CARDIAC ACTION OF DIMORPHOLAMINE

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Since the introduction of dimorpholamine (N,N'-dibutyl-N,N'-dicarboxymorpholine-ethylenediamine, 1064 Th) as a potent analeptic agent, not a few papers have appeared concerning its stimulating action on respiration and blood pressure. However, to the authors' knowledge, only two works have ever been published with respect to its action on the isolated heart. Using the isolated frog's heart, Fukushima (1) observed a positive inotropic action with 0.75 mg/ml of this compound, although the action was very weak and evanescent. According to his study, an isolated preparation of the dog's heart (Starling's heart-lung preparation) responded to this compound in a similar manner, whereas only a slight negative inotropic action could be induced in the isolated perfused rabbit heart. Kanda *et al.* (2) studied the action of dimorpholamine on the isolated frog heart. They used a higher dosage range of 0.15 to 0.3 mg/ml and found a definite positive inotropic action; still higher doses produced more marked positive inotropic action, followed after a lapse of time by a disturbance of heart rhythm.

As an exact knowledge of the cardiac action of an analeptic is important in evaluating usefulness of that compound in clinical medicine, the authors felt the necessity to reinvestigate the cardiac action of dimorpholamine in more detail. In the course of the study, a marked positive inotropic action was observed both in the isolated frog's heart (which was essentially the same as reported by Kanda *et al.*) and in the heart-lung preparation of the dog. Even in the isolated perfused rabbit heart, the authors could produce a positive inotropic action under certain conditions, which the authors at present are not able to specify (see Fig. 6). This report pertains to the detailed description of the action of this potent analeptic agent on the heart-lung preparation of the dog, with special reference to the possible role played by the adrenergic mechanism in the observed positive inotropic action.

METHODS

Twenty-two heart-lung preparations (HLP) were carried out according to the Kraye-Mendez modifications of the original Starling method, the details of which were described

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elsewhere before (3). To determine the oxygen consumption of the myocardium, samples of the arterial and venous blood were taken in some experiments and their oxygen contents were measured by the manometric method of Van Slyke and Neill (4). The oxygen consumption of the cardiac muscle was calculated, multiplying the arterio-venous oxygen difference by the corresponding coronary flow, measured continuously with a magnetic flow-meter.

Drugs used were: Dimorpholamine (Théraptique, Eizai; Atmurin, Tanabe), pentobarbital sodium (Mintal, Tanabe), atropine sulphate, reserpine (Serpasil, CIBA; Apoplon, Dai-ichi), adrenaline hydrochloride (Sankyo), tyramine hydrochloride (Tokyo Kasei) and nethalide. The last compound was synthesized at the Department of Chemical Pharma-

cology, Faculty of Pharmaceutical Sciences, University of Tokyo.

RESULTS

1) Cardiac action of dimorpholamine

Figs. 1 and 2 represent a typical experiment showing the effects of dimorpholamine on the dog HLP. After the control measurements were made, 70 mg of sodium pentobarbital was added to the venous reservoir to induce the impairment of heart contractility. After a new steady state was reached, 9 mg of dimorpholamine was injected into the rubber tubing leading to the venous cannula, which resulted in a marked positive inotropic action, as is reflected in a fall of right atrial pressure and an increase in systemic output. Concomitant with this action, there was an increase in the coronary sinus outflow associated with an increase in the oxygen consumption of the myocardium. Throughout this course, the heart rate remained unchanged, retaining its regular sinus rhythm. Usually the effect became manifest with 3 to 4 mg or more of this compound, and was correspondingly greater with larger of doses. Even in a dose of as high as 45

FIG. 1. Cardiotonic action of dimorpholamine. Dog, male, 10 kg (exp. 11'). From top to bottom: arterial pressure (AP), right atrial pressure (RAP), systemic output in ml/min—total output of left ventricle minus coronary flow—measured with a Weese stromuhr, and time in one-minute intervals. Other abbreviations used are: PB = sodium pentobarbital, DMA = dimorpholamine, HR = heart rate per minute, Cor. flow = coronary sinus outflow in ml/min. Total blood volume at the beginning was approximately 1300 ml.

mg, no untoward action was observed; there was no sign of the disturbances the heart rhythm, as reported by Kanda *et al.* in the isolated heart of the frog. In Table 1 are summarized the numerical data on the effects of 9 mg of dimorpholamine on the

FIG. 2. Time course of dimorpholamine action.

The same experiment as in Fig. 1. SOP=systemic output in ml/min, CF=coronary sinus outflow in ml/min, HR=heart rate per minute, DMA=dimorpholamine.

TABLE 1. Effect of dimorpholamine (9 mg) on the heart-lung preparations of the dog.

	Number of experiments	Control	After dimorpholamine
Systemic output ml/min	9	222±24.4	302±25.2*
Heart rate beats/min	10	101± 3.7	101± 3.6
Coronary sinus outflow ml/min/100 g	3	81	88
O ₂ consumption ml/min/100 g	3	1.66	2.49

Mean (±S.E.)

* $P < 0.05$

various aspects of the cardiac function.

As is shown in Fig. 3, there was a tendency towards tachyphylaxis in the positive inotropic action of dimorpholamine. Repeated administration of the agent at relatively short intervals resulted in a gradual diminution of the positive inotropic response and finally there was no inotropic response obtainable.

