Hemodynamic Effects of a New Inotropic Agent, Piroximone (MDL 19205), in Patients With Chronic Heart Failure

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The hemodynamic and neurohumoral effects of cumulative intravenous doses of piroximone (MDL 19205), a noncatecholamine, nonglycoside, imidazole derivative with positive inotropic and vasodilating properties, were studied in eight patients with severe congestive heart failure. A dose of 1.25 mg/kg in seven patients and 1.75 mg/kg in one patient increased cardiac index by 75% from 1.96 to 3.41 liters/min per m² and decreased systemic vascular resistance (−41%), right atrial (−66%) and pulmonary wedge pressure (−35%) (all \( p < 0.005 \)). Mean arterial pressure was slightly reduced from 78 to 71 mm Hg (\( p < 0.05 \)) and forearm blood flow increased by 42%. Plasma norepinephrine decreased from 830 to 542 pg/ml (\( p < 0.05 \)) and plasma renin activity tended to increase. In four patients, dobutamine (15 \( \mu \)g/kg per min) produced a comparable increase in cardiac index (+100%), but less decrease in pulmonary wedge pressure (−21 versus −41%, \( p < 0.05 \) versus piroximone) and, unlike piroximone, significantly increased heart rate (+22%, \( p < 0.05 \) versus piroximone) and heart rate-blood pressure product (+30%, \( p < 0.01 \) versus piroximone). In four other patients, a single intravenous dose of piroximone (1 mg/kg) resulted in a 35% increase in the first derivative of left ventricular pressure (dP/dt) from 796 to 1,068 mm Hg/s (\( p < 0.01 \)). Thus, piroximone is a potent inotropic agent with an acute hemodynamic profile that may be more favorable than that of dobutamine. Because the drug is orally absorbed, clinical trials of chronic efficacy are indicated.

Severe chronic congestive heart failure is characterized by a pronounced impairment in cardiac pump function. The resulting decrease in cardiac output is associated with tachycardia, left ventricular enlargement, increased left ventricular filling pressure and increased systemic vascular resistance (1). The ideal management of congestive heart failure, therefore, should cause an improvement in cardiac work while reducing aortic impedance and left ventricular filling pressure (2–4).

For more than a century, cardiac glycosides have been the mainstay of long-term therapy for congestive heart failure despite their narrow therapeutic index and modest inotropic activity (5). Sympathomimetics, although effective for the acute treatment of congestive heart failure, are not effective orally (6). Piroximone (MDL 19205) is a new orally active agent that has been shown in preclinical studies (7) to combine inotropic and vasodilator properties. This imidazole derivative apparently increases contractility by mechanisms independent of glycoside or beta-adrenergic receptors perhaps related, in part, to phosphodiesterase-inhibiting activity (8). It also possesses a direct action on vascular smooth muscle, resulting in a vasodilation independent of beta-adrenergic, muscarinic or histaminergic receptors (9).

This study was designed to determine whether piroximone has an inotropic effect in human beings, determine the optimal intravenous dose of piroximone in patients with refractory congestive heart failure and compare the hemodynamic effects of piroximone and dobutamine.

Methods

Study patients. Two groups of male patients with severe congestive heart failure were studied. Group I consisted of eight patients studied in the hemodynamic laboratory. Their mean age was 45 years (range 27 to 63). Five patients had congestive heart failure due to ischemic heart disease and three patients had cardiomyopathies of unknown origin. Four patients were in class III and four in class IV by the New York Heart Association functional classification. The duration of symptomatic disease ranged from 6 months to 6 years. All patients were in stable condition and had sinus
rhythm at the time of the study. The mean ejection fraction obtained under current therapy by gated blood pool scan was 16% (range 9 to 21, n = 5) and 18% (range 8 to 32, n = 6) by M-mode echocardiography on the day of the study. Cardiotoracic ratio was increased, averaging 0.64 (range 0.55 to 0.75).

