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Clinical Aspects of Phosphodiesterase Inhibitors

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The treatment of patients with congestive heart failure has undergone considerable change over the past 20 years. Prior to the 1980s therapy for heart failure primarily consisted of digitalis and diuretics. The recent introduction of angiotensin-converting enzyme (ACE) inhibitors has improved patients' quality of life and long-term survival (1,2). However, digitalis glycosides remain the only inotropic agents approved for oral administration. The search for a new inotropic drug initially included beta-agonists but these drugs were abandoned because of tolerance to their effects and a high death rate, presumably due to aggravation of underlying arrhythmias. In the last 10–15 years, the focus of the effort to develop new inotropic agents has been on phosphodiesterase (PDE) inhibitors.

The first clinical study on the new PDE inhibitors was published in 1978 (3). Since then several agents have been tested with varying results. Amrinone and milrinone are available for use intravenously but none of the PDE inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for oral administration. This chapter will review the results of clinical trials involving these drugs (Table 1).

I. MECHANISM OF ACTION

The contractile state of the heart is regulated in part by the adenyl cyclase (AC)–cyclic adenosine monophosphate system (cAMP). Adenyl cyclase is a membrane-bound protein, which, when stimulated by an appropriate effector (i.e., beta-agonists, prostaglandin E-1, etc.), increases cAMP (4,5). cAMP then phosphorylates an inactive protein kinase to its active form. These activated kinases phosphorylate myocardial slow-calcium channels, which increases the influx of calcium into the cell. This calcium then becomes available for loading of intracellular stores (i.e., predominantly the sarcoplasmic reticulum). Myofilaments are then activated when the cal-

Table 1 PDE Inhibitors (generic names)

Bipyridines
Amrinone (WIN 40680)
Milrinone (WIN 47203)
Imidazolones
Enoximone (MDL 17,043)
Piroximone (MDL 19,205)
Pyridazinones
Imazodan (CI-914)
CI-930

cium stored by the sarcoplasmic reticulum is released and interacts with troponin-C. This causes a conformational change in tropomyosin, resulting in cross-bridging of actin and myosin, which produces myofibril shortening and an increase in force. The release of calcium from troponin-C requires ATP if action–myosin dissociation is to occur.

cAMP is degraded by PDE. Any compound that prevents the degradation of cAMP (e.g., by blocking PDE) will cause an increase in intracellular calcium and, thus, an inotropic effect. The PDE inhibitors exert their positive effects on myocardial contractility via PDE III, which is the form of PDE in the heart (6).

In addition to increasing myocardial contractility, PDE inhibitors also produce arterial vasodilation. The hemodynamic changes occurring in patients include an increase in cardiac output, a decrease in systemic vascular resistance, and a reduction in left and right ventricular filling pressures. Heart rate and blood pressure are usually not affected significantly.

II. THE BIPYRIDINES

A. Amrinone

Amrinone was the first of the new PDE inhibitors to be investigated for the treatment of CHF as a positive inotrope (3,4,7). Amrinone was initially tested as an oral and intravenous drug. The intravenous form of amrinone was approved by the FDA in 1984. However, significant gastrointestinal effects and thrombocytopenia with the oral form of amrinone led to its withdrawal from clinical trials (5). Accordingly, only parenteral amrinone will be reviewed.

1. Pharmacokinetics

Amrinone treatment is initiated by an intravenous loading dosage of 0.75 μg/kg over 2–3 min followed by a maintenance dosage of 5–10 μg/kg/min. A second bolus may be given 30 min after the initial dose if warranted. The daily dosage should not exceed 10 mg/kg/day to avoid thrombocytopenia (8). Amrinone has a half-life of 3.6–5.8 hr. Some recent studies have suggested that the half-life may be as long as 12 hr in patients with congestive heart failure (9,10). Ten to 40% of the drug is excreted unchanged in the urine, while the remainder is conjugated in the liver before urinary excretion (9,10). Accordingly, the effects of the drug should be monitored closely in patients with impaired renal function.

