Phospho Di Esterase Inhibitors In Congestive Heart Failure

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Aggressive therapy is needed in the presence of resistance Acute Left Ventricular Failure, commonly seen after large Myocardial Infarction or following Cardio Pulmonary Bypass if myocardial function may be severely depressed. When Ac. pump failure is so severe that adequate Cardiac Output cannot be maintained, hypotension may ensure despite an elevated Perepheral Resistance, presenting picture of cardiogenic shock. Catecholamines or other sympathomimetic ammies maybe required in this setting. These agents exert potent inotropic effects by stimulation of the beta 1. adrenergic receptors. Both widely used agents Dopamine and Dobutamine have demonstrable positive inotropic value intravenously, still they have clear disadvantages (a) Down regulation of beta adrenergic receptors with reduced inotropic responsiveness[1] (b) An increase in HR and proarrhythmic effects[2,3]) (c) Increased MVO2 consumption[4] (d) Development of tolerance[5]. Their primary limitation by requiring 1.V administration[6].

Hence new inotropic agent to improve the limited contractile reserve of the heart would be important in treatment of CHF. The ideal inotropic agent should meet several criteria including it must be safe, relatively free of significant side effects. It must be able to improve haemodynamics at rest and with exercise and must be free of adverse haemodynamic effects such as vaso contriction and finally it must, if not prolong life, at least improve quality of life[7].

A new class of drugs has now been described that have both potent positive inotropic and vasodilator effects. They are non glycoside, non catecholamine drugs. Initial reports have documented that these drugs do not inhibit NQ-K-AtPase- nor is their inotropic effect diminished by reserpine induced depletion of endogenous catecholamine stores, pretreatment with Beta adrenergic or Alpha adrenergic blocking agent, H2 antagonists that block prostaglandin synthesis or drugs that selectively block the fast inward channel. Hence they are reffered as "non-glycoside-nonsympathomimetic" positive inotropic agents[8].

Although structurally dissimilar from one another and from the methyxanthines, these agents appear to inhibit phosphodiesterase (PDE) fraction III, the cyclic AMP specific cardiac phosphodiesterase, selectively and potently. Blocking the normal breakdown of cyclic nucleobide by PDE should also increase intracellular cyclic AMP levels increase contractility. Although the traditional PDE inhibitors, e.g., theophylline, exert this effect, but they are non selective and non potent.

Certain failure of inotropic effects of PDE inhibitors are predictable. A vasodilator effect accompanies the cardiac stimulation and a tendency towards tachycardia and possible aggravation of arrhythmias might be anticipated. Since the drug exerts this effect directly on cyclic AMP concentration and not on a receptor mechanism, tolerance due to a receptor down regulation would not be anticipated. Furthermore, inotropic effects of the drug would be expected to be most prominent when cyclic AMP levels are high due to Adenylate cyclose stimulation such as by sympathetic discharge.

The Bipyridine and Imidazolone derivatives are two groups of PDE inhibitor most studied as inotropic patient with CHF.

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Bipyridine Derivatives
1. Amrinone
2. Milrinone

Imidazolone Derivatives
1. Enoximone
2. Piroximone

Bipyridine Derivatives

1. **Amrinone**

Amrinone (5-Amino-3, 4-bipyridine-6 (IH one) has both inotropic and vasodilator properties. Its inotropic effects are independent of beta receptors, Na-K-AtPase and are at least partly due to PDE inhibition. Recent studies have documented that myocardial AMP does infact rise after exposure to the drug, presumably because of relatively selective inhibition of cyclic nucleotide PDE F III[9].

The acute hemodynamic effects of Amrinone allow immediate attainments of goals such as alleviation of high filling pressures and augmentation of cardiac output. A decline in MVO2 consumption together with a potential enhancement of collateral blood flow with negligible changes on HR and BP[9] indicates, its efficacy in agent for treatment of Ac.LV dysfunction. In cardiogenic shock refractory to catecholamines, the synergistic action of Amrinone may improve prognosis[10]. It is safe and effective agent for "short term" management of patient with CHF[11].

After the initial enthusiasm about clinical efficacy of 1.V Amrinone, results of oral studies on its long term use suggest that oral form of the drug is associated with numerous side effects esp. arrhythmias[12]. Thrombocytopenia[13]. GI disturbance, lack of sustained benefits[15] hence it seems unlikely that it would be helpful in long term management of CHF[16]. Amrinone shows excellent results in short term 1.V administration with substantial improvement in symptomatic and exercise capacity. It invariably produces increase - CO,CI,SV and decreases PCWP, LVEF but similar sustained effects were not seen on long term therapy[17]. Its efficacy seems to be dose related and potentially serious adverse side effects are observed at therapeutically, effective doses that preclude its clinical use.

Milrinone

Milrinone 1-6 dihydro-2 methyl-6-oxy (3,4-bipyridine) -5- Carbonifrile, a similar structure to Amrinone but chemical modification has improved its cardiovascular potency with a relatively lower incidence of adverse effects. It increases cardiac Index and decreases Pulmonary Capillary wedge pressure, right atrial pressure and systemic vascular resistance with I.V. infusion[18]. These effects were even sustained 48 hours of infusion[19]. These beneficial effects were generally seen with higher dose of Milrinone[20]. Beim et. al [21] by summarizing oral Milrinone therapy to 20 patients over a period of 6 months showed sustained 27% increase in resting left ventricular EF.