2) Effect of reserpinization

To reserpinize the animal, 0.1 to 0.3 mg/kg of the alkaloid was given intraperitoneally 24 hours before the experiments according to the method of Waud, Kottogoda and Krayer (5). When the preparation of the reserpinized animal was completed and heart failure was induced, 2 to 4 mg of tyramine was administered to the rubber-tubing just above the venous cannula. If no response was observed, the preparation was regarded as fully reserpinized. Tyramine in the HLP made from the non-reserpinized animal usually produced a marked positive inotropic and chronotropic action in a dose of 50 to 100 µg. The reserpinization of the donor dog was not conducted.

FIG. 3. An example of development of tachyphylaxis to dimorpholamine.
Dog, male, 12 kg (exp. 18).
Symbols are the same as in Fig. 1.

As is illustrated in Fig. 4, the response of the reserpinized heart to the positive inotropic doses of dimorpholamine was essentially the same as in the non-reserpinized heart, while the effect of tyramine was completely lost in the former.

3) Effect of adrenergic β -blocking agents

The tendency towards tachyphylaxis observed in the inotropic action of dimorpholamine made it a little difficult to evaluate the effectiveness of adrenergic blocking agents, since the comparison of the inotropic effect of dimorpholamine before and after the blocking agents became almost impossible. To avoid this difficulty, a dose of dimorpholamine was chosen, which was sure to produce a marked positive inotropic action if given to a normal HLP. This dose of dimorpholamine was administered to the HLP, to which a suitable amount of an adrenergic β -blocking agent, nethalide, had been administered beforehand,

FIG. 4. Action of dimorpholamine on the reserpinized heart.
Dog, male, 9 kg (exp. 7). Adr=adrenaline.
Other symbols are the same as in Fig. 1.

without any prior control observations of the effect of this dose of dimorpholamine. Fig. 5 represents such a kind of experiment. Pre-administration of nethalide into the venous reservoir in a dose of 20 mg, which completely abolished the action of 0.5 to 1.0 μ g of adrenaline was without any remarkable effect upon the positive inotropic action of dimorpholamine, indicating that the main part of the positive inotropic action of this compound has no connection with the adrenergic mechanism.

DISCUSSION

The present study clearly demonstrated that dimorpholamine could produce a marked positive inotropic action in the dog's heart without provoking any change in heart rate and rhythm. Such an action in a potent analeptic agent may be an additional advantage for its clinical use.

Fukushima (1) reported only a slight negative inotropic action of dimorpholamine in the rabbit heart. As already discussed by Sakuma *et al.* (6), there is certain species differences in the action of dimorpholamine on the cardiovascular system; the long-lasting pressor action of this compound is most evident in the dog and rather difficult to demonstrate in the rabbit. Fukushima's failure to demonstrate the positive inotropic action in the rabbit may be a reflection of this species difference. However,

FIG. 5. Effect of nethalide upon the cardio-tonic action of dimorpholamine.
Dog, male, 9 kg (exp. 19). PB=sodium pentobarbital, Neth=nethalide, DMA=dimorpholamine, Adr=adrenaline. Other symbols are the same as is Fig. 1.

FIG. 6. Action of dimorpholamine on the isolated perfused rabbit heart (Langendorff's preparation).
The magnitude of the contraction was recorded isometric using a strain-gauge transducer. Adr=adrenaline, DMA=dimorpholamine.

the authors could demonstrate a definite positive inotropic action in the isolated perfused rabbit heart under certain conditions which the authors are unable to specify at present (Fig. 6) and it is highly possible that dimorpholamine can produce a definite positive inotropic action, irrespective of animal species, if certain conditions are satisfied.

The disturbance of the heart rhythm, which Kanda *et al.* (2) found in the isolated frog's heart was never observed in the dog HLP. Neither could the authors find any disturbance of the heart beat in the isolated perfused rabbit heart. Although Kanda *et al.* did not specify the types of disturbances they observed, the experiments in this laboratory showed that most characteristic features were slowed A-V conduction, with a slight decrease in the sinus beat. It seems, therefore, that there is some species difference in the dromotropic and the chronotropic action of dimorpholamine.

Luducna and Long (7) demonstrated that the pressor action of dimorpholamine in the dog was due to the release of catecholamine from the adrenal gland and this action differed from that of nicotine in that it could not be abolished by hexamethonium. Sakuma *et al.* (6) confirmed their observations and concluded after a rather elaborate study with several blocking agents that the release of adrenaline was the main cause of the pressor effect in the dog. They classified the compound as a non-nicotinic catecholamine releasing agent.

The catecholamine-releasing effect of dimorpholamine demonstrated in the above two papers seems to be confined to the excito-secretory action on the adrenal medulla, since the positive inotropic action of this compound persisted after reserpinization, which completely abolished the action of as high a dose of tyramine as 8 mg, and also persisted in the presence of more than 10 mg of nethalide, which produced almost complete blockade of 0.5 to 1.0 μ g of adrenalin. Lack of the positive chronotropic action might be taken to be another evidence of the non-adrenergic nature of the cardiac action of this compound.

SUMMARY

The cardiac action of dimorpholamine was studied, using the dog heart-lung preparation. In doses of 3 to 4 mg and above, dimorpholamine produced a marked positive inotropic action, without provoking any change in the heart rate and rhythm. Concomitant with the positive inotropic action, there was an increase in the coronary flow, in association with an increase in the cardiac oxygen consumption. Pretreatment of the animals with reserpine did not modify the positive inotropic action of this compound. Neither was the positive inotropic action abolished by an adrenergic β -blocking agent, nethalide. Thus, it was concluded that the adrenergic mechanism have no connection with the observed positive inotropic action.

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