Cardiac Effects of Piretanide and Furosemide on Intact Anesthetized Dogs and on Isolated Atria

Shigetoshi CHIBA, M.D., Yasuyuki FURUKAWA, M.D.,
Kimiaki SAEGUSA, M.D., and Yasuhiro OGIWARA, M.D.

SUMMARY

The effects of piretanide and furosemide on systemic arterial blood pressure and heart rate were examined in the anesthetized dog and the effects on atrial rate and contractile force were assessed in isolated atrial muscle perfused with heparinized arterial blood from a donor dog. When piretanide was administered intravenously to intact dogs, the depressor and bradycardic responses were produced dose-dependently. There were no significant simultaneous chronotropic or inotropic changes in the isolated atrium. On the other hand, furosemide (1–3 mg/kg) did not induce significant changes in either systemic blood pressure or heart rate in the intact dog. The atrial rate and developed tension were also not affected in the isolated atrium. A potent beta-adrenoceptor blocking agent, propranolol (1 mg/kg i.v.), consistently produced a significant depressor response and a profound negative chronotropic effect in the intact dogs; significant negative chronotropic and inotropic effects were also observed in the isolated atrium. When large doses of piretanide and furosemide were injected intraarterially into the sinus node artery of the isolated atrium, atropine-insensitive negative chronotropic and inotropic effects were induced dose-dependently. The potency of the negative chronotropic effect of piretanide was slightly greater than that of furosemide, but the negative inotropic effect of piretanide was slightly smaller than that of furosemide. These data indicate that piretanide has a depressor effect without significant cardiac influences. However, a high dose of piretanide has negative chronotropic and inotropic effects. These effects were not observed with the doses of furosemide (1–3 mg/kg) employed in this study.

Additional Indexing Words:

Isolated dog atrium Cross-perfusion method Furosemide Piretanide

IN 1969, it was reported that furosemide decreased cardiac output and increased systemic vascular resistance in normovolemic subjects without cardiac or renal disease.¹⁾ In 1973, Dikshit et al²⁾ reported beneficial hemodynamic effects of furosemide in congestive heart failure after myocardial

From the Department of Pharmacology, Shinshu University School of Medicine, Matsumoto 390, Japan.

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infarction. Recently, it was reported that a new diuretic, piretanide Hoe 118, has the same action as furosemide at the loop of Henle³⁾ and on the compliance of peripheral veins.⁴⁾ Valette et al⁵⁾ reported that the hemodynamic effects of furosemide and piretanide were quite similar. However, it was difficult to investigate direct cardiac effects, since indirect cardiac factors may modify cardiac function in situ. Thus, we used isolated and cross-perfused atrial preparations^{6),7)} for analyzing both the direct and indirect cardiac effects of piretanide and furosemide.

METHODS

Fourteen mongrel dogs of either sex, weighing 8 to 18 kg, were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Immediately after intravenous administration of sodium heparin (500 units/kg), the right atrium was excised and plunged into cold physiological saline at approximately 4 to 10°C. The right atrium was isolated and cross-circulated with heparinized arterial blood from a donor dog according to the procedure described previously.^{6),7)} Briefly, the sinus node artery of the isolated atrium was cannulated at its origin in the right coronary artery. All arterial branches, except the sinus node artery, were carefully ligated. The excised right atrium was placed in a glass chamber and perfused with arterial blood from the carotid artery of the donor dog using a peristaltic pump (Harvard apparatus, model 1210). The perfusion pressure was kept constant at 100 mmHg. The perfusion rate at this pressure was approximately 3–8 ml/min and the time delay from the donor dog to the atrium was 2 to 4 min. The glass chamber was filled with the blood and maintained at a constant temperature of 37°C. Bipolar platinum electrodes were placed in contact with the atrial epicardium. The sinus rate was measured with a tachometer triggered by atrial electrograms, and isometric tension development was measured with a force displacement transducer (Grass FTO3B). The atrial muscle was maintained under a resting tension of 2 gm. The donor dogs were respired artificially with room air by using a respirator (Harvard apparatus, model 607). The systemic blood pressure and heart rate in the donor dog and the sinus rate and tension development in the isolated atrium from another dog were recorded simultaneously on a polygraph (Nihon Kohden). Drugs used were as follows: piretanide [4-phenoxy-3-(1-pyrrolidinyl)-5-sulfamoylbenzoic acid] (Hoechst A. G.), furosemide (Hoechst A. G.), dl-propranolol hydrochloride (Sumitomo Chemicals), acetylcholine chloride (Daiichi) and atropine sulfate (Takeda). The chemical structure of piretanide is shown in Fig. 1. Piretanide and furosemide were dissolved with

5 N NaOH (pH 9.8) and then dissolved in physiological saline.

The drug solution was either injected intravenously in a volume of 0.1–1 ml over a period of 10 sec into the jugular vein of the donor dog, or administered in a volume of 10 to 30 μ l over a period of 4 sec into the rubber tubing which conducted the blood to the arterial cannula of the isolated atrium preparation.

