Cardiovascular Effects of Imipramine in Intact Dogs and Isolated Dog Atria

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SUMMARY

The effects of imipramine were investigated on the blood pressure and heart rate in the intact dog and on the atrial rate and contractile force in the isolated atrial muscle perfused with arterial blood of the donor dog. A continuous infusion of small doses of imipramine (30 μ g/Kg/min, i.v., 30 min) produced an increase in the blood pressure and heart rate of the donor dog and the positive chronotropic and inotropic effects in isolated atria. These responses were blocked by treatment with propranolol. When a large dose of imipramine (1 mg/Kg/min, i.v., 15 min) was administered to the donor dog, the blood pressure fell and the heart rate initially increased and then decreased (i.e., 15 min later it decreased approximately 20% under the control level), and in isolated atria the developed tension initially increased and 15 min later decreased but the atrial rate maintained over the control level. Examined doses of imipramine caused a potentiation of norepinephrine-induced action, and a large dose of imipramine significantly diminished norepinephrine-induced reflex bradycardia and/or frequently inverted to tachycardia. Moreover acetylcholine-induced reflex tachycardia was suppressed by imipramine treatment.

From these results, it is concluded that imipramine may cause a hypotension mainly due to peripheral vasodilation, and may induce a suppression of baroreceptive reflex mechanism.

Additional Indexing Words:

Imipramine Intact dog Isolated atrium Reflex mechanism

A tricyclic antidepressant, imipramine, is widely used clinically to treat depression. Cardiovascular complications such as palpitation, orthostatic hypotension, electrocardiographic disturbances, various dysrhythmias, and in rare instances, even heart failure and cardiac arrest have been well documented.¹⁾⁻⁴⁾ There are many reports concerned with the pathogenesis of these conditions. It has been reported that imipramine acts by blocking the re-uptake of norepinephrine into the nervous system.⁵⁾⁻⁷⁾ In addition, it is reported that imipramine has central and peripheral anticholinergic

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activity, which is manifested clinically as atropine-like side effects.⁸⁾ Sigg et al⁹⁾ reported that cardiovascular reflex function was impaired by a blockade of pressoreceptor mechanisms due to a local anesthetic effect of imipramine. Moreover, it has been described that imipramine has a cardiodepressive action. Thus, it is still not clear whether direct cardiac effect of imipramine participates in these side effects or not. In the present study, we made an attempt to investigate direct and indirect cardiac effects of imipramine simultaneously, using the isolated atrial preparation perfused with donor dog's blood.^{10),11)}

MATERIALS AND METHODS

Eighteen mongrel dogs, weighing 10–20 Kg, were anesthetized with sodium pentobarbital, 30 mg/Kg, i.v. After treatment with 2,000 units of sodium heparin i.v., the right atrium was excised and plunged into a cold Tyrode solution at 4–10°C. The sinus node artery was cannulated via the right coronary artery and perfused with blood conducted from the carotid artery of the donor dog by aid of a peristaltic pump (Harvard Apparatus, Model 1,210). The perfusion pressure was maintained at 100 mmHg. The flow rate was 4.5–5.0 ml/min. The atrium was suspended in a bath filled with blood at a constant temperature of 37°C. The upper part of the crista terminalis of the atrium was connected directly to the force displacement transducer (Grass FTO3B) by a silk thread. Bipolar platinum electrodes were placed into contact with the atrial epicardium. The atrial rate was measured with a cardiograph triggered by the signal from the atrial depolarization of an electrogram. The isometric tension was recorded on an ink-writing rectigraph (Sanei Sokki Instrument) through a carrier preamplifier (Nihon Kohden RP-3), RC circuit and a high gain amplifier (Nihon Kohden RPH-2).

The donor dogs, weighing 8–16 Kg, were also anesthetized with 30 mg/Kg of sodium pentobarbital i.v. and artificially ventilated with room air by use of a Harvard respirator. Sodium heparin, 600 units/Kg, was administered intravenously at the beginning of the perfusion and 200 units/Kg was added at 1-h intervals. The systemic blood pressure of the donor dog was measured from the cannulated left femoral artery with a pressure transducer (Nihon Kohden RP-2), and heart rate was measured with a cardiograph triggered by the R wave of the lead II. Details of the isolated, blood-perfused canine atrial preparations were described in previous papers.^{10),11)}

The drugs used in these experiments were imipramine hydrochloride (Ciba-Geigy), (±)-norepinephrine hydrochloride (Sankyo), acetylcholine chloride (Dai-ichi), and (±)-propranolol hydrochloride (Sumitomo Chemicals). The drug was usually administered into the jugular vein of the donor dog. A continuous infusion was performed by use of an infusion pump (Harvard Apparatus Model 901).