Group II consisted of four patients who, while undergoing a routine diagnostic left heart catheterization, were expressly given piroximone to determine its effect on the first derivative of left ventricular pressure (dP/dt). The mean age obtained under current therapy by gated blood pool scan

In six patients, M-mode echocardiograms were obtained before the administration of the drug and the observance of the peak hemodynamic effects. Systolic and diastolic left ventricular dimensions were measured and the corresponding volumes estimated using a corrected prolate ellipse model (12). Stroke volume and ejection fraction were subsequently calculated using standard formulas. Forearm blood flow and venous capacitance were determined by plethysmography (13) in three patients during the control state and immediately after the last injection of the drug. Forearm vascular resistance was calculated by mean arterial pressure divided by forearm blood flow.

Group II. Four patients received a single dose of piroximone, 1 mg/kg intravenously, during a diagnostic left heart catheterization. Hemodynamic measurements, including left ventricular pressure recorded from a microtip catheter pressure transducer (Millar Instruments) and maximal left ventricular dP/dt, were obtained before and 10 minutes after the injection.

Neurohumoral reflexes and drug levels. In group I, plasma levels of norepinephrine by radioenzymatic assay (Upjohn Diagnostic) (14) and renin activity by radioimmunoassay (Roche Laboratories) (15) were determined during the control state (2 hours of rest in the supine position) and at peak effect of the drug. Plasma drug levels determined by high pressure liquid chromatography were measured after the first and last dose of piroximone.

PIROXIMONE ADMINISTRATION. Patients were evaluated in the postabsorptive state. Two sets of baseline control measurements were made at 30 minute intervals. A test bolus of 0.25 mg/kg of the saline solution of piroximone (2 mg/ml) was then given intravenously and followed by successive intravenous doses of 0.5 mg/kg administered every 15 minutes. Administration of piroximone was stopped when two successive sets of hemodynamic data (cardiac output and pulmonary wedge pressure) varied by an average of less than 10%. Total dose was 1.25 mg/kg in seven patients and 1.75 mg/kg in one patient.

Hemodynamic measurements were made 10 minutes after each dose. After the final dose of piroximone, these measurements were repeated at 30 minutes and then hourly until return of all values to within 10% of the baseline level.

DOBUTAMINE ADMINISTRATION. In four patients (Cases 2, 5, 7 and 8), dobutamine was progressively administered to a rate of 15 μg/kg per min. The hemodynamic data were obtained at the end of 15 minutes of stable infusion.

Statistical analysis. Time course variability of hemodynamic measurements with piroximone and dobutamine was analyzed using analysis of variance for repeated measures (16). Subsequent pairwise tests between mean values were performed using the Bonferroni test (17). Intergroup
comparisons for control values, maximal percent changes as well as changes in ejection fraction, renin and plasma norepinephrine were made by Student’s t test for paired values. Analysis by two variable linear regression was used to compare plasma levels of the drug and hemodynamic response.

**Results**

**Control measurements.** Duplicate control values obtained at 30 minute intervals before piroximone varied by less than 6% for cardiac index and pulmonary wedge pressure. The differences in other variables were only minimal and not statistically significant. Similarly, only minor differences were found between control values in the group given piroximone and dobutamine. All patients showed significant abnormalities of their hemodynamic measurements at rest compatible with the diagnosis of severe congestive heart failure: mean cardiac index (± standard deviation) 1.96 ± 0.25 liters/min per m², pulmonary wedge pressure 24.6 ± 5.6 mm Hg, right atrial pressure 9.5 ± 3.5 mm Hg and systemic vascular resistance 1,523 ± 389 dynes·s·cm⁻⁵.

