Amelioration of Heart Failure by MDL 17043 and MDL 19205, Novel Positive Inotropic Drugs, in Dog Heart-Lung Preparations

Toshikazu Goto, M.D., Kazuo Nunoki, M.D., Keisuke Satoh, M.D., and Norio Taira, M.D.

SUMMARY
The efficacies of MDL 17043 and MDL 19205 in ameliorating heart failure were assessed in dog heart-lung preparations in which cardiac function had been severely depressed by pentobarbital. Six preparations were used for each drug. Both drugs in doses of 1-30 μmol similarly improved cardiac function in a dose-dependent manner and at 30 μmol improved it beyond control values. AV conduction impaired by pentobarbital was restored by 30 μmol of the 2 drugs. In these doses, however, neither of the drugs produced a significant increase in heart rate or arrhythmias. These results indicate that the 2 drugs would be of use in the treatment of heart failure.

Additional Indexing Words:
Cardiac function Cardiotonic Positive inotropy

MDL 17043, 1-3-dihydro-4-methyl-5-[4-(methylthio)-benzoyl]-2H-imidazol-2-one,1,2) and MDL 19205, 4-ethyl-1,3-dihydro-5-(4-pyridinyl-carbonyl)-2H-imidazol-2-one,3,4) are newly developed positive inotropic drugs. An increase in intracellular cyclic AMP (cAMP) through inhibition of cAMP phosphodiesterase has been postulated to be the mechanism underlying their positive inotropic action.5,6) These drugs exert a pronounced positive inotropic effect in anesthetized1-4,7) and conscious dogs,1,3) isolated cat atrial and papillary muscle preparations and guinea-pig atria,2,4) while producing only a moderate increase in atrial or heart rate. The clinical usefulness of MDL 17043 in the treatment of congestive heart failure has already been documented.8-10)

In dog heart-lung preparations, these drugs have already been reported to be effective in ameliorating pentobarbital-induced heart failure.1,3) The
aim of the present experiments was to compare the effects of these 2 drugs in restoring cardiac function in dog heart-lung preparations depressed by pentobarbital and to obtain information about their effects on atrioventricular (AV) conduction under identical experimental conditions.

**MATERIALS AND METHODS**

Twelve heart-lung preparations, 6 for MDL 17043 and 6 for MDL 19205, were made from mongrel dogs of either sex, weighing 8–11 Kg, anesthetized with sodium pentobarbital (30 mg/Kg i.v.). The preparations were similar to those described by previous workers. The extracorporeal blood circulation circuit consisted of silicone rubber tubing, a Windkessel chamber, a Starling pneumatic resistor (giving a pressure load comparable to the mean systemic arterial blood pressure), a heat exchanger (to control the temperature of the circulating blood) and a blood reservoir. The blood reservoir had been primed with 450–560 ml of arterial blood obtained from other mongrel dogs anesthetized with sodium pentobarbital (30 mg/Kg i.v.) and given sodium heparin (500 units/Kg i.v.). The level of blood in the reservoir was maintained at 5 cm above the level of the tricuspid valve. Aortic blood pressure (given by the Starling pneumatic resistor) was maintained at 80 mmHg and monitored with a pressure transducer (Nihon Kohden, MPU-0.5) through a side arm of the aortic cannula. Cardiac output (which did not include coronary blood flow) was measured with the flow probe of an electromagnetic flowmeter (Nihon Kohden, MFV-2100) interposed between the aortic cannula and the Starling pneumatic resistor. Left and right atrial pressures (LAP and RAP) were measured with pressure transducers (Gould Statham, P23ID), respectively. Left ventricular pressure (LVP) was measured with a Mikro-tip® catheter pressure transducer (Millar Instruments) inserted into the left ventricle via the left subclavian artery. The maximum rate of rise of LVP (LV dP/dt max) was obtained electronically with an electronic differentiator (San-ei Instrument, 1323). Heart rate was measured with a cardiotachometer (San-ei Instrument, 1321). AV conduction time was measured with an AV interval counter (Data Graph, HT-31) at a resolution of 1 msec. To determine cardiac function curves which relate cardiac output to LAP, the level of blood in the reservoir was elevated step-wise by 5 cm for 30 sec up to 10 cm above the initial level. Such a procedure is designated as a competence test (CT). To produce heart failure, pentobarbital was administered into the blood reservoir initially at 50 mg and then in 25 mg steps, until cardiac output was decreased to about 80% of control level. MDL 17043 and MDL 19205 (Merrell Dow) were dissolved in 1N
Fig. 1. Effects of MDL 17043 (A) and MDL 19205 (B) on cardiac output, left atrial pressure, right atrial pressure, LV dP/dt max, heart rate and AV conduction time in 2 dog heart-lung preparations. CT = competence test.

NaOH in concentrations of 100 μmol/ml as stock solutions. The stock solutions were diluted with 0.9% NaCl immediately before use and administered into the blood reservoir. Doses referred to are cumulative.

Values are given in terms of mean±SE, unless otherwise stated. Differences between mean values were analyzed by Student’s t-test and taken to be significant when p values were less than 0.05.
Fig. 2. Cardiac function curves determined with MDL 17043 (A) and
MDL 19205 (B) in dog heart-lung preparations. Data points are means±SE
of 6 preparations for each drug. Control (○), failure (●). MDL 17043
or MDL 19205 in cumulative doses: 3 μmol (△), 10 μmol (▲), 30 μmol
(□).

