Inotropic and Chronotropic Activity of a New Cardiotonic Agent, DM 9278 (1,2,3,4,8,9,10,12-octahydropyrido[2,1-b]pyrido[2,3-f]quinazolin-9-one), on Isolated Dog Atrial and Ventricular Muscles

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SUMMARY

The cardiac effects of DM9278 were studied in isolated and blood-perfused atrial and ventricular preparations from mongrel dogs. In spontaneously beating isolated right atria, DM9278 caused positive chronotropic and inotropic responses in a dose-related manner (1—100 μg). DM9278 produced relatively larger positive inotropic than positive chronotropic effects as compared with effects of aminophylline or papaverine. DM9278 increased the developed tension in left ventricles electrically driven at 1.5—2.0 Hz. Positive inotropic and chronotropic responses to DM9278 in both atrial and ventricular preparations were suppressed slightly but not significantly by 1—3 μg of propranolol, which completely blocked the positive chronotropic and inotropic effects of norepinephrine (0.01—0.1 μg). From these results, it is concluded that DM9278 has direct cardiotonic properties in isolated dog heart tissues, showing relatively selective positive inotropic activity.

Additional Indexing Words: Isolated dog atria Isolated dog ventricle Sinus rate Contractility Propranolol

ALTHOUGH digitalis is a potent cardiotonic agent, its toxicity is widely recognized. Recently, several new cardiotonics such as amrinone, phosphodiesterase inhibitors and sympathomimetics have been synthesized and investigated in several laboratories.1-6) DM9278 is a newly synthesized imidazoquinazoline derivative,7) which inhibits phosphodiesterase like other agents (e.g. aminophylline) that possess positive inotropic activity. The present study investigated the effects of DM9278 on pacemaker activity and con-
tractility in isolated and blood-perfused canine atrial and ventricular preparations.8,9)

**METHODS**

Fifteen mongrel dogs of either sex, weighing 10—16 Kg were anesthetized with sodium pentobarbital (30 mg/Kg i.v.). After i.v. administration of sodium heparin (500 units/Kg), the right atrium was quickly excised and plunged into cold saline at 4—10°C. The sinus node artery was cannulated via the right coronary artery of the isolated right atrium and perfused with fresh arterial blood conducted from the carotid artery of the donor dog by aid of a peristaltic pump (Harvard Apparatus, model 1210). The perfusion pressure was constantly maintained at 100 mmHg by use of a pneumatic resistance in parallel with the perfusion circuit. The flow rate was 2—5 ml/min. The atrium was suspended in the bath filled with blood at a constant temperature of 37°C. The atrial rate was measured with a tachometer, which was triggered by atrial electrograms. The isometric developed tension was measured with a force displacement transducer (Grass FTO3B).

The donor dogs, weighing 12—18 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, 500 units/Kg, was administered intravenously at the beginning of the perfusion and 200 units/Kg were added at 1-h intervals.

The effects of DM9278 were investigated in 5 isolated ventricular preparations. The left ventricle was quickly excised and immersed in saline at 4—10°C. The muscle was perfused through the cannulated anterior de-

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**Fig. 1. Chemical structure of DM9278 (1,2,3,4,8,9,10,12-octahydro[2,1-b]pyrido[2,3-f]quinazolin-9-one).**
scending branch of the left coronary artery. The blood was led from the carotid artery of the donor dog as in the atrial preparation. The ventricular muscle was electrically driven with rectangular pulses using an electronic stimulator (Nihon Kohden, MSE-3). The stimulus strength was about twice the threshold voltage (5 msec duration and 1—5 volts). Details of the preparations have been described in previous papers.8),9)

The drugs used in these experiments were DM9278 (1,2,3,4,8,9,10,12-octahydro[2,1-b]pyrido[2,3-f]quinazolin-9-one) (synthesized by Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan, Fig. 1), dl-norepinephrine hydrochloride (Sankyo), dl-propranolol hydrochloride (Sumitomo Chemicals), papaverine hydrochloride (Iwaki Seiyaku) and aminophylline (Eisai). Each drug was administered into the sinus node artery of the isolated atrium or into the anterior descending branch of the left coronary artery of the isolated left ventricle over a period of 4 s.