**Hemodynamic response to piroximone.** In group I, the first dose of piroximone significantly increased cardiac index and left ventricular work index and decreased right atrial pressure and systemic resistance. Those changes were further enhanced by the next doses, and at peak effect (Table 1) cardiac index was increased from 1.96 ± 0.25 to 3.41 ± 0.48 liters/min per m² (p < 0.005), whereas pulmonary wedge pressure decreased from 24.6 ± 5.6 to 15.6 ± 2.9 mm Hg (p < 0.005). Right atrial pressure decreased from 9.5 ± 3.5 to 3.1 ± 1.9 mm Hg (p < 0.005), systemic vascular resistance from 1,523 ± 389 to 872 ± 177 dynes·s·cm⁻⁵ (p < 0.005). Heart rate did not change significantly from 92.5 ± 12 to 96.1 ± 13 beats/min. The mean arterial pressure progressively decreased from 78 ± 10 to 71 ± 6 mm Hg, becoming significant (p < 0.05) only at the highest dose. The ejection fraction obtained by M-mode echocardiography increased from 18 ± 8.7 to 32.3 ± 13.5% (n = 6, p < 0.005), mainly because of a marked decrease in end-systolic volume, but the rate-pressure product of heart rate and systolic blood pressure remained unchanged (96.76 ± 16.28 to 96.86 ± 14.14). In all but one patient, these effects were obtained with a total dose of 1.25 mg/kg. In one patient, the dose of 1.75 mg/kg was needed to reach the optimal effect. As illustrated by sequential measurements of cardiac index and pulmonary wedge pressure (Fig. 1), 1 hour after

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Mean ± SD C 92.5 ± 12 9.5 ± 3.5 36.3 ± 7 24.6 ± 5.6 77.5 ± 9.8 1.96 ± 0.25 1.523 ± 389 265 ± 108 1,399 ± 208

p Value NS 0.005 0.01 0.005 0.05 0.005 0.005 0.005 0.005

C = control state; CI = cardiac index; HR = heart rate; LVWI = left ventricular work index; MAP = mean arterial pressure; NS = not significant, p = probability; P = piroximone (1.25 mg/kg except Case 7 1.75 mg/kg); PA = mean pulmonary artery pressure; PAR = pulmonary arteriolar resistance; PCW = pulmonary capillary wedge pressure; SD = standard deviation; SVR = systemic vascular resistance.
of piroximone. The hemodynamic changes were comparable although slightly less striking than those obtained with the higher dose in group I. Cardiac index increased by 53%, pulmonary wedge pressure decreased by 38% and systemic vascular resistance by 28%. The acute change in cardiac contractility was estimated by the modification of left ventricular maximal dP/dt, which showed a 35% increase from 796 ± 92 to 1,068 ± 97 mm Hg/s (p < 0.01).

**Piroximone plasma levels.** Although similar intravenous doses of piroximone produced a wide variety of plasma levels, some relation between dose and blood levels was noted. Indeed, after the first dose of 0.5 mg/kg, plasma levels were generally close to 0.9 μg/ml (range 0.447 to 2.094) and after 1.25 mg/kg (cumulative dose), plasma levels approached 2 μg/ml (range 1.3 to 2.8). In total, 18 levels were obtained after intravenous doses ranging from 0.5 to 1.75 mg/kg. Two variable linear regression showed a significant correlation between plasma levels and absolute or relative (%) changes of all hemodynamic variables with the exception of heart rate and pulmonary resistance: cardiac index, r = 0.68 (Fig. 2); pulmonary wedge pressure, r = 0.61; left ventricular work index, r = 0.67; systemic vascular resistance, r = 0.66 (all p < 0.01); arterial, pulmonary and right atrial pressures, r = 0.51 (p < 0.05).

**Neurohumoral response to piroximone.** Control plasma levels of norepinephrine were elevated (mean 830 ± 357 versus 175 ± 30 pg/ml in the control state) and consistently decreased after piroximone to 592 ± 157 pg/ml (p < 0.05). Plasma renin activity tended to increase from 32.7 ± 51 to 53.8 ± 72 ng/ml per h, but this increase did not reach the level of significance.

**Hemodynamic response to dobutamine.** In four patients, dobutamine, 15 μg/kg per min, also produced marked changes in cardiac index from 2.03 ± 0.13 to 4.07 ± 0.52
lites/min per m² (p < 0.01) and left ventricular work index from 1,560 ± 330 to 3,021 ± 643 g/m² (p < 0.05) and decreased pulmonary wedge pressure from 26 ± 6 to 21 ± 5 mm Hg (p < 0.05). Mean arterial pressure was not significantly modified, but heart rate increased from 90 ± 16 to 111 ± 23 beats/min (p < 0.05). Systemic vascular resistance decreased from 1,607 ± 274 to 768 ± 211 dynes·s·cm⁻⁵ (p < 0.01), but pulmonary arteriolar resistance was not modified despite the increase in cardiac output leading to an insignificant increase of pulmonary pressure.

