Functional and Metabolic Effects of Propafenone in the Rat Heart-lung Preparation

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The effects of propafenone on cardiac function and myocardial metabolism were assessed in the isolated rat heart-lung preparation. Propafenone 0.3, 3 or 30 $\mu g \cdot ml^{-1}$ was administered 5 min after the start of perfusion. Heart rate decreased in the 30 $\mu g \cdot ml^{-1}$ group significantly following the drug administration. The highest dose of propafenone (30 $\mu g \cdot ml^{-1}$) reduced cardiac output significantly, and this dose was associated with a higher incidence of arrhythmias than the other groups. Although there were no significant differences in myocardial lactate and glycogen concentrations among groups, ATP content in the 30 $\mu g \cdot ml^{-1}$ group was significantly less than that in the control group. As therapeutic plasma concentration of propafenone is about 0.6 (range 0.06 to 1.0) $\mu g \cdot ml^{-1}$, 30 $\mu g \cdot ml^{-1}$ is 50 times greater than its concentration. These results suggest that the negative inotropic and chronotropic effects of propafenone are almost same with those of lidocaine which we have previously reported. (Key words: myocardial metabolism, propafenone, rat heart-lung preparation)

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Propafenone is an effective class I antiarrhythmic drug which controls ventricular dysrhythmias[1–4]. However, its side effects have been described by several studies[5–7], and Japanese Ministry of Health and Welfare has published that three patients were dead by the adverse effects of propafenone in 1990.

We have previously reported the functional and metabolic effects of lidocaine in the rat heart-lung preparation[8]. Lidocaine has the same class I antiarrhythmic property with propafenone. It is, therefore, of interest to evaluate the functional and metabolic effects of propafenone in the same preparation. This technique obviates confounding neurohumoral effects of *in vivo* studies.

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Methods

The techniques used were identical to those used in an earlier study[8]. Briefly, 32 male Wistar-Kyoto rats (290–320g) were anesthetized with 50 $mg \cdot kg^{-1}$ of pentobarbital intraperitoneally. A tracheostomy was performed, and intermittent positive pressure ventilation was instituted with air. The chest was opened and flooded with icecold saline and the heart arrested. Cannulae were inserted into the aorta and the superior and inferior venae cavae. The cannula in the superior vena cava was used for the monitor of right atrial pressure.

The heart lung preparation was perfused

with a solution containing red blood cells collected from another rat and Krebs Ringer bicarbonate buffer, with hematocrit of 25% and pH of 7.4. The concentrations (mM) of the buffer constituents were: NaCl 127, KCl 5.1, $CaCl_2$ 2.2, KH_2PO_4 1.3, $MgSO_4$ 2.6, $NaHCO_3$ 15 and heparin. The perfusate blood pumped from the aorta passed through a pneumatic resistance and was collected in a reservoir kept at 37°C and then returned to the inferior vena cava. In this model, no other organs except heart and lung were perfused, cardiac output was determined by the inflow, provided the heart did not fail, and systolic arterial pressure was regulated by the pneumatic resistance.

Heart rate was recorded with a bioelectric amplifier (Nihonkohden AB-621G) and cardiac output was measured with a electromagnetic blood flow meter (Nihonkohden MFV-1200). Arterial pressure and right atrial pressure were measured with transducers (TP101T and LPU-0.1A) and carrier amplifiers (Nihonkohden AP-621G).

All hearts were perfused initially with cardiac output of 30 ml·min^{-1} and systolic arterial pressure of 80 mmHg. Five min after the start of perfusion, propafenone 0.3 μg·ml^{-1}, 3 μg·ml^{-1}, or 30 μg·ml^{-1} was added to the reservoir except in the control group. During perfusion, atrioventricular (A-V) block was defined as asynchrony of atrial and ventricular electrical activity.

Thirty min after the start of the experiment, the hearts were freeze-clamped and freeze-dried for six days. An aliquot was extracted with perchloric acid and centrifuged at 3000 -g. Adenosine triphosphate (ATP) and lactate were determined spectrophotometrically by standard techniques[9]. Another piece of freeze-dried sample was placed in 30% KOH and digested at 100°C. Tissue glycogen was extracted, hydrolyzed and assayed as glucose equivalents[10]. The values were expressed as micromoles per gram of dry weight.

Statistical analysis used one way analysis of variance followed by the Dunnett test for comparing with the control values. The incidence of A-V block, ventricular rhythm or stand still was analyzed by chi-square test. A probability of $P < 0.05$ was regarded as statistically significant. The data are given as means ± SD.

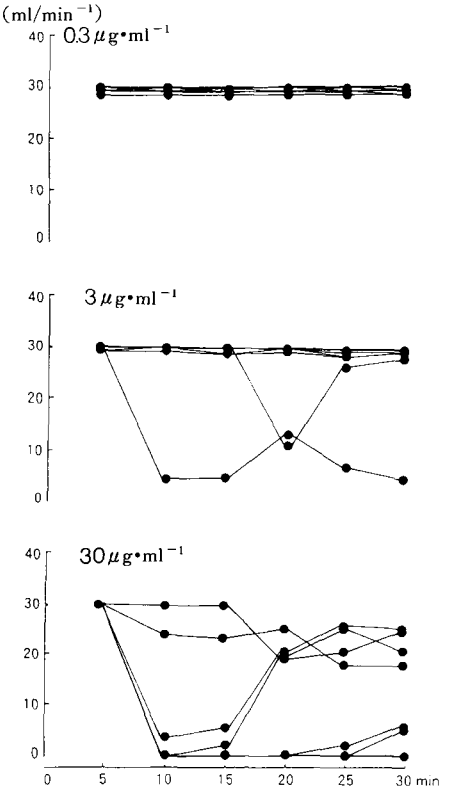

Fig. 1. Changes in cardiac output after administration of propafenone.

