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Current therapy for heart failure remains inadequate. New positive inotropic agents that augment myocardial contractility have been introduced. The positive inotropic effects of these nonglycoside, nonsympathomimetic agents are due, at least in part, to inhibition of cardiac phosphodiesterase activity and hence to an increase in myocardial cyclic AMP levels. These agents also have vasodilator properties through their effects on the enzyme phosphodiesterase in the vascular smooth muscle. Recent developments in the preclinical pharmacology, mechanism of action, and clinical experience with these new inotrope vasodilators are presented in this review. The role these drugs will play in revising our therapeutic strategy in congestive heart failure remains to be defined. (Henry Ford Hosp Med J 1986;34:188-92)

Current therapy for heart failure is aimed at improving myocardial contractility by reducing volume overload or systemic vascular resistance. Digitalis glycosides and sympathomimetic drugs have long been used to improve the contractile state of the myocardium. The efficacy of chronic digitalis therapy in patients with heart failure and sinus rhythm has recently been challenged (1), and sympathomimetic agents are limited by their chronotropic side-effects and their need for intravenous administration.

The requirements of a clinically useful inotropic agent have been summarized in a recent review by Braunwald and Colucci (2). An ideal agent should produce hemodynamic improvement (both at rest and with exercise), have persistent clinical and hemodynamic effects, be well tolerated and relatively free of side-effects, and prolong survival. No such agent currently exists. Several "new" positive inotropic agents are undergoing trials, including a new class of nonglycoside, nonsympathomimetic drugs.

Most inotropic agents stimulate myocardial contractility by either inhibition of Na^+/K^+ ATPase, activation of membrane-bound adenylcyclase, or inhibition of cyclic AMP phosphodiesterase (3). Recently, a new class of drugs which increase calcium sensitivity of the myofilaments partly by increasing the affinity of troponin to calcium has been described (4). This review focuses primarily on one class of these newer inotropic agents that have phosphodiesterase inhibitory properties and potential as therapeutic agents in the management of patients with heart failure.

Preclinical Evaluation of Positive Inotropic Efficacy of Phosphodiesterase Inhibitors

The newer agents being developed for treatment of heart failure generally fall into three main classes of chemical structure: 2(1H)-pyridones, also referred to as bipyridines, which include amrinone and milrinone; 2H-imidazol-2-ones which include enoximone (MDL 17,043) and piroximone (MDL 19,205); and 4,5-dihydro-3(2H)-pyridazinones of which imazodan (CI-914) and CI-930 are the most prominent examples. Thorough characterization of preclinical pharmacology including positive inotropic efficacy and studies designed to elucidate the mechanism of action have been reported for these agents and are summarized here briefly.

Amrinone and milrinone

The preclinical pharmacology of amrinone and milrinone has been studied extensively (5,6). The two agents have similar properties, with milrinone characterized as 10 to 30 times more potent than amrinone. The cardiovascular responses to amrinone have been evaluated in vitro and in vivo in dogs, cats, monkeys, and man. In vitro treatment of isolated cat atria and papillary muscles with amrinone (3 to 1000 µg/mL) produces dose-dependent increases in atrial and papillary muscle-developed tension (5). Intravenous administration of 1 to 10 mg/kg of amrinone to anesthetized dogs produces dose-related increases in contractility (dP/dtmax), slight increases in heart rate, and slight decreases in blood pressure (5). Oral doses of amrinone to conscious dogs (1 to 10 mg/kg) produce an increase in cardiac contractile force with a long duration of action. Similarly, intravenous administration of 0.01 to 0.1 mg/kg of milrinone to anesthetized dogs produces significant changes in contractility (23% to 87%), whereas heart rate and blood pressure are relatively unaffected (6). Oral doses of milrinone (0.1 to 1.0 mg/kg) to conscious dogs produce a dose-related increase in contractility.