RESULTS

Effects of intravenous administration of piretanide to the donor dog which cross-circulated to the isolated atrium

When piretanide was intravenously administered to the donor dog, a depressor response was produced dose-dependently. However, the heart rate was not modified significantly over a dose range of 1–10 mg/kg. Neither chronotropic nor inotropic effects were observed in the isolated atrium. Fig. 2(A) shows a typical response to intravenous administration of piretanide to a donor dog.

When furosemide was given intravenously (1 and 3 mg/kg) to the donor dog, no significant response was observed on the systemic arterial blood pressure and heart rate. By contrast, an intravenous injection of 1 mg/kg

Piretanide

Fig. 1. Chemical structure of piretanide [4-phenoxy-3-(1-pyrrolidinyl)-5-sulfamoylbenzoic acid].

Fig. 2. Cardiovascular effects of piretanide (A) and propranolol (B) when administered into the jugular vein of a support dog.

Fig. 3. Effects of piretanide, furosemide and propranolol on mean arterial blood pressure (MABP) and heart rate (HR) of donor dogs ($n=5$), and on contractile force (CF) and atrial rate (AR) of isolated atria ($n=5$). Control MABP was 106 ± 4.6 mmHg (mean $\pm$ SEM) and control HR was 158 ± 13.0 beats/min in support dogs. The control atrial rate was 102 ± 5.6 beats/min and the control contractile force was 3.9 ± 0.6 gm in isolated atria ($n=5$).

of propranolol induced a marked depressor response with profound bradycardia in the donor dog and negative chronotropic and inotropic responses in the isolated atrium. Fig. 2(B) shows a record during intravenous administration of 1 mg/kg of propranolol to a donor dog. Data are summarized in Fig. 3.

Effects of intraarterial injection of piretanide into the sinus node artery of the isolated atrium

When piretanide was injected into the cannulated sinus node artery of the isolated atrium, slight dose-dependent negative chronotropic and inotropic effects were induced. The threshold dose for inducing significant responses was approximately 1 mg. The solvent induced a positive inotropic effect without changes in atrial rate. Furosemide also induced slight negative chronotropic and inotropic responses in isolated atria. Data are summarized in Fig. 4.

The piretanide-induced negative chronotropic and inotropic effects were not modified by atropine ($3-10 \mu\text{g}$) in doses which completely inhibited acetylcholine ($0.3 \mu\text{g}$)-induced negative chronotropic and inotropic effects in 2 experiments. Fig. 5 shows records of the effects of $3 \mu\text{g}$ of atropine on

Fig. 4. Inotropic and chronotropic effects of pirtanide, furosemide and solvent when given selectively into the cannulated sinus node artery of the isolated atrium ($n=5$).

Fig. 5. Effects of 3 μ g of atropine on responses to 0.3 μ g of acetylcholine (ACh) and 3 mg of pirtanide in an isolated dog atrium.

acetylcholine- and pirtanide-induced cardiac responses.

DISCUSSION

It has been reported that pirtanide is a potent 'loop' diuretic, with a principal site of action in the thick ascending limb of the loop of Henle.⁸⁾⁻¹⁰⁾ Furosemide has been found to increase venous capacitance¹¹⁾ and to relieve pulmonary edema.¹²⁾ The loop diuretics are effective for the treatment of edema of cardiac origin.^{1), 2), 8)} It is considered that successful diuretic therapy should serve to increase cardiac output by reducing systemic vascular resistance. However, the direct cardiac effects of these diuretics have not been adequately characterized.

In the present study, we used cross-circulated dog atrial preparations to observe simultaneously the direct and indirect cardiac effects of the test drug. We previously investigated the chronotropic and inotropic effects of several

Fig. 6. Dose-response curves for the chronotropic and inotropic responses to verapamil, propranolol, nicorandil, furosemide and piretanide. A continuous line indicates the maximum negative chronotropic and inotropic responses. These results were obtained from 4–10 experiments. Vertical lines represent SEM.

cardioactive substances in isolated and blood-perfused dog atrial preparations.^{13)–15)} Thus, we can compare the actions of other cardioactive substances with piretanide and furosemide (Fig. 6). It is clear that two potent loop diuretics, piretanide and furosemide, have no significant direct cardiac effects over a relatively large dose range. An extremely large dose of piretanide or furosemide has slight negative chronotropic and inotropic properties. The piretanide-induced negative chronotropic and inotropic effects were not mediated *via* cholinergic mechanisms, since they were not inhibited by atropine. These data indicate that therapeutic doses of piretanide have no direct cardiac action, but that extremely large doses of piretanide have a cardiac depressant property. Furthermore, they imply that beneficial cardiac effects of piretanide may be due to secondary effects of either its potent diuretic actions or other extra-cardiac factors, such as hypotension.

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