Sustained Hemodynamic and Clinical Effects of a New Cardiotonic Agent, WIN 47203, in Patients with Severe Congestive Heart Failure

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SUMMARY The hemodynamic and clinical effects of WIN 47203, a newly synthesized noncatecholamine, nonglycosidic inotropic agent, were studied in 11 patients with severe chronic congestive heart failure. Intravenous WIN 47203 increased cardiac index from $1.93 \pm 0.36$ to $2.87 \pm 0.45$ l/min/m$^2$ ($p < 0.001$) and reduced pulmonary capillary wedge pressure from $27.0 \pm 8.4$ to $16.3 \pm 6.1$ mm Hg ($p < 0.001$). Mean systemic arterial pressure decreased from $75.2 \pm 6.7$ to $72.4 \pm 6.3$ mm Hg ($p < 0.01$) and systemic vascular resistance from $1591 \pm 397$ to $1071 \pm 293$ dyn-sec-cm$^{-5}$ ($p < 0.001$); heart rate was unchanged. Oral WIN 47203 produced similar hemodynamic improvement. Hemodynamic monitoring of six consecutive doses did not demonstrate evidence for attenuation of effectiveness. Chronic therapy with WIN 47203 produced substantial symptomatic improvement and increased maximal oxygen uptake at 1 week. Patients were further improved after 4 weeks of WIN 47203, and maximal oxygen uptake increased from $9.0 \pm 1.9$ to $11.6 \pm 2.5$ ml/kg/min ($p < 0.01$ vs control). No overt clinical or laboratory manifestations of toxicity were observed. Withdrawal of WIN 47203 in two patients in whom clinical benefit was not sustained resulted in clinical and hemodynamic deterioration, which was reversed by reinitiation of the drug. Therefore, this study demonstrates the acute and sustained cardiotonic efficacy of WIN 47203 in man. If long-term administration remains well tolerated and without side effects, this drug appears to be very promising for treatment of chronic severe congestive heart failure.

PATIENTS with congestive heart failure become increasingly symptomatic as the severity of the disease progresses. In the advanced stage of the disease, patients are severely incapacitated despite optimal therapy with diuretics, digitalis and vasodilators. Amrinone, a nonglycosidic, nonadrenergic cardiotonic agent, improves ventricular performance and reduces symptoms at rest and during exertion. However, amrinone therapy is complicated by various side effects, e.g., thrombocytopenia, gastrointestinal intolerance, hepatotoxicity, and fever. These side effects occur most often during the first month of therapy. WIN 47203 is a new nonglycosidic, nonadrenergic cardiotonic agent with a chemical structure analogous to that of amrinone. In vitro and in vivo, WIN 47203 is a more potent inotropic agent than amrinone. Moreover, oral WIN 47203 administered to normal volunteers for 4 weeks has not been associated with untoward effects. We undertook the present study to evaluate the hemodynamic and clinical responses and safety of prolonged administration of WIN 47203 to patients with severe congestive heart failure.

Methods

Subjects

Therapy with WIN 47203 was offered to 11 patients with chronic congestive heart failure who were severely incapacitated despite treatment with diuretics, digitalis and nitrates. Eight of the patients had not benefited from therapy with arteriolar vasodilators, which were therefore discontinued. The severity of the functional impairment was confirmed by a maximal oxygen uptake below 12 ml/kg/min in every patient (average 9.0 ml/kg/min, range 6–11.2 ml/kg/min). The nature, benefits and risks of the study were fully explained and all patients gave informed consent. The protocol was approved by the Committee on Clinical


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The average age of the patients was 60 ± 2 years (range 42–70 years). Heart failure resulted from coronary artery disease in nine patients and from idiopathic cardiomyopathy in two. No patient had hypertension or a recent myocardial infarction. Nine patients were in sinus rhythm and two had atrial fibrillation. Six patients who had episodes of nonsustained ventricular tachycardia during 24-hour Holter monitoring were treated successfully with procainamide. Left ventricular ejection fraction obtained by gated radionuclide imaging averaged 24% (range 16–37%). Patients were admitted to the coronary care unit at least 48 hours before hemodynamic evaluation. A strict dietary regimen including 2 g of sodium was prescribed and nitrates were discontinued. Patients continued to receive their usual daily doses of digoxin and diuretic during the study. The average serum digoxin level at the start of therapy was 1.1 ± 0.3 ng/ml.