2. Hemodynamic Effects

Like other PDE inhibitors, amrinone is not only a positive inotropic agent but also possesses vasodilatory properties that make it a potent preload and afterload reducer (3,11–17; Table 2). The hemodynamic effects of amrinone in a representative sample of clinical studies are summarized in Table 2. Amrinone has minimal effects on heart rate and mean arterial blood pressure in most patients. However, in patients with left ventricular filling pressures below 10–15 mmHg, reflex tachycardia and hypotension may occur (18). Blood pressure must be closely monitored to adjust the dosage because of amrinone's vasodilatory properties. Although the inotropic effect of the drug would be expected to aggravate pre-existing myocardial ischemia by raising the workload of the heart, myocardial oxygen demand appears to be decreased secondary to a reduction in resting wall tension (14).

3. Electrophysiological Effects

Patients with congestive heart failure have a high incidence of sudden death. The cause of death is usually either pump failure or fatal arrhythmias. Approximately 90% of patients with severe heart failure have frequent multiform ventricular extrasystoles and as many as 70–80% have episodes of ventricular tachycardia (8,16–

Table 2 Hemodynamic Data on Current Phosphodiesterase Inhibiting Drugs: Amrinone and Milrinone

		Mean % Change From Baseline							
Dosage	Pts(n)	CO	PCWP	RA	SVR	PVR	HR	MAP	Ref
Amrinone									
40 μg/kg/min IV	8	+37	−17	−49	−23	–	NS	NS	11
40 μg/kg/min IV	8	+46	−25	−37	−19	–	NS	NS	12
0.75–3.0 mg/kg IV	8	+49	−26	−26	−29	−39	NS	NS	13
0.50–3.5 mg/kg IV	8	+46	−46	−33	−32	−24	NS	NS	3
2.5 mg/kg IV	9	+69	−16	−18	−40	−50	NS	NS	14
1.5–3.5 mg/kg IV	11	+47	−41	–	–	–	NS	NS	15
10–20 mg/kg/min IV	14	+30	−20	−21	−17	−8	NS	NS	16
1.18–1.50 mg/kg IV	6	+13[a]	−17	−18	−18	−5	+8	−2	17
	8	+44	−46	−42	−32	−24	+1	−7	
Milrinone									
125 μg/kg±36 IV	18	+45	−39	−38	−37	–	+8	−13	24
67±13 μg/kg/min IV	10	+50	−29	−38	−34	–	+3	−8	25
50–75 μg/kg LD flu	79	+34	−26	–	−25	–	+7	−6	26
0.5–1.0 μg/kg/min									
12.5 to 75 μg/kg IV	15	+55	−45	−54	−36	–	+11	−15	27
12.5 to 75 μg/kg/min IV	7	+76	–	−53	–	–	+8	−13	28
25 μg/kg LD	11	−49	−40	−42	−33	–	−2	−4	29
7.5 mg po	11	+−	–	–	−34	–	+1	−5	30
25 μg/kg IV	7	+−	−23	–	−29	–	+6	+1	30

HR, heart rate; MAP, mean arterial blood; RA, right artrial pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; CO/CI, cardiac index; SVR, systemic vascular resistance.

[a]Cardiac output.

19). Since any compound that increases cAMP has the potential to be arrhythmogenic, it is essential to study the electrophysiological properties of these drugs.

Naccarelli and colleagues performed hemodynamic and electrophysiological studies in 15 patients with New York Heart Association (NHYA) class II–IV heart failure before and during infusion with amrinone (16). Vasoactive and antiarrhythmic drugs were discontinued at least 5 half-lives before the initial baseline study. Amrinone had no significant effect on PR QRS, QTc, AH, or HV intervals. Ventricular effective refractory period and maximal corrected sinus node recovery time also were unaffected. However, there was a statistically significant decrease in atrial effective refractory period, but by only 6%. There was no change in the inducibility of ventricular tachycardia by programmed electrical stimulation.