Table 1
Positive Inotropic Effects of New Agents for Congestive Heart Failure in Conscious Dogs

Compound (Reference)	Dose (mg/kg)	% Increase Contractility
Amrinone (11)	10.0	45
Milrinone (11)	1.0	45
Enoximone (7)	10.0	49
Piroximone (8)	3.0	54
Imazodan (11)	1.0	40
CI-930 (11)	0.1	42

Table 2
Inhibition of Guinea Pig Cardiac Phosphodiesterase by New Cardiotonic Agents: Theophylline and Papaverine (14)

	IC_{50} (μmol/L)				
	PDE I		PDE II		PDE III
Agent	cAMP	cGMP	cAMP	cGMP	cAMP
Amrinone	>1000	>1000	720	580	46
Milrinone	310	340	220	200	2.5
Enoximone	>1000	>1000	860	450	14
Imazodan	>1000	>1000	750	530	8.2
CI-930	820	>1000	400	360	2.9
Papaverine	24	27	6.0	5.1	3.8
Theophylline	230	310	210	170	340

Enoximone and piroximone

The in vivo and in vitro pharmacology for enoximone and piroximone have been extensively evaluated (7,8). In the anesthetized dog, enoximone (7) and piroximone (8) (0.1 to 10 mg/kg) result in a dose-related positive inotropic response accompanied by a minor increase in heart rate and a minor decrease in blood pressure. These hemodynamic changes were not altered by alpha or beta blockade (9,10). Both compounds lead to a vasodilatory response in the canine pump-perfused hindlimb preparation. This action was not attenuated by alpha, beta, cholinergic, or histaminergic blockade, thus indicating that these compounds produce vasorelaxation by a direct mechanism (9,10). Oral administration of enoximone (7) and piroximone (8) to conscious dogs produces a dose-related increase in contractility, with piroximone being approximately three times as potent as enoximone (Table 1).

Imazodan (CI-914) and CI-930

Studies on imazodan (11-14) and CI-930 (11) have been reported. Imazodan has a dose-related increase in positive inotropic activity in excised guinea pig atrial and rabbit papillary muscle preparations. In anesthetized dogs, imazodan (0.001 to 1.0 mg/kg intravenously) increases myocardial contractility of 10% to 150% and decreases aortic blood pressure up to 31%. Minimal heart rate changes occurred relative to the positive inotropic responses. The positive inotropic responses were not blocked by propranolol. Forelimb perfusion studies in the anesthetized dog showed that imazodan also produces a direct peripheral vasodilator action. CI-930 has similar actions to those of imazodan with an approximate fivefold to tenfold increase in potency. Table 1 describes the relative oral potencies of amrinone, milrinone, enoximone, piroximone, imazodan, and CI-930 in the conscious dog (7,8,11). As evident from these data, CI-930 is the most potent of these agents.

Mechanism of action

Since the pioneering work of Sutherland and Rall (15), who first described the role of cyclic AMP as the "second messenger" which mediates the response of cells to hormones and neurotransmitters, research into many aspects of cyclic nucleotide metabolism has expanded significantly. Regarding potential biochemical mechanisms to augment myocardial contractility, phosphodiesterase inhibition remains an attractive mechanism. Inhibition of cAMP phosphodiesterase within the myocardial cell and the consequent increase in intracellular cAMP serve to open the calcium slow channel. The increased intracellular concentration of calcium entering from the slow channel causes the release of additional calcium stored in the sarcoplasmic reticulum, which in turn initiates contraction via interaction with the contractile protein, troponin C.

Recently, several different molecular forms (isozymes) of phosphodiesterase have been separated from tissues of several species and characterized kinetically (16). In cardiac tissue isolated from guinea pigs, three molecular forms of phosphodiesterase exist.

Classical inhibitors of phosphodiesterase (PDE), ie, theophylline, isobutylmethylxanthine (IBMX), and papaverine, inhibit nonselectively all three forms of PDE. Of considerable interest and significance was the discovery that the new cardiotonic agents described in this review inhibit selectively the cyclic AMP specific form (PDE III) relative to their effects on PDE I and II. The effects of several cardiotonics on inhibition of cardiac PDE III are compared in Table 2 (17).