Hemodynamics

After 24 hours of bed rest, the patients underwent right-heart catheterization performed with a flow-directed, balloon-tipped thermodilution catheter (Edwards Laboratories). Mean pulmonary arterial, pulmonary wedge and right atrial pressures were recorded on a photographic recorder (Electronics for Medicine). Cardiac output was determined by the thermodilution technique using iced 5% dextrose in water and obtained in triplicate with less than 10% variation. Systemic arterial pressure was measured directly using an indwelling catheter inserted percutaneously into the radial artery. Derived hemodynamic variables, including cardiac index, stroke volume index and systemic vascular resistance, were calculated from standard formulas. Cardiac index was below 2.5 l/min/m² in every patient. An electrocardiographic lead was monitored continuously throughout the study.

Exercise Capacity Assessment

Treadmill exercise was performed according to the protocol of Patterson et al.12 Patients were tested at the same time of day at least 4 hours after taking their medications. Before therapy with WIN 47203, two exercise tests were performed to determine reproducibility. Measurements of mixed expired oxygen, mixed expired carbon dioxide, expired volume, expired gas temperature and barometric pressure were performed at rest and every 30 seconds throughout exercise using a metabolic measurement cart (Beckman Instruments). The patients were breathing through a mouthpiece attached to a low-resistance, nonbreathing, three-way valve with a nose clamp. The oxygen analyzer (OM-11 Beckman Instruments) and carbon dioxide analyzer (LB-2, Beckman Instruments) were calibrated using an analyzed mixture of approximately 4% carbon dioxide and 16% oxygen in nitrogen. This calibration was made within 1 hour of the testing. Oxygen uptake (ml/kg/min) was calculated using standard formulas.12 Maximal oxygen uptake was defined by the failure of oxygen uptake to increase despite a higher work load.13

Outpatient Follow-up

After discharge from the hospital, patients were asked to weigh themselves daily and to maintain a diary of their symptoms. They were evaluated every week; blood samples were withdrawn for clinical laboratory tests and urinalysis was performed. Electrocardiographic tracings with rhythm strips as well as determinations of maximal oxygen uptake were obtained after 1 and 4 weeks of therapy.

Drug Administration and Withdrawal

WIN 47203 was first administered intravenously to all patients. The first two patients received an initial bolus of 50 μg/kg. Subsequently, the initial bolus was reduced to 25 μg/kg. Patients who failed to demonstrate an increase in cardiac index of at least 30% or to above 2.5 l/min/m² received an additional bolus of 50 μg/kg 10–15 minutes after the initial bolus. If 50 μg/kg failed to produce an adequate hemodynamic response, 75 μg/kg was administered after 10–15 minutes. After a washout period of at least 16 hours, oral WIN 47203 was administered at an initial dose of 2.5 mg. Patients who failed to demonstrate a satisfactory response (as previously defined) received 5 mg of WIN 47203 the next day. When the adequate dose of WIN 47203 had been established, the effects of six consecutive doses, administered at 6-hour intervals, were hemodynamically monitored in those patients able to tolerate prolonged invasive monitoring. Catheters were then removed and chronic therapy continued at the dose established during hospitalization. Patients who showed little or no clinical improvement after at least 2 weeks of therapy were readmitted for hemodynamic evaluation. After hemodynamic monitoring of the effects of two consecutive doses, WIN 47203 therapy was discontinued and the patients were closely monitored. Clinical deterioration associated with a return of hemodynamic variables to or below values before WIN 47203 was considered an indication to resume therapy.

Statistical Analysis

The results are expressed as mean ± SD. Maximal hemodynamic changes were tested for significance with the paired t test. The statistical significance of duration of action and effects of consecutive administration of WIN 47203 was determined by analysis of variance. Two-way analysis of variance was used to test for differences between values during control and WIN 47203 therapy and for carryover effects. If statistical significance was obtained, further individual comparison testing was done using Dunnett’s test.