4. Side Effects and Drug Interactions

Intravenous amrinone should not be given in the same tubing as furosemide and must be prepared in solutions not containing dextrose to prevent precipitation. It should be utilized within 24 hr of preparation to optimize effect. Hypotensive episodes have been reported when it is used concomitantly with disopyramide (8). Additional side effects that have been reported include gastrointestinal (GI) intolerance (anorexia, nausea, abdominal pain, and diarrhea), central nervous system manifestations (headache, lightheadedness, and paresthesia), and dose-dependent thrombocytopenia (requiring daily monitoring of platelet counts (5,8).

B. Milrinone

Milrinone is a bipyridine with more than 10 times the potency of amrinone on a per milligram basis (5,20–23). Only the intravenous form of the drug received FDA approval in 1987. However, to date, it has not been made available commercially. Initial results with the oral cogener are still in progress and suggest that the drug is effective and well tolerated.

1. Pharmacokinetics

Intravenous milrinone is initiated with a loading bolus of 25–50 μg/kg given over 1 min. The peak effect occurs within 2–5 min. Milrinone has a duration of action that ranges from 30 min to 2 hr and a half-life of approximately 2 hr (5,23). The drug is primarily excreted unchanged in the urine (5).

The oral dosage of milrinone is 7.5–12.5 mg every 4–6 hr to a maximum of 50 mg/day. Onset of action following the oral preparation is between 10 and 30 min. The peak effect of milrinone occurs at 15–20 min and hemodynamic effects persist for approximately 4 hr.

2. Hemodynamic Effects

Studies with intravenous milrinone have demonstrated that milrinone, like amrinone, reduces both preload and afterload in addition to increasing contractility (24–30) (Table 2). Heart rate and systemic arterial pressure are not significantly changed. Monrad et al. reported that these hemodynamic effects are not accompanied by an increase in oxygen demand, suggesting that the increased oxygen consumption expected by an increase in contractility is offset by the salutary effect on preload (24). There does not appear to be significant tolerance to the effects of the drug up to at least 48 hr of therapy (26).

3. Electrophysiological Effects

Davidenko et al. studied the electrophysiological properties of milrinone in canine cardiac false tendons and found that action potential duration was minimally increased by dosages of 10–20 μg/ml (31). Re-entrant arrhythmias were either blocked or facilitated depending on the initial level of the block. Subsequently, Goldstein et al. studied 10 patients with NYHA class III or IV heart failure who underwent electrophysiological studies before and during infusion of milrinone for 18 hr (32). All cardioactive drugs except diuretics were discontinued at least 5 half-lives before baseline measurements were made. The cardiac rhythm was continuously recorded by Holter monitoring for 48 hr before and during a 48 hr infusion of milrinone. Milrinone enhanced 1:1 maximal atrioventricular conduction but did not significantly affect atrioventricular effective or functional refractory periods. Programmed electrical stimulation induced ventricular tachycardia in 5 of the 10 patients at baseline but none during infusion of milrinone. There was a statistically increased incidence of nonsustained ventricular tachycardia, although no patients were classified as having demonstrated proarrhythmic effects. This study suggests that milrinone could be antiarrhythmic or proarrhythmic depending on the patient.

4. Studies with Oral Milrinone

Early studies with oral milrinone have reported improvement in exercise tolerance within a few days to weeks following initiation of the drug (31). However, the results of studies following treatment for several months have been mixed, with some showing a maintained improvement in exercise duration and others no difference from controls (33).

The largest study of oral milrinone included 230 patients with class II or III failure who were randomized to receive milrinone, milrinone and digoxin, digoxin alone, or placebo (33). Diuretics were allowed to supplement therapy in all patients. There was a significant improvement in exercise duration following 3 months with all therapy compared to placebo. However, there was no additive effect of milrinone to digoxin.

A large multicenter trial is currently in progress designed to look specifically at the issue of long-term survival on milrinone as an adjunct to digoxin, diuretics, and captopril in patients with severe failure (34).

5. Side Effects and Drug Interactions

Milrinone appears to be well tolerated with few confirmed side effects. The only statistically significant reported side effect appears to be a mild headache in some patients (34). However, because of the vasodilating effects of the drug, hypotension may occur in patients with pulmonary capillary wedge pressures less than 15 mm Hg.