By applying a linear regression analysis, an excellent correlation between inhibition of PDE III in vitro and positive inotropic activity in vivo across several structural classes was identified. This correlation strongly suggests that inhibition of cardiac PDE III represents a principal component of the positive inotropic action of these classes of compounds (11). Furthermore, all of the newer agents described possess vascular relaxant effects which may be associated with inhibition of one of the molecular forms of PDE present in vascular tissue (17).

Clinical Experience with Phosphodiesterase Inhibitors

Amrinone and milrinone

Amrinone, a bipyridine derivative, the prototype of this generation of inotropic agents, has recently been approved for intravenous use in patients with congestive heart failure. Both intravenous and oral forms of the drug have been shown to improve hemodynamics and myocardial energetics at rest and with exercise (18,19). Parenteral amrinone has hemodynamic effects similar to dobutamine in patients with congestive heart failure (20). While the hemodynamic effects are sustained during amrinone infusion, tachyphylaxis seems to occur after eight to 24 hours of dobutamine infusion. Comparison of dobutamine,

dopamine, and amrinone showed that amrinone caused less chronotropic response than dopamine (21).

The initial intravenous dose of amrinone is 0.5 to 1.5 mg/kg, given as a bolus, followed by an infusion of between 5 to 10 mg/kg/min, titrated to the hemodynamic response. The onset of action is rapid, occurring within ten minutes; however, its half-life is three to six hours which may be a disadvantage in some clinical settings of acute heart failure. Potential side-effects include hypotension, reversible thrombocytopenia, fever, gastrointestinal intolerance, and hepatotoxicity (22). The initial enthusiasm for the use of oral amrinone for long-term therapy has diminished because the results of double-blind, placebo-controlled studies failed to show significant benefits in exercise capacity or cardiac function (23,24).

Milrinone is another bipyridine derivative, with ten to 30 times the potency of amrinone. Several studies have demonstrated its beneficial hemodynamic and clinical effects (25). Milrinone is better tolerated than amrinone and does not have the hematopoietic side-effects. Since it is largely excreted through the kidneys, milrinone should be used with caution in patients with renal dysfunction. Baim et al (26) have reported their experience of long-term therapy with milrinone in 100 patients. Side-effects leading to drug withdrawal including headache, muscular weakness, insomnia, and increased ventricular arrhythmias occurred in only 4% of the patients. The drug was well tolerated with hemodynamic and clinical improvement; however, the mortality rate was 63% after one year of therapy. Advanced functional class, impaired renal function, reduced ejection fraction, and the presence of nonsustained ventricular tachycardia on 24 hr holter monitoring were some of the predictors for early mortality. In a study of 20 patients on chronic milrinone therapy, Holmes et al (27) noted increased complex ventricular arrhythmias in 40% of the patients. Further studies comparing placebo to milrinone are needed to characterize the utility of this drug.

Enoximone (MDL 17,043) and piroximone (MDL 19,205)

MDL 17,043 (enoximone) is an imidazole derivative with similar hemodynamic effects to those of amrinone and milrinone (28). The hemodynamic effect of intravenous MDL 17,043 in patients is comparable to dobutamine except that dobutamine has a slightly higher chronotropic effect (29). Oral MDL 17,043 is rapidly absorbed with an elimination half-life of about 20 hours. The drug is well tolerated during follow-up, and side-effects include gastrointestinal distress, headache, agranulocytosis, ventricular ectopy, and abnormal liver function tests (28). No improvement in survival was demonstrated in patients treated with this drug despite the acute hemodynamic benefit and symptom palliation.

Piroximone (MDL 19,205) also shows favorable hemodynamic effects when administered acutely (30). Petein et al (31) noted that despite the acute hemodynamic effects and short-term clinical benefit, long-term administration of oral MDL 19,205 was not effective in symptom palliation. The apparent lack of favorable long-term effect may be related to the patient population or dosage used or may reflect the general use of these "new" inotropic agents.

Imazodan (CI-914) and CI-930

We have recently reported the hemodynamic effects of a new type III phosphodiesterase inhibitor, CI-914, in 13 patients with severe congestive heart failure (32). CI-914 is a dihydro-pyridazinone derivative and in vitro has ten times the potency of amrinone (33). It shows only slight stimulation of calcium release and has no direct effect on sarcoplasmic reticulum, mitochondrial function, adenylcyclase, or on NA^+/K^+ ATPase activity (33).

