Experimental Studies

Improvement of Cardiac Performance by Pimobendan, a New Cardiotonic Drug, in the Experimental Failing Dog Heart

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SUMMARY

The cardiotonic effect of pimobendan was studied in 6 dog heart-lung preparations in which cardiac function had been severely depressed by pentobarbital. Pimobendan in doses of 1–10 mg improved cardiac function in a dose-dependent manner and at 10 mg improved it beyond the control. These doses of pimobendan, however, produced neither a significant increase in heart rate nor arrhythmias. The results indicate that the drug may be of use in the treatment of heart failure. (*Jpn Heart J* **34**: 213–219, 1993.)

Key Words:

Heart failure Positive inotropic drug Ca-sensitizer PDE inhibitor

PIMOBENDAN (UD-CG 115 BS) is one of the newer positive inotropic agents. The inotropic properties of this benzimidazole-pyridazinone derivative have been shown in isolated guinea pig papillary muscles.^{1),2)} Two mechanisms contribute to this inotropic activity: An inhibition of cAMP-phosphodiesterase (type III),³⁾ and an increase in the calcium sensitivity of cardiac myofibrils.^{4)–6)} Consequently, pimobendan exerts a vasodilatory as well as a positive inotropic effect. Many newer positive inotropic drugs have been developed, such as amrinone, milrinone, sulmazole, enoximone, piroximone, vesnarinone, and MCI-154, hopefully as substitutes for digitalis. Previously, we investigated the effects of such drugs on experimental heart failure produced by pentobarbital.^{7)–11)} Thus, it was of interest to see whether pimobendan is as efficacious at improving the experimental failing heart as other newer positive inotropic drugs.

MATERIALS AND METHODS

Six heart-lung preparations were obtained from mongrel dogs of either sex, weighing 10–14 kg and anesthetized with sodium pentobarbital (30 mg/kg i.v.) as described previously.^{7)–11)} The composition of the circuit of the extracorporeal

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circulation was also the same as in previous experiments.⁷⁻¹¹⁾ A blood reservoir, connected to the right atrium, was primed with about 530 ml blood obtained from other mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg i.v.) and given heparin calcium (500 U/kg i.v.). Before the extracorporeal (500 U/kg i.v.) circulation was initiated, heparin calcium was administered into the right atrium. By means of a heat exchanger, the temperature of blood in the blood reservoir was maintained at about 38.5°C. Aortic pressure, which was provided by a Starling pneumatic resistor, was maintained at 80 mmHg. Cardiac output (not including coronary arterial inflow) was measured with an electromagnetic flow meter (Nihon Kohden, MFV-2100), the flow probe (Nihon Kohden, FF-100T) of which was placed between the brachiocephalic cannula and the Starling resistor. Right atrial pressure was measured with a pressure transducer (Nihon Kohden, LPU-0.1) through a cannula inserted into the auricle of the right atrium. Left atrial pressure was measured with a pressure transducer (Gould, P23ID) through a cannula inserted into the auricle of the left atrium. Left ventricular pressure was measured with a micromanometer-tipped catheter (Mitsui Toatsu, MTS-047C) introduced into the left ventricle via the left subclavian artery. The maximum rate of rise of left ventricular pressure (LV dp/dt max) was obtained with an electronic differentiator (San-ei Instrument, 1323). Atrioventricular (AV) conduction time was measured with an AV interval counter (Data Graph, HT-31) triggered by bipolar electrograms obtained from the surface of the right atrium and from the surface of the right ventricle near the apex. Heart rate was measured with a cardiometer (San-ei Instrument, 1321) triggered by right atrial electrograms. All cardiac variables described above were recorded on rectilinear pen recorders (San-ei Instrument, Recti Horiz 8S).

After the variables described above had become steady, competence tests were carried out to determine cardiac function curves. In the competence tests, the level of blood in the reservoir, which had been adjusted to about 5 cm above the level of the tricuspid valve, was elevated twice in a stepwise manner by 5 cm for 30 sec in each step. After the reproducibility of the responses to competence tests had been confirmed, sodium pentobarbital (75–200 mg) was added to the reservoir to produce cardiac failure, in which cardiac output was decreased by about 50% of control values. Competence tests were also performed in the failing heart. Pimobendan (1–10 mg) was cumulatively administered into the reservoir and a competence test was carried out after each dose of pimobendan.

The drugs used were sodium pentobarbital (Tokyo Kasei, Tokyo) and pimobendan (Dr. Karl Thomae GmbH, Biberach). Pimobendan was dissolved in N-methyl-2-pyrrolidone together with tartaric acid in an amount equal to that of pimobendan to give a concentration of 10 mg/ml.

Values are expressed in terms of mean $\pm$ SE, unless otherwise noted. Statistical analysis was performed by analysis of variance and significant differences were isolated using Dunnett's test.¹²⁾

RESULTS

The basal values of cardiac variables of 6 heart-lung preparations used are presented in Table I. Before the administration of pentobarbital, left atrial pressure and cardiac output were 7.0 $\pm$ 0.6 mmHg and 382 $\pm$ 41 ml/min, respectively, under basal conditions. On elevation of the level of blood in the reservoir to 10 cm above the basal level, left atrial pressure and cardiac output rose to 9.9 $\pm$ 0.9 mmHg and 1320 $\pm$ 63 ml/min, respectively. After the administration of sodium pentobarbital (146 $\pm$ 51 mg, mean $\pm$ SD), left atrial pressure and cardiac output were 10.1 $\pm$ 1.0 mmHg and 187 $\pm$ 48 ml/min under basal conditions, and 24.5 $\pm$ 3.6 mmHg and 795 $\pm$ 43 ml/min when the level of blood in the reservoir was elevated by 10 cm, respectively. Consequently the cardiac function curve was shifted down and towards the right by pentobarbital.