III. THE IMIDALZOLONES

A. Enoximone

Enoximone is an imidazolone being evaluated for intravenous and oral use (35–45). In addition to inhibition of subfraction III PDE, it also appears to activate slow-calcium channels (35).

1. *Pharmacokinetics*

In most studies, enoximone has been given at a dosage of 0.5–2.0 mg/kg intravenously (IV) at a rate of up to 12.5 mg/min (Table 3). The dosage of oral enoximone is 75–150 mg every 8 hr (37,38). Earlier studies used significantly higher dosages but reported a greater incidence of side effects. The onset of action for the oral dosage is 10 min with a peak effect at 1 hr (44). Enoximone has a half-life of 20 hr and is metabolized to MDL 19,438 with a half-life of 25 hr (44). This metabolite has approximately 20% of the hemodynamic effect of the parent compound in dogs (35).

2. *Hemodynamic Effects*

Enoximone, like other PDE inhibitors, decreases the left ventricular filling pressure and systemic vascular resistance and increases cardiac output (Table 3). Hemodynamic changes correlate positively with increases in dosage (35,36,39). Heart rate is not significantly changed in most patients except at dosages greater than 1.5 mg/kg (36–40). Arterial systemic pressure is usually unchanged or decreased. Preliminary studies with oral enoximone have reported improvements in exercise capacity and symptoms (37,38). Hemodynamic improvement occurs in approximately 90% of the patients initially. However, only 50% of the patients maintained these effects at 4 weeks and 25% when oral therapy is given for more than 3 months (42). Enoximone also increased plasma renin and decreased plasma norepinephrine levels. Arginine vasopressin was not significantly changed (42).

3. *Electrophysiological Effects*

Miles et al. studied the electrophysiology of enoximone in a group of patients with heart failure (41). Most patients were receiving therapy with digoxin and antiar-

Table 3 Hemodynamic Data on Current Phosphodiesterase Inhibiting Drugs: Enoximone and Piroximone

Dosage	Pts(n)	Mean % Change From Baseline							
		CO	PCWP	RA	SVR	PVR	HR	MAP	Ref
Enoximone									
3.0 mg/kg IV	44	+55	−29	−30	−33	–	+6	−5	39
10.5 mg/kg IV	44	+68	−42	−46	−44	–	+13	−14	39
150 mg po	12	–	–	–	–	–	−3	+3	37
50–100 mg po	6	+50	−51	–	−42	−68	−5	−4	38
3.7 mg/kg IV	38	+75	−42	−50	−42	−29	+9	−10	40
18.4 mg/kg po	38	+45	−35	−38	−34	−24	+2	−10	40
3–6 mg/kg po	20	+28[a]	−46	−60	−3	–	+9	–	42
1.5 mg/kg IV	16	+76	−48	−50	−52	−29	+10	−19	43
0.5 mg/kg IV q 15–20	12	+83	−48	−54	−47	−31	+3	−10	44
4.5 mg kg total									
6 mg/kg po q 6	10	+56	−19	−NS	−35	–	NS	NS	45
IV 0.5 mg/kg q 15–20	13	+76	−27	46	−46	−49	+2	−6	46
po 2 mg/kg	13	+76	−15	−25	−39	−45	+5	−2	46
Piroximone									
1.7 mg/kg po	12	+51	−31	−45	−34	−29	+3	−6	47
1.25 mg/kg IV	8	+74	−36	−67	−43	−33	+4	−8	47

Abbreviations as in Table 2.

rhythmic drugs during the study, making it difficult to interpret the results. They reported a small but statistically significant increase in the sinus cycle length, and a decrease in atrial–His, atrial functional refractory period, atrioventricular (AV) nodal effective and functional refractory period, minimal atrial pacing cycle length maintaining 1:1 AV conduction, ventricular effective and functional refractory period when compared with both amrinone and milrinone.

In a double-blind placebo crossover study with oral enoximone, Choraria et al. evaluated 12 patients with NYHA class II–III heart failure for 6 weeks (37). Holter monitoring 2 weeks into the study revealed an increase in premature ventricular complexes and couplets. No R-on-T phenomenon or sustained runs of ventricular tachycardia longer than 10 beats were noted.