An increase in cardiac index of 26% (P < 0.01), a decrease in pulmonary wedge pressure of 21% (P < 0.001), a right atrial pressure of 30% (P < 0.02), and systemic vascular resistance of 23% (P < 0.02) occurred following intravenous CI-914 administration without significant changes in heart rate, mean blood pressure, and pulmonary vascular resistance. Similar changes were noted with oral administration of the drug. Peak plasma concentration after oral dosage occurred 2.3 ± 2.2 hours after ingestion; however, the elimination of this drug appears to be nonlinear. The hemodynamic effects of the drug were sustained ten to 12 hours after oral administration (Figure) and appear to be related to the combined effect of the drug as well as its active N-acetyl metabolite (17).

Seven of the 13 patients who received long-term therapy for 12 weeks or more showed improvement in functional class and exercise capacity, although no significant change in left ventricular ejection fraction was seen. Three of these patients remain on therapy after 20 months and have had improvement in symptoms. The drug was well tolerated without gastrointestinal, hematopoietic, and hepatic side-effects. One patient developed symptomatic ventricular tachycardia while on the drug and was treated with antiarrhythmic agents. Although the CI-914 agent has some promising characteristics as an inotrope, further studies are required to elucidate the exact mechanism of action and efficacy.

CI-930 is also a dihydro-pyridazinone derivative, a structural analogue of CI-914, except for the presence of an additional methyl group on position five of the pyridazinone ring. It is three to five times more potent in vitro than CI-914 (11). We studied the hemodynamic response to this drug in ten patients with severe congestive heart failure (34). Significant acute hemodynamic effects with a 35% increase in cardiac index (P < 0.002), a 35% decrease in pulmonary wedge pressure (P < 0.05), a 40% decrease in right atrial pressure (P < 0.05), and a 26% decrease in systemic vascular resistance (P < 0.05) occurred 15 minutes following intravenous CI-930. Similar effects were noted after oral CI-930, and the hemodynamic effects were sustained 12 to 18 hours after the oral dose. The sustained hemodynamic effects of this drug are most likely a result of an active N-acetyl metabolite (35) rather than a direct action of the drug because its plasma half-life was only 1.1 to 6.4 hours in the patients studied. The drug was well tolerated and has potential for treatment of heart failure. The role of this new class of inotropic agents in the management of patients with heart failure needs to be defined. Although broadly classified as phosphodiesterase inhibitors, these inotropic agents differ significantly from the classic PDE inhibitors in that they selectively inhibit the PDE isoenzyme III.

Several open label studies of the new agents claim superiority in symptom palliation for patients treated but inadequately controlled with conventional drug therapy (18,25). However, results of the only reported placebo-controlled trial with amrinone did not show significant improvement in exercise capacity or cardiac function (23,24). Evidently cardiac deterioration continues despite the hemodynamic and clinical benefits during long-term therapy (15). Theoretical concerns have been raised about the rationale for stimulating the failing myocardium (36). Whether these agents accelerate disease progression by exhausting the myocardial energy stores or adversely influence survival by aggravating ventricular arrhythmias is unclear. The adverse effects may be related to an exacerbation of ischemia with use of these agents or may be due to the direct toxic effects of elevated cyclic AMP levels (37). These concerns are best addressed in careful, long-term, placebo-controlled trials for each of these agents. These trials are currently underway, and the results will soon be reported. These drugs are still investigational and need to be tested further as potential therapeutic agents in the management of patients with heart failure.