RESULTS

1. Effects of imipramine infused into the jugular vein of the donor dog

When imipramine was given into the jugular vein of the donor dog at a relatively small infusion rate of $30 \mu\text{g/Kg/min}$, the systemic blood pressure and heart rate of the donor dog immediately increased. In the isolated atrium perfused with donor's arterial blood, the developed tension and atrial rate were also increased gradually. Fig. 1 shows a typical experiment of imipramine, and the results are summarized in Fig. 2. In the donor dog, systemic blood pressure and heart rate increased immediately, but in the isolated atrium, increases in atrial rate and developed tension occurred approximately 2.5 min after the onset of infusion, since the time to pass through the circuit was about 2.5 min.

After the treatment with $100 \mu\text{g/Kg}$ of propranolol, an increase in the blood pressure and heart rate of the donor dog and the developed tension and atrial rate of the isolated atrium were significantly blocked.

When imipramine was infused at a relatively large dose of 1 mg/Kg/min for 15 min, in the donor dog, systemic blood pressure immediately decreased and heart rate initially increased and then decreased after 1 min. In the isolated atrium, developed tension and atrial rate initially increased and reached maximal values 2 or 3 min later and then gradually decreased but the atrial rate was not suppressed under control levels. After an infusion of imipramine was stopped, the systemic blood pressure of the donor dog began to recover to control level, but heart rate of the donor dog and

Fig. 1. Effect of a continuous infusion of imipramine into the jugular vein of the donor dog at a relatively small dose of $30 \mu\text{g/Kg/min}$ on the blood pressure and heart rate in the donor dog (A), and the developed tension and atrial rate in an isolated atrium (B). The isolated atrium was perfused with arterial blood led from the donor dog.

Fig. 2. Effects of a continuous infusion of imipramine at a rate of 30 µg/Kg/min on the blood pressure and heart rate in donor dogs (A), and the developed tension and atrial rate in isolated atria (B) in 5 experiments. Values are mean ± S.E.M. + $p < 0.05$; *** $p < 0.01$; by paired t -test.

the developed tension and atrial rate of the isolated atrium still continuously decreased, or only slightly increased as shown in Fig. 3.

2. Changes in effects of norepinephrine before and after an infusion of imipramine

When norepinephrine was injected into the jugular vein of the donor dog, the systemic blood pressure increased, and mostly heart rate reduced because of the baroreceptor reflex in the donor dog, and the rate and developed tension of the isolated atrium increased. During an infusion of small doses of imipramine at a rate of 30 µg/Kg/min, norepinephrine-induced responses of the donor dog and isolated atrium were usually potentiated, but the response of decreased heart rate of the donor dog was not usually changed. Fig. 4 shows summarized results of effects of norepinephrine at 3 different doses given into the jugular vein of donor dogs before and after the infusion of imipramine at the rate of 30 µg/Kg/min for 30 min.

When norepinephrine was injected into the jugular vein of the donor dog after an infusion of large doses of imipramine at a rate of 1 mg/Kg/min

Fig. 3. Effects of a continuous infusion of imipramine at the rate of 1 mg/Kg/min in 5 experiments. Values are mean±S.E.M.
+ $p < 0.05$; ++ $p < 0.02$ by paired t -test.

Fig. 4. Effects of a small dose of imipramine injected into the jugular veins of donor dogs at a rate of 30 µg/Kg/min for 30 min on actions of norepinephrine given i.v. (0.3-3 µg/Kg) to donor dogs in 5 experiments.
+ $p < 0.05$; ++ $p < 0.02$, by paired t -test.

for 15 min, the systemic blood pressure in the donor dog and the rate and developed tension in the isolated atrium were increased much more than those before imipramine treatment. However the decrease of heart rate of the donor dog disappeared and only a positive chronotropic response was produced after treatment with large dose of imipramine. Fig. 5 shows a typical effect of norepinephrine before and after an infusion of imipramine at the rate of 1 mg/Kg/min for 15 min, and the results are summarized in Fig. 6.

