Chronotropic and Inotropic Effects of a New Angiotensin Converting Enzyme Inhibitor, MC-838 (altiopril calcium), on the Dog Heart

Shigetoshi CHIBA, M.D., Yasuyuki FURUKAWA, M.D.,
Kimiaki SAEGUSA, M.D., and Yasuhiro OHBA, B.S.

SUMMARY

The effects of calcium (–)-N-[(S)-3(N-cyclohexylcarbonyl-D-alanyl)-thio]-2-methylpropion]-L-prolinate (MC-838, altiopril calcium), an inhibitor of angiotensin converting enzyme, were investigated in 9 isolated atrial preparations and 7 intact anesthetized donor dogs. In 7 intact dogs, 1–10 mg/Kg of MC-838 caused a decrease in systemic blood pressure, but no significant influence on heart rate was observed. At the same time, in isolated atria perfused with donor's blood, significant increases in developed tension and slight increases in sinus rate were observed with 3 and 10 mg/Kg of MC-838. Intraarterial MC-838 at 10–300 μ g did not induce significant cardiac effects and MC-838 at 1–3 mg caused an increase in developed tension and a slight increase in sinus rate. The positive inotropic and chronotropic effects were not blocked by adequate doses of propranolol, which significantly blocked norepinephrine-induced positive chronotropic and inotropic effects. It is concluded that a large amount of MC-838 has slight cardiotonic properties which are not mediated via a beta-adrenergic mechanism.

Additional Indexing Words:

Isolated canine atria Chronotropism Inotropism Propranolol
Converting enzyme inhibitor

MC-838 (altiopril calcium), like captopril, is an active inhibitor of angiotensin converting enzyme.¹⁾ Previously, Chiba et al (1983)²⁾ reported that a large amount of captopril has direct cardiac depressant activity, in addition to releasing catecholamine by a tyramine-like action. Although the converting enzyme converts angiotensin I to angiotensin II and degrades bradykinin,³⁾ angiotensin and bradykinin have no direct cardiac effects on the canine myocardium at physiological concentrations.^{4),5)} Thus, captopril-induced cardiac actions may be not induced by either angiotensin or kinin systems. In the present experiments, we investigated the effects of MC-838

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

Received for publication September 17, 1987.

Accepted March 1, 1988.

on SA nodal pacemaker activity and contractility using the isolated and blood-perfused dog atrial and ventricular preparations developed by Chiba et al.^{6),7)}

METHODS

Eighteen mongrel dogs of either sex, weighing 10–18 Kg, were anesthetized with sodium pentobarbital (30 mg/Kg, i.v.). The right atrium was then perfused with blood from the carotid artery of a heparinized donor dog using a peristaltic pump. The perfusion pressure was kept constant at 100 mmHg because the SA nodal pacemaker activity is sensitive to changes in perfusion pressure.^{8),9)} The atrium, which was usually subjected to a tension of 2 g, was suspended in a bath filled with blood maintained at a constant temperature of 37°C. The atrial rate was measured with a tachometer which was triggered by the potential waves of atrial electrograms. Isometric tension development was measured with a force displacement transducer (Nihon Kohden, AP-620G) connected to the upper part of the crista terminalis with a silk suture. The details of the preparation are described in a previous paper.⁶⁾ MC-838 (altipril calcium) was administered intravenously to 7 donor dogs, and changes in the systemic blood pressure and heart rate in the intact anesthetized dogs, and atrial contractility and atrial rate in the isolated atrium, were measured simultaneously.

In 9 isolated atrial preparations, the MC-838 solution was given intra-arterially in a volume of 0.01–0.03 ml, and its chronotropic and inotropic effects were studied and analyzed pharmacologically. In 2 experiments, a part of the left ventricular muscle weighing approximately 20 g was excised and perfused with heparinized blood through the anterior descending branch of the left coronary artery, using the same perfusion system as for the isolated atrial preparation.¹⁰⁾ Ventricular muscle was electrically paced at 2.0 Hz, 5 volts, 1 msec width.

Drugs used in this study were calcium (–)-N-[(S)-3-(N-cyclohexylcarbonyl-D-alanyl)thio]-2-methylpropionyl]-L-prolinate (MC-838, altipril calcium, C₁₉H₂₉N₂O₅ 1/2 Ca; MW: 415.55; Chugai Pharmaceutical Co., Ltd.), epinephrine hydrochloride (Sankyo), norepinephrine hydrochloride (Sankyo), propranolol hydrochloride (Sumitomo Chemicals), papaverine hydrochloride (Iwaki Seiyaku), calcium chloride and aminophylline (Eisai).