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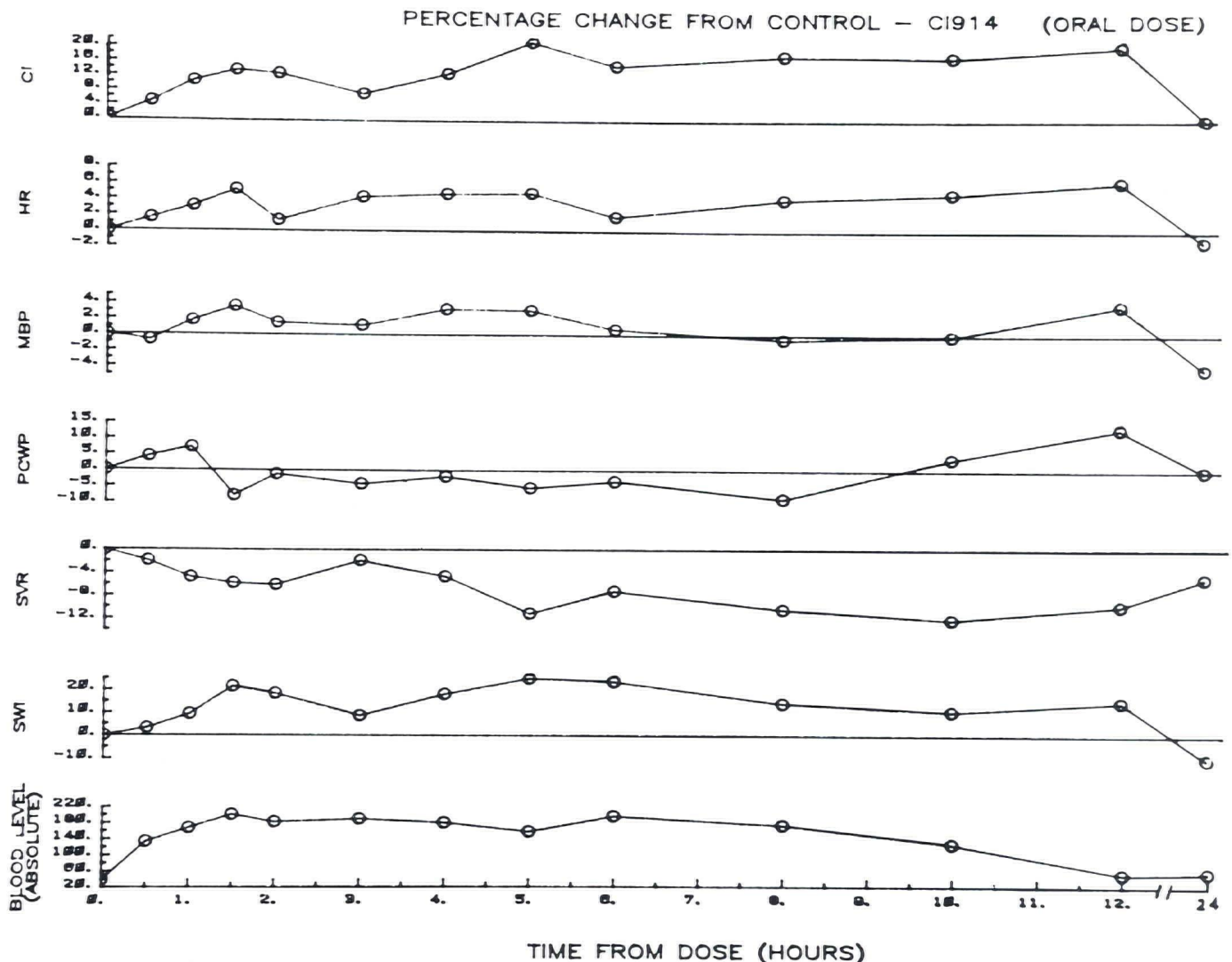
Figure—Time course of the hemodynamic response to oral CI-914 in 13 patients. CI = cardiac index, HR = heart rate, MBP = mean systemic arterial pressure, PCWP = pulmonary capillary wedge pressure, SVR = systemic vascular resistance, and SWI = stroke work index. (From Jafri SM, Burlew BS, Goldberg AD, Rogers A, Goldstein S. Hemodynamic effects of a new type III phosphodiesterase inhibitor (CI-914) for congestive heart failure. Am J Cardiol 1986;57:254-9. Reprinted with permission.)

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