Results

Hemodynamics

The maximal hemodynamic response to i.v. WIN 47203 at an average bolus of 34.8 μg/kg (range 25–75
### Table 1. Maximal Hemodynamic Effects of Intravenous WIN 47203

<table>
<thead>
<tr>
<th>Pt</th>
<th>HR (beats/min) C W</th>
<th>SAP (mm Hg) C W</th>
<th>CI (l/min/m²) C W</th>
<th>PCW (mm Hg) C W</th>
<th>RAP (mm Hg) C W</th>
<th>SVR (dyn-sec-cm⁻⁵) C W</th>
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<td>69 68</td>
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<td>30 22</td>
<td>8 2</td>
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<tr>
<td>Mean</td>
<td>90.3 88.5</td>
<td>75.2 72.4</td>
<td>1.93 2.87</td>
<td>27.0 16.3</td>
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<td>± SD</td>
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<td>±6.7 ±6.3</td>
<td>±0.36 ±0.45</td>
<td>±8.4 ±6.1</td>
<td>±6.4 ±4.4</td>
<td>±397 ±293</td>
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</table>

*p* < NS < 0.001 < 0.001 < 0.001 < 0.001

Abbreviations: HR = heart rate; SAP = mean systemic arterial pressure; CI = cardiac index; PCW = mean pulmonary capillary wedge pressure; RAP = mean right atrial pressure; SVR = systemic vascular resistance; C = control; W = WIN 47203.

μg/kg) is detailed for the 11 patients in table 1. Cardiac index increased from 1.93 ± 0.36 to 2.87 ± 0.45 l/min/m² (*p* < 0.001), pulmonary capillary wedge pressure fell from 27.0 ± 8.4 to 16.3 ± 6.1 mm Hg (*p* < 0.001), and right atrial pressure fell from 9.4 ± 6.4 to 5.4 ± 4.4 mm Hg (*p* < 0.001). A very marked fall in pulmonary capillary wedge pressure (19 mm Hg) was observed in patients 4 and 8, who nevertheless had an increase in cardiac index. Systemic arterial pressure decreased from 75.2 ± 6.7 to 72.4 ± 6.3 mm Hg (*p* < 0.01). The systemic vascular resistance fell from 1591 ± 397 to 1071 ± 293 dyn-sec-cm⁻⁵ (*p* < 0.001); heart rate did not change significantly. In every instance, the maximal increase in cardiac index occurred within 10 minutes after i.v. administration of WIN 47203. The cardiac index was still significantly elevated at 30 minutes, but had returned to the control level by 60 minutes.

WIN 47203 was administered orally to 10 patients. Eight received 5 mg and two 2.5 mg. The maximal improvement in left ventricular performance produced by oral administration was similar to that after the i.v. bolus (fig. 1). The time course of the hemodynamic response to an oral dose of 5 mg is shown in figure 2. The maximal increase in cardiac index occurred 60–90 minutes after oral administration. Cardiac index remained significantly elevated for 2 hours and pulmonary capillary wedge pressure significantly lowered for 3 hours. The hemodynamic response for six consecutive doses was monitored in six patients (fig. 3). The maximal changes in cardiac index and pulmonary capillary wedge pressure were similar after the first, third and sixth doses. Although a sustained increase in cardiac index was observed in some patients before the sixth dose, the average cardiac index before the sixth dose was not statistically different from the initial control value.

**Clinical Response**

Eight of the 10 patients receiving chronic therapy with WIN 47203 were substantially improved after 1 week of therapy. Their weight remained unchanged, and fatigue and dyspnea were reduced at rest and during exercise. An average increase in maximal oxygen uptake of 1.0 ml/kg/min (range 0.5–2.2 ml/kg/min) confirmed the symptomatic improvement. However, almost all of the patients noticed that the initial clinical benefits lasted 3–5 hours after oral administration; thus, their symptoms often returned before the next.

![Figure 1. Stroke volume index and pulmonary capillary wedge pressure in 11 patients during the control period (closed circles) and at maximum response (open circles) after i.v. and oral WIN 47203. Values are mean ± sd.](image-url)
dose. Patients 6 and 9, who were not clinically improved, were readmitted after 2 and 3 weeks, respectively, of chronic therapy. After withdrawal of the drug, their clinical and hemodynamic status deteriorated (fig. 4). Reinstitution of WIN 47203 reversed the deterioration in both patients. Patient 3 was readmitted elsewhere for ventricular tachycardia and hemodynamic deterioration after 3 weeks of therapy. WIN 47203 was discontinued for the patient’s personal, nonmedical reasons, and the patient remained in severe chronic heart failure. All the remaining patients were further improved after 4 weeks of therapy with WIN 47203. Their weight remained constant. Maximal oxygen uptake increased from 9.0 ± 1.9 to 11.6 ± 2.5 ml/kg/min (p < 0.01 vs control) (fig. 5). Although less remarkable than after 1 week of WIN 47203 therapy, a recrudescence of congestive symptoms just before the next dose was still observed by some patients. No overt clinical manifestations of toxicity were observed during the 4 weeks of therapy. No electrocardiographic changes were noted on serial tracings or rhythm strips. Blood platelet count and serum glutamine oxaloacetic transaminase were unchanged (276 ± 92 vs 273 ± 96 × 10⁹/mm³ and 28 ± 9.6 vs 26.1 ± 14.3 Karmen units/ml, respectively).