Data were analyzed by a paired *t*-test.

RESULTS

Cardiovascular effects of MC-838 administered i.v. to the donor dog:

When MC-838 was administered intravenously to the donor dog, a hypotensive effect was induced in a dose-related manner. At 10–300 $\mu\text{g}/\text{Kg}$, a slight but not significant depressor effect was induced. Figure 1 shows an example of the effects of increasing doses of 1 to 10 mg/Kg of MC-838. In this case, intravenous MC-838 caused a dose-dependent decrease in the systemic blood pressure and a slight increase in heart rate. However, the isolated atrial muscle was not influenced significantly. Figure 2 shows another example, indicating slight increases in atrial rate and the developed tension of the isolated atrium. At a dose of 1 mg/Kg , the systemic blood pressure usually decreased significantly and the heart rate was increased slightly, but no significant influence was observed in isolated atria. At 3 or 10 mg/Kg , MC-838 caused a profound decrease in the systemic blood pressure, but no influence on heart rate was observed. In isolated atria, an increase in developed tension was usually observed, but an increase in atrial rate was not significant in the majority of cases. Figure 3 shows the effects of small doses

Fig. 1 (left). Effects of MC-838 on the systemic blood pressure (SBP) and heart rate (HR) of a donor dog, and on the atrial rate (AR) and developed tension (DT) of an isolated atrium perfused with the donor's arterial blood.

Fig. 2 (right). Effects of MC-838 on the SBP and HR of a donor dog, and on the AR and DT of an isolated atrium.

Fig. 3. Comparisons of effects of epinephrine and MC-838 on the SBP and HR of donor dogs, and the AR and DT of isolated atria. Each point represents the mean value. Vertical bars represent the standard errors of the mean, and the numbers indicate the number of observations.

of epinephrine and 1 to 10 mg/Kg of MC-838. Epinephrine caused slight changes in systemic blood pressure and heart rate in the donor dogs, and strong increases in atrial rate and developed tension in isolated atria. On the other hand, MC-838 usually caused a marked hypotension in donor dogs, and a positive inotropic effect in isolated atria.

Chronotropic and inotropic effects of MC-838 on isolated atria:

When MC-838 was injected intraarterially into the cannulated sinus node artery of the isolated atrium, positive inotropic effects were observed in relatively large doses, but positive chronotropic effects were not usually induced. The threshold dose for inducing positive inotropic effects was approximately 100 µg. At 1 mg, MC-838 frequently caused a marked increase in developed tension, but only a slight increase in atrial rate. At higher doses of more than 300 µg, calcium chloride caused a marked increase in contractile force in the same perfusion system. However, the dose of calcium contained in 1 mg of MC-838 did not induce any inotropic effect. As previously reported, norepinephrine, papaverine and aminophylline usually caused positive chronotropic and inotropic effects in a dose-related manner^(11,12) (Fig. 4). However, MC-838 had the lowest potency of these agents; an increase in atrial rate was

Fig. 4. Dose-response curves to percent changes in the sinus rate and developed tension after administration of norepinephrine (NE), MC-838, papaverine and aminophylline via the cannulated sinus node artery of isolated atria.

Fig. 5. Absence of blocking effects of propranolol on MC-838-induced positive chrono- and inotropic effects in an isolated canine atrium.

not clear even at large doses.

Effect of propranolol on MC-838-induced cardiac actions:

When norepinephrine was given into the cannulated sinus node artery of the isolated atrium, positive inotropic and chronotropic effects were induced

Fig. 6. Effects of propranolol on MC-838- and norepinephrine-induced increase in the sinus rate and developed tension of isolated atria. Vertical bars represent the standard errors of the means.

in a dose-related manner. These norepinephrine-induced effects were inhibited by pretreatment with propranolol. On the other hand, the MC-838-induced positive inotropic effect was not inhibited by propranolol. Figure 5 shows that increases in atrial rate and developed tension of 1 and 3 mg of MC-838 are not blocked by 10 μ g of propranolol. As shown in Fig. 6, norepinephrine-induced positive chronotropic and inotropic effects were significantly suppressed by propranolol, but MC-838-induced positive effects were not modified.

Effect of MC-838 on isolated and blood-perfused left ventricular muscle:

In 2 ventricular muscle preparations, an intraarterial injection of MC-838 was performed in a dose range of 100 μ g to 3 mg. At 100 and 300 μ g, MC-838 had no significant change in the developed tension. At 1 mg, MC-838 caused an increase of 20% in the developed tension; a 3 mg dose produced a 35% increase.