Comparison between hemodynamic effects of piroximone and dobutamine in four patients (Fig. 3). Although the increase in cardiac index was slightly greater after dobutamine than after piroximone (+100 versus +76%), the difference was not statistically significant and was mostly due to a chronotropic effect. Indeed, the changes in stroke index induced by both drugs were comparable (+68 versus +61%). However, dobutamine administration led to a significant (p < 0.05) increase in heart rate (+22%, p < 0.05) not seen after piroximone (+7%, difference not significant). Both drugs similarly reduced the right atrial pressure, although dobutamine was significantly less effective in lowering the pulmonary wedge pressure (−21 versus −41%, p < 0.05). The changes in pulmonary artery pressure occurred in opposite directions after dobutamine and piroximone administration (+10 versus −20%, p < 0.01). Systemic vascular resistance decreased with both drugs, the effects of dobutamine being more pronounced (−52 versus −46%, p < 0.05). Finally, the modification of the rate-pressure product (heart rate × systolic blood pressure) produced by the two drugs were strikingly different (p < 0.01); after piroximone administration, the rate-pressure product remained unchanged (−5%, not significant), whereas dobutamine increased it by 30%.

No side effects were recorded during the entire trial. In particular no angina or arrhythmias were seen. Instead, at least five patients spontaneously mentioned a subjective improvement, particularly decreased orthopnea.

During the study, laboratory data consisting of a complete blood count, electrolyte battery, blood chemistries for renal and hepatic function, blood glucose, uric acid and urinalysis were monitored. Data were collected before drug administration and 1 and 7 days later. No significant changes were seen in any of these variables after piroximone therapy.

Discussion

Mechanisms of action of piroximone. The mechanism of action of piroximone remains largely unknown. It probably depends on several actions resulting in at least two cardiovascular effects: positive inotropism and peripheral vasodilation. The in vitro positive chronotropic effect ob-

![Figure 3](Image)
served in several preparations (7,8) was not seen in our patients who have heart failure, at the doses of piroximone administered, and did not seem to play a role in the drug's hemodynamic effect. Piroximone does not appear to modify Na\(^+\)K\(^+\) ATPase, but it does have a phosphodiesterase inhibition activity (8). The importance of this mechanism remains to be clarified. Studies on various muscle preparations have confirmed an increase in contractile force not mediated either by beta-adrenergic or histaminic activity. In dogs, piroximone increases left ventricle dP/dt to the same extent whether propranolol is present or not (18). Moreover, the combination of piroximone and isoproterenol produces an additive effect on guinea pig atrial rate and a synergistic effect on contractile force (18). Piroximone also has a vasodilating effect on an isolated perfused dog limb (18). Since this action is enhanced by adrenergic blockade and unaltered by sympathectomy, or by beta-adrenergic, muscarinic or histaminic blockade, the vasodilation is likely a direct effect on the vascular smooth muscle (9).