4. Side Effects and Drug Interactions

The incidence of adverse effects appears to be dose dependent, increasing considerably when the cumulative dosage exceeds 1.5 mg/kg (35,36,39). Side effects with intravenous enoximone have included hypotension and an increased frequency of new episodes of ventricular tachycardia (39). Up to 7% of the patients had CNS manifestations, 5% had gastrointestinal manifestations, with 4% having other problems. Twenty-eight percent of the patients had > 2 g/dl drop in hemoglobin, which was deemed clinically important (39). Oral enoximone has side effects in as many as 75% of patients although therapy needed to be discontinued in only 7% (44). The major problems affect the gastrointestinal tract and include diarrhea, loose stools, nausea, vomiting, and abdominal cramping (44). Patients may also experience fluid accumulation and thrombocytopenia (5). The absorption of enoximone is reduced in patients taking tetracycline, phenytoin, phenylbutazone, and chlorthiazide (42).

B. Piroximone

Relatively little information is available on this imidazolone compound, which also inhibits PDE III. It has been studied both as an oral preparation and as an intravenous solution. The drug has been given at an intravenous loading dosage of 1.7 mg/kg and then followed by an oral dosage of 0.5 mg/kg (100–400 mg) every 6 hr (48).

Piroximone's hemodynamic effects include an improvement in cardiac output and a reduction in preload and afterload (Table 3). It produces a small but significant decrease in arterial pressure. The drug decreases plasma norepinephrine and raises renin levels. In an initial open-label study, the drug failed to demonstrate any sustained clinical benefits in a group of 11 patients with severe heart failure evaluated over a 2–10 month (mean of 5.6 months) period (48).

The side effects of long-term treatment included diarrhea and worsening of heart failure. Determination of the frequency of this and other side effects will require a greater number of studies in patients.

IV. THE PYRIDAZINONES

A. Imazodan

Few published reports are currently available to determine the usefulness of this drug or its analog CI-930. In vitro it has a potency 10 times that of amrinone (49).

The oral dosage of this medication has ranged from 3 to 30 mg (49,50). Peak plasma levels occur approximately 2 hr after an oral dose is given. There is a

Table 4 Hemodynamic Data on Current Phosphodiesterase Inhibiting Drugs: CI 914 and CI 930

Dosage	Pts(N)	Mean % Change From Basline CO	PCWP	RA	SVR	PVR	HR	MAP	Ref
CI-914									
0.1–30 mg IV	13	+26	−21	−31	−23	−14	+3	+6	49
3.30 mg/kg PO	13	+19	−11	−9	−9	−7	+4	−1	49
CI-930									
0.5–2.1	9	+35	−43	−44	−30	−20	+0	−9	51

Abbreviations as in Table 2.

positive correlation between dosage and maximal blood levels obtained (49). Studies in dogs have demonstrated that imazodan is a coronary vasodilator (50). The drug increases cardiac output and decreases afterload and preload, as do other PDE inhibitors (Table 4).

Oral imazodan appears to be well tolerated with minimal renal, hepatic, or gastrointestinal problems. No significant thrombocytopenia has been noted.

B. CI-930

The initial studies of this drug began in the mid 1980s (50). CI-930 is currently given as an intravenous preparation at a dosage of 0.5–2.1 μg/kg/min. Preliminary data on its hemodynamic effects are shown in Table 4. CI-930 increases plasma atrial natriuretic peptide. There is not sufficient information available to allow us to comment on potential side effects.

V. SUMMARY

The phosphodiesterase inhibitors have inotropic and vasodilator properties. Unlike other drugs that increase contractility, they do not raise myocardial oxygen consumption. However, despite initial optimism about these agents, only intravenous amrinone and milrinone have been approved for use in patients with heart failure to date. The results of trials with oral congeners have not demonstrated clear advantages over other forms of therapy for heart failure. There have also been questions raised about whether these drugs adversely affect patient survival. Trials involving large numbers of patients should provide an answer to this and help to determine whether there is any long-term benefit of therapy with this class of drugs.

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