**Results**

*Effects of DM9278 on isolated and blood-perfused canine atria*

When DM9278 was administered into the cannulated sinus node artery of the isolated atrium, positive inotropic and chronotropic responses were induced in a dose-related manner. A representative record of effects of increasing doses of DM9278 is shown in Fig. 2. Norepinephrine usually induced both positive chronotropic and inotropic effects. Two phosphodiesterase inhibitors, papaverine and aminophylline, also induced dose-dependent positive

![Fig. 2. Chronotropic and inotropic responses to increasing doses of DM9278 injected into the sinus node artery of an isolated and blood-perfused canine atrium. AR=atrial rate.](image-url)
chronotropic and inotropic responses, as reported previously.\textsuperscript{10,11}) Summarized data are shown in Fig. 3. The order of potency for chronotropism was norepinephrine $>$ DM9278 $>$ papaverine $>$ aminophylline, and the order for inotropism was norepinephrine $>$ DM9278 $>$ papaverine $>$ aminophylline.

\textit{Effects of DM9278 on isolated left ventricular preparations}

When DM9278 was injected into the anterior descending branch of the left coronary artery of isolated and paced left ventricular muscle, an increase
Positive inotropic effects of norepinephrine and DM9278 injected into the anterior descending branch of the left coronary artery of left ventricular muscle. Points represent mean values and vertical bars represent standard errors. Numbers represent the number of observations. Control developed tension was 5.5 ± 0.7 Gm (mean ± SE) in 5 preparations. The muscle was paced at 1.5—2 Hz, 1—5 msec duration and 2—5 volts.

Effects of propranolol on positive chronotropic and inotropic responses to DM9278 and norepinephrine

When propranolol was injected intraarterially, norepinephrine-induced chronotropic and inotropic effects were consistently inhibited. As shown in Fig. 6, positive chronotropic and inotropic effects of 0.01 μg of norepinephrine were significantly inhibited by 1 or 3 μg of propranolol. On the other hand, these doses of propranolol never significantly inhibited positive chronotropic and inotropic responses to 30 μg of DM9278, although DM9278-induced responses were slightly suppressed by propranolol treatment. Even in the ventricular preparation, effects of 30—100 μg of DM9278 were not inhibited by 3 μg of propranolol in 2 preparations (data not shown).
DISCUSSION

In this study, it has been demonstrated that a newly synthesized agent, DM9278, has a mild and relatively selective positive inotropic activity. It is well known that phosphodiesterase inhibitors have mild cardiac stimulant properties. Previously, we reported that aminophylline has positive chronotropic and inotropic effects in isolated and blood-perfused canine atrial preparations. In that report, it was shown that aminophylline-induced cardiac stimulation was more potent than pentoxifylline-induced stimulation. We also reported that a potent phosphodiesterase inhibitor, papaverine, induced relatively greater positive chronotropic and inotropic effects in the same preparations. In the case of papaverine, a large dose frequently induced initial negative chronotropic and inotropic responses, indicating that large doses of papaverine may have an inhibitory effect on entry of Ca++ ions into the cell.

As a cyclic AMP phosphodiesterase inhibitor, the potency of DM9278 is 14 to 56 times greater than that of papaverine (unpublished data). Papaverine is about 11 times as potent as theophylline. More recently, Yamagishi et al reported that the ranking order of inhibitory potencies of DM9278, nicardipine, papaverine, HWA285 and aminophylline for phosphodiesterase

Fig. 6. Effects of propranolol on DM9278 and norepinephrine (NE)-induced chronotropic and inotropic actions in 4 isolated dog atria. Control developed tension was 2.2 ± 0.3 Gm (mean ± SE) in 4 isolated atria.
is almost the same as the order of their pancreatic exocrine secretory potencies in the isolated and blood-perfused canine pancreas. They believe that cyclic AMP is an important intracellular mediator of fluid secretion in the pancreas. In this study, the order of potencies of examined compounds for cardiac pacemaker activity and contractility is almost the same as the order of inhibitory potencies for phosphodiesterases.

Inhibition of phosphodiesterases causes an increase in intracellular cyclic AMP which, in turn, increases pacemaker activity and contractile force in the heart. In isolated canine atrial preparations, it was demonstrated that dibutyryl cyclic AMP produces positive chronotropic and inotropic effects in a dose-related manner. On the other hand, glucagon, which causes an increase in cyclic AMP via activation of adenylate cyclase, induced a predominant positive chronotropic effect. A relatively small dose of glucagon induced only an increase in sinus rate, unaccompanied by an increase in developed tension. Thus, both an intracellular increase in cyclic AMP and another factor may be necessary to produce an increase in cardiac contractile force. In contrast with glucagon, DM9278 induced a relatively dominant inotropic effect. Thus, in addition to phosphodiesterase inhibition, DM9278 may exert some action on the cardiac contractile process.

References

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