**Hemodynamic effect of piroximone.** In these patients with severe congestive heart failure, piroximone consistently improved cardiac performance by increasing cardiac output and stroke volume while reducing filling pressure (Fig. 4). Moreover, despite a slight but significant reduction in aortic pressure, plasma norepinephrine consistently decreased during piroximone administration. This paradoxical response, previously observed during vasodilator therapy (19), could be related to an improvement in cardiac performance or to the effects of altered pulsatile pressure on carotid baroreceptors (20). Likewise, the tendency of plasma renin activity to increase after piroximone therapy might reflect changes in renal artery baroreceptor function or renal blood flow. The improvement in left ventricular function was obtained without altering the rate-pressure product of heart rate and systolic blood pressure and was clearly dose-dependent as shown by the significant relation between almost all hemodynamic variables and plasma levels of piroximone. Although experimental data strongly suggest a dual mode of action (inotropism and vasodilation), it remains difficult to separate these two effects on the basis of hemodynamic measurements alone. The increase in left ventricular maximal dP/dt observed in the four patients studied during left heart catheterization supports the presence of an inotropic effect (21,22). Although left ventricular dP/dt may not accurately assess cardiac contractility, this isovolumic index is known to be highly sensitive to acute changes in inotropic state (23) and insensitive to modification of afterload (24), except when the changes induce a premature opening of the aortic valve (25). This is unlikely to be the case in our patients because the arterial diastolic pressure remained stable (66 versus 65 mm Hg). Similarly, peak dP/dt can be increased by augmentation of preload (22). In our patients, however, peak dP/dt increased despite a significant decrease (−38%) in wedge pressure. These data suggest that the observed change in dP/dt probably underestimated the actual improvement in contractility induced by piroximone.

The 41% decrease in systemic vascular resistance observed after piroximone is compatible with a direct vasodilating effect. Although purely mechanical dilation of the vessels induced by the increase in cardiac output cannot be excluded (26), the modest decrease in arterial pressure is suggestive of drug-induced vasodilation.

Despite the marked increase in left ventricular work index, the rate-pressure product remained unchanged. The product of heart rate and systolic blood pressure has been shown to be a reliable index of myocardial oxygen consumption in a variety of clinical settings (10,11). This relation between rate-pressure product and myocardial oxygen consumption may be modified slightly by interventions that either alter ventricular volume or myocardial contractility (27,28). The effect of piroximone on this relation is unknown. However, it is likely that an increase in oxygen consumption induced by an increase in contractility would be counterbalanced by a reduction in preload and afterload.

**Comparison between piroximone and dobutamine.** Dobutamine, a potent beta-agonist, has been found useful in improving left ventricular function in patients with congestive heart failure (29,30). The results obtained with piroximone and dobutamine, 15 μg/kg per min, in four

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**Figure 4.** Changes in pulmonary capillary wedge pressure (PCW) and stroke volume index from control state to peak effect after piroximone in eight patients with congestive heart failure.
patients are summarized in Figure 3. Piroximone produced a comparable increase in stroke volume as did dobutamine, but with a lower pulmonary wedge pressure and a lesser increase in heart rate (p < 0.05). The effect on systemic resistance was slightly but significantly more pronounced after dobutamine (-53 versus -46%, p < 0.05 dobutamine versus piroximone). However, previous studies (31) suggested that the decrease in resistance during dobutamine infusion may be largely mechanical or reflex, or a combination of both, in origin. On the contrary, experimental data (9) support a direct effect of piroximone on vascular smooth muscle. In our patients, after piroximone therapy, the decrease in resistance was sufficient with regard to the change in cardiac output to produce a significant decrease in both mean and systolic blood pressure (-12 and -10%, p < 0.05 versus control) and this is likely to be the resultant of a true vasodilation. Another important difference between piroximone and dobutamine was the effect on the rate-pressure product that remained nearly unchanged after piroximone administration, but increased by 30% after dobutamine. Thus, if the increase in contractility was equivalent after both drugs, piroximone may be more beneficial from the point of view of myocardial oxygen consumption because of its vasodilating actions and the absence of a strong positive chronotropic effect.

**Theerapeutic implications.** The results of the present study indicate that piroximone given intravenously is a potent inotropic agent with vasodilating properties that produce a marked increase in cardiac output and left ventricular work with a decrease in systemic resistance. These results, comparable with those obtained with dobutamine, are achieved with a greater reduction in filling pressure. Moreover, in contrast to dobutamine, piroximone produces only minimal changes in heart rate and systolic pressure. This may make it particularly attractive in the setting of ischemic heart disease. Furthermore, piroximone is available in an oral form that has proven to be the equal of the parenteral form in long-term treatment of congestive heart failure.

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**References**

25. Wildenthal K, Mierzwiski DS, Mitchell JH. Effect of sudden changes