Fig. 5. Effect of a large dose of imipramine injected into the jugular vein of the donor dog at a rate of 1 mg/Kg/min for 15 min on actions of norepinephrine given i.v. (1 µg/Kg) to the donor dog.

Fig. 6. Effect of a large dose of imipramine injected into the jugular veins of donor dogs at a rate of 1 mg/Kg/min for 15 min on actions of norepinephrine given i.v. (1-3 µg/Kg) to donor dogs in 4 experiments. Values are mean ± S.E.M. + $p < 0.05$; ++ $p < 0.02$; +++ $p < 0.01$ by paired t -test.

3. *The changes in effects of acetylcholine before and after infusion of imipramine*

When acetylcholine was injected into the jugular vein of the donor dog, the systemic blood pressure of the donor dog fell and changes in heart rate were various and responses in the rate and developed tension of the isolated atrium were not observed since acetylcholine might be almost destroyed during passing through the circuit before reaching to the isolated atrium. A large dose of $10\text{ }\mu\text{g/Kg}$ of acetylcholine caused reflex tachycardia with marked hypotension. During an infusion of imipramine, the hypotensive responses of the donor dog to acetylcholine were not modified. However, acetylcholine-induced reflex tachycardia was suppressed, but not significantly. Fig. 7 shows the results of $10\text{ }\mu\text{g/Kg}$ of acetylcholine before and after the infusion of imipramine at an infusion rate of 1 mg/Kg/min for 15 min.

Fig. 7. Effect of a large dose of imipramine injected into the jugular veins of donor dogs at a rate of 1 mg/Kg/min for 15 min on actions of acetylcholine given i.v. ($10\text{ }\mu\text{g/Kg}$) to donor dogs in 5 experiments.

DISCUSSION

It has been reported that imipramine causes a hypotensive effect which might be due to a direct action on the myocardium resulting in a diminution of cardiac output.^{9),12),13)} However, in the present study, we demonstrated that a large dose of imipramine caused an immediate hypotension during augmenting cardiac function (heart rate and contractility), by use of the intact animal and isolated heart preparations. Therefore, it is assumed that the depressor response to imipramine is not due to its cardiac depression but mainly vasodilating action, and that it is partially due to its cardiac depressive action because direct negative chronotropic and inotropic effects

were also induced after a continuous infusion of a large dose of imipramine.

It is well known that imipramine has a potentiating property of norepinephrine-induced action by a blockade of re-uptake of norepinephrine into the sympathetic nerve terminals.⁵⁾ In the present study, the enhancement of norepinephrine-induced actions was consistently observed by the treatment with any examined dose of imipramine. However, norepinephrine-induced reflex bradycardia in the donor dog was significantly suppressed and frequently inverted to tachycardia by large doses of imipramine. It is reported that imipramine has an anticholinergic property.¹⁴⁾⁻¹⁶⁾ As shown in this study, imipramine never inhibited acetylcholine-induced hypotension which was completely blocked by atropine treatment. It is suggested that imipramine may depress vagal excitation reflexly induced by a hypertension, and may have no atropine-like property in examined doses. On the other hand, acetylcholine-induced reflex tachycardia was also attenuated by larger doses of imipramine treatment. Therefore, it seems that imipramine may suppress sympathetic excitation, too.

When larger doses of imipramine were administered to the donor dog, the heart rate of the donor dog initially increased and then decreased to significantly lower than the control level. At the same time, in the isolated atrium perfused with the same blood concentration of imipramine in the donor dog, the atrial rate maintained almost the control level after initial increases. It is considered that imipramine depresses a tonic sympathetic tone and bradycardia might appear in the in situ donor dog heart. Especially in pentobarbital-anesthetized dog, since sinus acceleration was usually induced as vagal tone was depressed, imipramine-induced bradycardia might be clearly observed as shown in Fig. 3.

On the other hand, in the atrial muscle, large doses of imipramine produced significant negative inotropic effect although atrial rate still maintained its control level. It is suggested that imipramine may produce more dominantly direct depressive action on myocardium than on pacemaker activity.

From previous studies and present experiments, it is concluded that imipramine caused a hypotension mainly due to peripheral vasodilation and cardiovascular responses to imipramine might be modified by (1) its suppressive action on neural reflex mechanisms, (2) its uptake blocking property, and (3) its direct cardiac depressant effects.

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