DISCUSSION

In the present study, it was demonstrated that only high doses of MC-838 have positive inotropic effects in both atrial and ventricular muscle.

Although MC-838 contains Ca^{++} ions, the same doses of Ca^{++} did not induce any significant inotropic effect. MC-838 did not produce a significant increase in atrial rate. The positive inotropic response to MC-838 was not inhibited by propranolol at doses which significantly suppressed the norepinephrine-induced increase in developed tension. Thus, the MC-838-induced cardiac stimulating effect may not be mediated via beta-adrenergic mechanisms. However, the mechanism producing this positive inotropic action of MC-838 is not clear. There is no experimental evidence that MC-838 either inhibits phosphodiesterase or has a cardiac glycoside-like action.

Recently, it was demonstrated that one active converting enzyme inhibitor, captopril, caused positive chronotropic and inotropic responses in extremely high doses.²⁾ These responses were completely blocked by propranolol treatment. Therefore, it was postulated that a large amount of captopril causes a release of catecholamine from sympathetic nerve terminals, and has direct cardiac depressant properties. Although both MC-838 and captopril have strong hypotensive properties, their actions on myocardium and on adrenergic nerve fibers appear to be different.

The cardiac actions of MC-838 may not be useful clinically because they are only produced by large doses. However, MC-838 has no adverse actions on the heart. It has been well recognized that catecholamines may cause deterioration of the condition of cardiac patients by increasing the oxygen consumption of cardiac muscle. Since catecholamine load is not good for cardiac disease patients, especially for ischemic heart disease patients, MC-838 may be useful therapy for hypertensive patients with cardiac disease. Moreover, a large dose of MC-838 may bring about an improvement in cardiac function in patients with beta-adrenoceptor blockade.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Kazushige Sakai, Chugai Pharmaceutical Co., for the generous gift of MC-838 (altipril calcium).

REFERENCES

1. Sakai K, Aono J, Shiraki Y, Hinohara Y, Akamatsu A, Tanaka S, Kuromatsu K: MC-838 (altipril calcium): A novel orally active angiotensin converting enzyme inhibitor. *Tohoku J Exp Med* **152**: 363, 1987
2. Chiba S, Watanabe H, Kobayashi M: Chronotropic and inotropic effects of captopril on the dog heart. *Jpn Heart J* **24**: 269, 1983
3. Douglas WW: Polypeptides—angiotensin, plasma kinins, and others. *in* The Pharmacological Basis of Therapeutics, 6th Ed, ed by Gilman AG, Goodman LS, Gilman A, McMillan, p 647, 1975

4. Kobayashi M, Furukawa Y, Chiba S: Positive chronotropic and inotropic effects of angiotensin II in the dog heart. *Eur J Pharmacol* **50**: 17, 1978
5. Kobayashi M, Furukawa Y, Chiba S: Chronotropic and inotropic effects of bradykinin on isolated, blood-perfused canine atrium. *Jpn Heart J* **21**: 121, 1980
6. Chiba S, Kimura T, Hashimoto K: Muscarinic suppression of the nicotinic action of acetylcholine on the isolated, blood-perfused atrium of the dog. *Naunyn-Schmiedeb Arch Pharmacol* **289**: 315, 1975
7. Chiba S, Yabuuchi Y, Hashimoto K: Comparison of the effects of norepinephrine and acetylcholine between intraarterial and extravascular administration to the isolated, blood-perfused canine atrium. *Jpn J Pharmacol* **25**: 433, 1975
8. Hashimoto K, Tanaka S, Hirata M, Chiba S: Responses of the sino-atrial node to change in pressure in the sinus node artery. *Circ Res* **21**: 297, 1967
9. Chiba S: Pharmacologic analysis of stretch-induced sinus acceleration of the isolated dog atrium. *Jpn Heart J* **18**: 398, 1977
10. Chiba S: Effect of pentobarbital, verapamil and manganese on the frequency-force relationship of the isolated atrium and ventricle of the dog heart. *Eur J Pharmacol* **40**: 225, 1976
11. Chiba S, Imai Y: Pharmacological analysis of papaverine-induced positive chronotropic and inotropic effect. *Eur J Pharmacol* **35**: 169, 1976
12. Watanabe H, Furukawa Y, Chiba S: Cardiovascular effects of aminophylline and pentoxifylline on intact dogs and isolated dog atria. *Jpn Heart J* **23**: 235, 1982