Following the addition of pimobendan (1–10 mg), the cardiac function curve depressed by pentobarbital was shifted upwards and to the left in a dose-dependent manner (Fig. 1). At 3 mg of pimobendan, almost complete improvement of the depressed cardiac function was accomplished on the basis of the cardiac function curve.

Under basal conditions, right atrial pressure rose from 1.9 $\pm$ 0.1 cm H₂O in control to 3.2 $\pm$ 0.3 cm H₂O in heart failure. The elevated right atrial pressure was lowered with pimobendan (1–10 mg) in a dose-dependent manner.

The decrease in LV dP/dt max in the failing heart and its improvement with pimobendan are presented in Fig. 2.

Changes in heart rate and AV conduction time are shown in Fig. 2. Heart rate was 151 $\pm$ 7 beats/min in the control and decreased to 138 $\pm$ 5 beats/min in the failing heart.

Heart rate was increased with increasing doses of pimobendan. At 3 mg

Table I. Cardiac Variables for 6 Dog Heart-Lung Preparations Before (Control) and After Administration of Pentobarbital

	Cardiac output (ml/min)	Left atrial pressure (mmHg)	Right atrial pressure (cmH ₂ O)	LV dP/dt max (mmHg/sec)	Heart rate (beats/min)	AV conduction time (msec)
Control	382 $\pm$ 41	7.0 $\pm$ 0.6	1.9 $\pm$ 0.1	1216 $\pm$ 29	151 $\pm$ 7	112 $\pm$ 4
Pentobarbital 146 $\pm$ 51 (SD)mg	187 $\pm$ 48*	10.1 $\pm$ 1.0*	3.2 $\pm$ 0.3	953 $\pm$ 54*	138 $\pm$ 5	122 $\pm$ 3

Values are expressed in terms of mean $\pm$ SE values unless otherwise noted.

* P<0.05 against the respective control values.

Fig. 1. Cardiac function curves obtained by elevating the height of the venous blood reservoir. Data points are means $\pm$ SE of 6 preparations. Control ($\circ$), failure ($\bullet$). Pimobendan in cumulative doses: 1 ($\triangle$), 3 ($\blacktriangle$), 10mg ($\square$).

Fig. 2. Effects of pimobendan on LV dP/dt max (A), right atrial pressure (B), heart rate (C) and AV conduction time (D). Data points are means $\pm$ SE of 6 preparations. C=control; F=failure produced by pentobarbital. * $P < 0.05$.

pimobendan, heart rate recovered to the control level (Fig. 2). AV conduction time was prolonged from 112 ± 4 msec in the control to 122 ± 3 msec in the failing heart, which in turn was shortened by pimobendan (Fig. 2). No arrhythmias

were induced by pimobendan at any of the doses used.

DISCUSSION

From the results presented here, it is evident that pimobendan is effective in improving cardiac performance depressed by pentobarbital. Almost complete restoration of the cardiac performance of the failing heart, in which cardiac output had been reduced to about 50% of the control value, was attained with 3 mg pimobendan. At this dose, heart rate almost recovered to the control value, whereas LV dP/dt max increased by about 7%. At 10 mg pimobendan, LV dP/dt max increased by 66% of the control value, whereas heart rate increased by only 8 beats/min over the control value. Thus, the force-rate separation of pimobendan was marked. These results were deducible from the cardiovascular profile of pimobendan delineated in the isolated, blood-perfused dog heart preparations.¹³⁾ In the blood-perfused dog heart preparations, pimobendan showed a sizeable force-rate separation; pimobendan increased sinus-rate by about 19% at the dose that produced a 50% increase in the force of contraction of the ventricular myocardium. In the present heart-failure conditions, pimobendan showed a force-rate separation to a similar extent. The definite force-rate separation is considered to be essential for a positive inotropic drug that is used for heart failure. Additionally, pimobendan produced no arrhythmias. Pimobendan has been shown to be more potent than amrinone, a prototype positive inotropic drug; when compared at doses that restored the depressed cardiac function curve to the control in the dog heart-lung preparation, the cardiotonic potency of pimobendan appears to be more than 3 times that of amrinone.⁸⁾ Furthermore, amrinone failed to restore the depressed cardiac function curve to the control even with high doses,⁸⁾ whereas pimobendan improved the depressed cardiac function curve over the control with 10 mg.

In similar previous experiments, sulmazole⁹⁾ and MCI-154,¹¹⁾ cardiotonic agents having a Ca-sensitizing action, improved the depressed cardiac function curve compared to the control like pimobendan did, whereas the non-selective PDE inhibitor trapidil¹⁴⁾ failed to restore the depressed cardiac function curve, even at the high doses at which amrinone failed to do so.⁸⁾ Thus, in the failing heart, the Ca-sensitizing action of the drugs appears to contribute to their cardiotonic property to improve the depressed cardiac function curve compared to the control, although the cardiovascular profiles of pimobendan and the other PDE inhibitors without such action are similar in the normal heart. However, this is not actually so. The specific PDE III inhibitors enoximone or piroximone improved the depressed cardiac function curve compared to the control as did pimobendan, sulmazole⁹⁾ and MCI-154.¹¹⁾ The specific PDE III inhibitor

amrinone, however, did not exert such an effect.⁸⁾ Thus, it is impossible to explain the advantage of pimobendan on the basis of its characteristics as a Ca-sensitizer.

Even at the highest doses, pimobendan did not increase heart rate and did not accelerate AV conduction. Furthermore, pimobendan, unlike digitalis, produced no arrhythmias. These results indicate that pimobendan is a potentially useful drug for the treatment of congestive heart failure.

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