Discussion

The present study shows that WIN 47203, which is a relatively more potent analog of amrinone, improves left ventricular performance when administered intravenously and orally to patients with severe chronic heart failure. Chronic administration of WIN 47203 produces sustained clinical improvement and increases maximal oxygen uptake as early as 1 week after initiation of therapy.

Amrinone has been shown to substantially augment ventricular performance and to improve exercise capacity in patients with severe heart failure refractory to therapy with digitalis glycosides, diuretics and vasodilators.5-7 These benefits were partially vitiated by side effects, including thrombocytopenia, which appeared to be dose-related, and gastrointestinal symptoms.8 This latter problem was most often the limiting factor of amrinone use in patients who were less severely compromised. WIN 47203 is 20–30 times more potent than amrinone in both in vitro and in vivo animal studies.9 The present study suggests that i.v. or oral WIN 47203 is more potent than amrinone in man as well. Thus, it was of interest to see whether administration of relatively lower doses of the more potent analog of amrinone would induce comparable hemo-
dynamic and functional benefits with the avoidance of adverse effects such as thrombocytopenia and gastrointestinal disturbances. Thus far, in patients treated for up to 4 weeks, this has been the case.

Since our experience with amrinone suggested a poor correlation between the magnitude of acute hemodynamic improvement achieved and the long-term clinical results, the aim of the i.v. and oral titration of WIN 47203 in the present study was to increase cardiac index by at least 30% or to greater than 2.5 l/min/m² without trying to attain the plateau of the dose-response curve. Thus, higher doses would probably produce even greater hemodynamic changes, although a substantial reduction in pulmonary capillary wedge pressure may limit the benefit of higher doses of the drug in some patients.

When WIN 47203 is administered every 6 hours, the initial and optimal symptomatic improvement is not fully sustained to the end of the dose period. This suggests that the half-life of WIN 47203 in man is relatively short. Therefore, more frequent administration or a sustained-release form of the drug will be required to achieve a continuous effect throughout the day. Indeed, pulse therapy, which might afford unique benefits during an earlier stage of the disease process, was not particularly advantageous nor was it well tolerated in the presence of severe chronic heart failure.

As with amrinone, the hemodynamic mechanisms by which WIN 47203 improves cardiac performance are complex. Both an increase in myocardial contractility and a decrease in impedance to left ventricular ejection probably contribute to the hemodynamic effects of WIN 47203. Its positive inotropic action has been observed in both in vitro and in vivo experiments with normal and failing canine hearts. In these studies, i.v. and oral WIN 47203 increased left ventricular rate of pressure development by 90%. Although the decreased impedance could be due to a withdrawal of heightened sympathetic tone, a direct vasodilator action of WIN 47203 is also present. This drug significantly lowers diastolic blood pressure in the hind limb preparation. To what extent the improvement in cardiac performance resulted from the positive inotropic action and from the direct vasodilator action of WIN 47203 cannot be stated at the present time.

Like amrinone, WIN 47203 does not increase myocardial contractility through activation of the mechanisms attributed to digitalis glycosides or to catecholamines. WIN 47203 has similarly been demonstrated to inhibit phosphodiesterase from guinea pig heart tissue. Although a positive correlation has been found in the guinea pig heart between the degree of phosphodiesterase inhibition and peak inotropic response produced by WIN 47203, there appears to be a temporal dissociation between the inotropic effect and the rise in cyclic AMP. Thus, the positive inotropic effect may not be directly related to the phosphodiesterase inhibition, and the mechanism of action of WIN 47203 remains to be elucidated.

