in human and dog ECG (from Kanno *et al.*, 1987).

▲=Prolongation. 0=No change. ▼=Shortening.

Underlines show the results differed from those reported in humans and dogs.

accepted elongation of the APD_{90} in other species by the above-mentioned mechanism. The different results were considered to be due to the reason that in the rat the slow inward current became inactive and phase 2 shortened progressively with growth [11, 29]. On the other hand, there was a significant prolongation of QT interval on the right precordial positions in the unipolar precordial chest lead ECGs after the injections of LC and PN. These results suggest that the prolongation of QT interval by these two drugs was not due to the prolongation of AP duration but conceivably some delay of ventricular conduction time, especially on the right ventricle. The slowing of the phase 0 (decrease in V_{max}) by these drugs might participate with such a delay in ventricular conduction. The reason for localized QT prolongation could not be investigated in this study, although there is a possibility that the structural and/or functional difference of the bundle branch-purkinje fiber network is present between the right and left ventricles. At present it is said that the right and left distribution of such network in this species has not been established [22]. Furthermore, some reports have indicated that QT prolongation with a notched T wave was related to the desynchronized repolarization process occurring in certain portions of the heart ventricle [6, 7].

It has been reported that VP has a direct myocardial depressant action by inhibition of calcium influx, while it might produce a reflex increase in myocardial contractility and heart rate following a dose-dependent peripheral vasodilation [21]. Most of studies in dogs showed no increase in heart rate by VP treatment [9, 17, 21]. However, the present study showed a significant increase in heart rate which lasted for 2 min after the injection at the dose

of 0.6 mg/kg or less. Such change in heart rate was blocked by the PN pretreatment. These results suggest that the cause of increased heart rate (shortening of RR interval) in rats can be explained by the sympathetic nervous reflex responding to the peripheral vasodilation. The presence of some variation in such reflex effects on cardiac function by the sympathetic nerve has been known among animal species and anesthetic conditions [1, 3, 27], whereas the sympathetic nervous tone may be predominant in the rat [28]. Therefore, the difference in response to VP on heart rate between the rat and dog may be due to the species difference in depressing effects of anesthesia on the central nervous system associated with the sympathetic nervous reflex.

The plasma concentration levels of the four drugs were determined in the present study because of possible relation to the ECG changes, and found to be essentially similar to those in other species (i.e., dogs and humans), indicating bi-phasic decline curves [2, 5, 9, 12, 13, 16]. Therefore, the above-mentioned different results between rats and other species are not due to the difference in pharmacokinetics of the drugs used in this study, but probably to some characteristics on the function on structure of rat heart and the differences in baroreflex to these drugs.

This study elucidated the characteristics of ECG changes by antiarrhythmic drugs in the adult rat, and the results will provide a valuable standard to assess the effects of these drugs in the case of examination using this animal species.

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