Results

Propafenone depressed cardiac function dose-dependently (fig. 1). The values of cardiac output in one of the 3 μg·ml^{-1} dose group and four of the 30 μg·ml^{-1} dose group were below 10 ml·min^{-1} at the end of the experiment. Two hearts in the highest dose group failed to recover (zero cardiac output) at that time. Although there was no significant difference in cardiac output between the 3 μg·ml^{-1} dose group and the control group, there was significant difference between the 30 μg·ml^{-1} dose group and the control group at the end of the experiment. Heart rate in the highest dose group decreased significantly following the drug administration (table 1).

Table 1. Changes in heart rate (beats·min^{-1})

	5	10	15	20	25	30 min
Control	304±17	311±22	295±21	293±15	287±16	277±27
0.3 μg·ml^{-1}	271±33	297±36	283±28	267±33	257±25	257±27
3 μg·ml^{-1}	278±23	256±48	259±31	244±41	246±59	249±59
30 μg·ml^{-1}	287±26	87±50*(n=3)	76±56*(n=4)	106±48*(n=4)	98±58*(n=5)	94±53*(n=6)

n=8; each group except as specified.
*$P < 0.05$ vs control.

Table 2. Incidence of A-V block, ventricular rhythm or stand still

	10	15	20	25	30 min
0.3 μg·ml^{-1}	0	0	0	0	0
3 μg·ml^{-1}	1	1	1	1	1
30 μg·ml^{-1}	7*	6*	5*	5*	5*

n = 8; each group.
*$P < 0.05$ vs other groups.

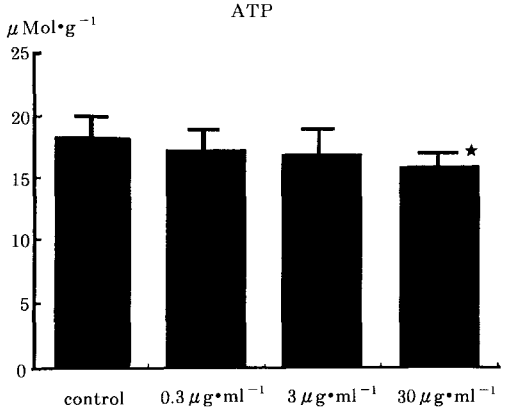

Fig. 2. Myocardial concentrations of ATP. *$P < 0.05$ versus control.

The incidence of A-V block, ventricular rhythm or arrest in the highest dose group was significantly greater than those in the other groups (table 2).

Although there were no significant differences in lactate and glycogen concentrations among all groups (range from 24.0 to 29.6 and 67.0 to 73.4 μMol·g^{-1}, respectively.), ATP contents in the highest dose group was significantly less than that in the control group (fig. 2).

Discussion

Propafenone is a class I antiarrhythmic drug which depresses the maximum rate of depolarization without changing resting membrane potential[11], and shortens or prolongs the action potential duration dose dependently[11–13]. This drug also has weak calcium channel blocking and β-blocking properties[11,12,14]. When comparing with lidocaine, propafenone has been reported to exert greater electrophysiologic and antiarrhythmic actions in the conscious dog with acute myocardial infarction[15]. Some investigators also have suggested the efficacy of propafenone in suppressing ventricular arrhythmias in clinical situations[1–4]. However, another investigators have reported that propafenone has a limited role in the treatment[15] or may aggravate electrically provoked ventricular tachycardia[7]. In addition, Nathan et al.[6] have described a patient who developed intractable ventricular tachycardia, which proved fatal, after receiving two doses of propafenone.

In this study, propafenone, 0.3 and 3 did not but 30 μg·ml^{-1} did decrease heart rate and cardiac output significantly. The marked depression of cardiac function may have caused the decrease of myocardial ATP content as a result. It has been shown that propafenone has negative inotropic actions in the experimental[11–13] and clinical settings[3,16]. However, the therapeutic plasma concentration of propafenone is about 0.6 (range 0.06 to 1.0) μg·ml^{-1}[1]. Therefore, 30 μg·ml^{-1} is 50 times greater than its concentration. This fact is consistent with the previous report that 50 times therapeutic concentration of lidocaine (100

$\mu g \cdot ml^{-1}$) reduced heart rate, cardiac output and myocardial ATP content in the same preparation[8]. These results suggest that the negative inotropic and chronotropic effects of propafenone are almost same with those of lidocaine in the isolated rat heart.

In conclusion, we cannot extrapolate the data from *in vitro* animal study to human clinical situation. However, we conclude that propafenone is relatively safe, though it should be used cautiously in patients with impaired cardiac function.

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