Chronic therapy with WIN 47203 decreased symptoms of heart failure and increased maximal oxygen uptake during exercise in our patients. The augmentation of maximal oxygen uptake was similar to that after amrinone. Since the increase in maximal oxygen uptake was observed as early as 1 week after the initiation of therapy, it appears likely that improved cardiac performance and oxygen delivery to exercising muscles was responsible. Subsequently, an amelioration of symptoms and increased physical activity at submaximal work loads afforded by WIN 47203 therapy may have contributed to the further increase in maximal oxygen uptake at 4 weeks.

Chronic administration of WIN 47203 for 4 weeks was very well tolerated. Only a single untoward event occurred — ventricular tachycardia in a patient who had been treated with procainamide for nonsustained runs of ventricular tachycardia documented before therapy with WIN 47203. We do not know whether WIN 47203 contributed to the genesis of the ventricular tachycardia. However, no overt clinical or laboratory manifestations of toxicity were observed in the remaining patients. Thus, if long-term administration of WIN 47203 is well tolerated, this drug appears to be very promising for the treatment of chronic heart failure.

References
The Neurohumoral and Hemodynamic Response to Orthostatic Tilt in Patients with Congestive Heart Failure

T. Barry Levine, M.D., Gary S. Francis, M.D., Steven R. Goldsmith, M.D., and Jay N. Cohn, M.D.

SUMMARY Thirty-five patients with varying degrees of congestive heart failure were subjected to 60° upright tilt. Eight of the patients with normal resting hemodynamics had elevated resting plasma norepinephrine levels (PNE) (p < 0.001), but their response to upright tilt was similar to that in normal subjects: All had increases in heart rate, plasma norepinephrine (from 263 ± 32 to 483 ± 78 pg/mg, p < 0.02) and plasma renin activity (from 4.8 ± 0.9 to 13.7 ± 7.6 ng/ml/hour, p < 0.05). In 27 patients with high resting pulmonary wedge pressure and low cardiac index, resting PNE was higher (668 ± 71 ng/ml), but PNE, plasma renin activity and heart rate did not increase significantly during tilt despite a fall in pulmonary capillary wedge pressure and cardiac index. In 18 of these patients, PNE rose during tilt, whereas in nine it did not change or fell; the resting hemodynamics and the hemodynamic response to tilt were not significantly different in these two groups. These data suggest that an abnormality of mechanoreceptor or baroreceptor function is common in patients with CHF. This abnormality corresponds in part to the severity of the resting hemodynamic abnormality, but among patients with severe CHF, the reflex neurohumoral abnormality may provide independent information about the severity of the disease.

Upright tilt normally induces a fall in cardiac filling and stroke volume that elicits a neurohumoral response characterized by increases in circulating norepinephrine (PNE) levels and plasma renin activity (PRA). This neurohumoral response is thought to play an important role in the increases in heart rate and systemic vascular resistance that maintain arterial pressure in the upright position. The stimulus for this neurohumoral response appears to reside primarily in the cardiopulmonary area through mechanoreceptors at the junctions of the vena cava and right atrium and the pulmonary veins and left atrium, and in the left ventricle. The importance of this neurohumoral response in the support of arterial pressure is reflected by evidence that pharmacologic or pathologic inhibition of this response leads to orthostatic hypotension.

In congestive heart failure (CHF), PNE is usually increased and PRA is frequently increased. If these increased plasma levels are indicative of heightened activity of these neurohumoral vasoconstrictor systems, then the stimulatory response to orthostatic stress may be altered. An understanding of the circulatory and humoral response to this stress also might provide insight into the mechanism of the heightened sympathetic and renin-angiotensin activity in CHF.

In the present study, we examined the response to orthostasis in patients with symptoms of CHF and widely divergent resting hemodynamics. Responses in this group were compared with those in a group of normal subjects subjected to the same orthostatic stress.

Methods

Thirty-five patients (31 men and four women), ages 20–80 years (mean 55.1 years), who had varying degrees of CHF were studied. All patients had been limited symptomatically by dyspnea on exertion, orthopnea or exercise intolerance for at least 6 months. All had cardiomegaly, as defined by a cardiothoracic ratio exceeding 0.5 on a standard chest x-ray. Twenty-two patients were classified as having ischemic cardiomyopathy on the basis of a history of angina and myocardial infarction (angiography demonstrated significant coronary artery disease in 15 of these patients), and 13
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