Fig. 3. Dose-effect curves of MDL 17043 (A) and MDL 19205 (B)
on right atrial pressure. Data points are means±SE of the same 6 prepara-
tions that are presented in Fig. 2. C=control; F=failure produced by
pentobarbital. *p<0.05, **p<0.01 against control.
RESULTS

Experiments were performed on 2 groups of 6 dog heart-lung preparations each, one group for MDL 17043 and the other for MDL 19205. Typical experiments with MDL 17043 and MDL 19205 are shown in Fig. 1 A and B, respectively. The mean values for the cardiac variables in these 2 groups before (control) and after administration of sodium pentobarbital are presented in Table I. Doses of sodium pentobarbital administered to MDL 17043 and MDL 19205 groups were 92 ± 20 and 125 ± 22 (S.D.) mg, respectively. With these doses of sodium pentobarbital, cardiac output (Figs. 1 and 2) decreased, and RAP (Figs. 1 and 3) and LAP (Figs. 1 and 2) increased. LV dP/dt max was depressed to nearly 70% of its control values (Fig. 4). Heart rate was decreased but not significantly (Fig. 5). AV conduction time was prolonged (Fig. 6). Cardiac function was depressed as reflected by the right and downward shift of the cardiac function curve (Fig. 2). However, there were no significant differences either during the control period or after pentobarbital administration, in values of cardiac variables between MDL 17043 and MDL 19205 groups (Table I).

With administration of the 2 drugs in a cumulative manner up to 30 µmol, cardiac output increased and LAP decreased in a similar way (Figs. 1 and 2). Cardiac function was similarly improved by both drugs as reflected by left and upward shifts of cardiac function curves and with 30 µmol of the 2 drugs the cardiac function curves likewise shifted to the left beyond the respective control curves (Fig. 2). RAP was restored to control levels with doses of 10–30 µmol (Fig. 3). LV dP/dt max was restored nearly to its control
values with 10 µmol and improved markedly beyond them after administration of 30 µmol of each drug (Fig. 4). AV conduction time was also restored with doses of 3-30 µmol (Fig. 6). Heart rate tended to increase, but did not exceed control values even at the highest dose (30 µmol) of each drug (Fig. 5). In no preparation did an arrhythmia occur.

**DISCUSSION**

In the present experiments both MDL 17043 and MDL 19205 improved cardiac function of heart-lung preparations which had been severely depressed by pentobarbital, and at their highest doses (30 µmol) cardiac function became better than it had been under control conditions; at these doses LV dP/dt max was increased beyond its control values and cardiac function curves shifted to the left beyond the control curves. Thus, the present results are generally consistent with those obtained by Dage et al.\(^{1,3}\)

Previous studies\(^{1-4,7-10}\) have shown that both drugs possess a peripheral vasodilating action leading to unloading the heart. It has been also shown that MDL 17043, in spite of a marked positive inotropic effect, did not increase myocardial O₂ consumption significantly.\(^{7,9}\) Thus, our present results taken together with those of other authors indicate that MDL 17043 and MDL 19205 are potentially useful in the treatment of heart failure.

There has been no report of the dromotropic effect of these drugs. In the present experiments, AV conduction time prolonged by pentobarbital
Fig. 6. Dose-effect curves of MDL 17043 (A) and MDL 19205 (B) on AV conduction time. Data points are means±SE of the same 6 preparations that are shown in Figs. 2, 3, 4 and 5. *p<0.05, **p<0.01 against control.

Table 1. Cardiac Variables of the Dog Heart-Lung Preparation before (Control) and after Administration of Sodium Pentobarbital

<table>
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<tr>
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<th>Cardiac output (ml/min)</th>
<th>Left atrial pressure (mmHg)</th>
<th>Right atrial pressure (mmHg/cmH₂O)</th>
<th>LV dP/dt max (mmHg/sec)</th>
<th>Heart rate (beats/min)</th>
<th>AV conduction time (msec)</th>
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<tr>
<td>A (n=6)</td>
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<td>Control</td>
<td>658±44</td>
<td>5.6±1.2</td>
<td>2.5±0.2</td>
<td>2125±158</td>
<td>139±8</td>
<td>124±6</td>
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<td>Pentobarbital</td>
<td>527±40**</td>
<td>8.8±1.3**</td>
<td>3.6±0.2**</td>
<td>1523±89**</td>
<td>134±6</td>
<td>137±4*</td>
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<td>92±20 (S.D.)mg</td>
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<tr>
<td>B (n=6)</td>
<td></td>
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<tr>
<td>Control</td>
<td>612±40</td>
<td>6.6±1.2</td>
<td>2.6±0.2</td>
<td>2263±133</td>
<td>150±10</td>
<td>113±8</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>518±33**</td>
<td>9.2±1.2**</td>
<td>3.9±0.4**</td>
<td>1660±82**</td>
<td>140±7</td>
<td>128±8**</td>
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<td>125±22 (S.D.)mg</td>
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A, for MDL 17043; B, for MDL 19205.
* p<0.05, ** p<0.01 against respective control values.

was restored to control levels by these drugs. However, even with the highest dose (30 μmol) AV conduction time was not shortened beyond the control value. Thus, the 2 drugs can also be used in the treatment of AV conduction disturbances.
ACKNOWLEDGMENT

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REFERENCES