Besides its vasodilatory effect, Ludmor et al[22] demonstrated 45% increase in positive dp/dt in a dose related manner with a decrease in intracardiac pressures. It is also been demonstrated[23] that a further rise in CI and reduction in Filing pressure with dp/dt unchanged at a higher dose of Milrinone is consistent with a positive inotropic effect. There is a trend towards increased frequency of isolated or repetitive PVCs without evidence of sustained ventricular tachycardia[24]. Similar views also supported by Goldstein[25] that Milrinone does not aggravate existing arrythmias and is unlikely to expose patients to greater risk.

In comparison to pure vasodilator Nitroprusside[26] the reduction in arterial pressure was same but increase in cardiac index and decrease in left ventricular end diastolic pressure gives a strong evidence that Milrinone exerts positive inotropic action that contributes significantly to drugs overall hemodynamic effects and is a potent vasodilator as well. Milrinone has also showed great reduction in right atrial pressure and left ventricular end diastolic pressure and for any given increase in dp/dt it resulted in a greater decrease in systemic vascular resistance than dobutamine[27].

Milrinone is a new bipyridine inotropic agent 10 to 15 times more potent than Amrinone and is active both intravenously and orally and it increases exercise capacity[28] and does not cause increase in myocardial oxygen consumption[29]. Comparative hemodynamic effects studied with Dobutamine[30] and

Nitroprusside shows that Milrinone has significant clinical advantage in short term intravenous treatment of patients with heart failure. However it has been suggested that Milrinone alone or in combination with digoxin has no advantage over Digoxine alone. On the contrary it showed a trend towards increasing ventricular completes and palpitation, however Milrinone alone has relatively lower incidence of adverse side effects and high level of patient acceptability. It does not improve overall mortality in patients with advanced heart failure.

Imidazolone Derivatives Enoximone

Enoximone (1,3, Dihydro-4-Methyl 5{4-(methythio) benzoyl}-24-Imidazole-2-one) has been shown to produce salutory acute hemodynamic effects. It is an imidazole derivative and PDE inhibitor with both positive inotropic and direct vasodilating properties[32]. Neither the inotropic nor the vasodilatory properties of this agent are inhibited by ∝ or B adrenoreceptor, cholinergic or histaminergic blockade[33]. It does show sustained hemodynamic improvement and an associated improvement in myocardial efficiency[34]. It augments myocardial contractility by an increase in peak rate of left ventricular pressure rise of 15% with a decrease in capillary wedge pressure and systemic vascular resistance[35] confirming its efficacy as a positive inotropic and vasodilating agent. Though continuous infusion does show increase in CI by 55% and decrease in PCWP by 44% but the tendency of arrythmias in form of ventricular tachycardia and hypotension was observed[36].

Enoximone in oral form showed a sustained improvement at 26 weeks[37] with increase in exercise capacity. There was also observed increase in radionuclide ejection fraction. Enoximone was well tolerated orally with no adverse side effects including ventricular Tachycardia[38]. In comparison to Dobutamine and Nitroprusside[39], it showed an equal improvement in CI and stroke volume while left ventricular filling pressure was reduced more significantly by Enoximone suggesting it to be a better alternative in comparison to a pure vasodilator or a pure positive inotropic agent. Hence Enoximone given intravenously or orally causes marked hemodynamic improvement in patients with congestive heart failure but its value in long term management of such patients is not clear.

Piroximone

Pyroximone is another orally active imidazole derivative that combines inotropic and vasodilator properties. It has demonstrated improved hemodynamic effects on long term oral administration[40]. Both right and left ventricles were unloaded with oral Piroximone with myocardial oxygen extraction being unchanged[41] suggestive of its efficacy in a long term therapy in oral form. In a combined intravenous and oral study[42] similar beneficial effects were observed with an increase in cardiac index and decrease in pulmonary capillary wedge pressure and systemic vascular resistance. Though oral form produced statistically significant increase in CI but it also documented worsening of ventricular arrythmias. The mortality rate remained unchanged in this group of patients. Hence Piroximone may cause short term hemodynamic improvement but caused great concern with reported high morbidity and mortality of this agent.

Conclusion

Despite optimal current therapy with digitalis glycoside, potent diuretics, vasodilators, patients generally face a declining clinical course. The aim of treatment is essentially amelioration of symptoms and prolonged survival. These are not synonymous and need to be considered relative to the nature, severity, and stage of the disease. Digitalis glycosides are the only inotropic agents clinically available to increase the contractile force hence improve the ventricular function but are limited in terms of their modest potency and associated toxicity[43]. The systemic vasodilator offers an innovative approach in both acute and chronic heart failure. By reducing increase LV systolic wall tension (ventricular afterload) and a reduction in aortic impedance, vasodilators increase the CO and decrease the elevated filling pressure (Ventricular Preload) by diminishing venous tone, thus reducing myocardial demand. The activation of Renin-Angiotensive Aldosterone system in chronic congestive heart failure and decrease of angiotension II generation by converting enzyme blockade improves cardiac function by peripheral vasodilation[44].

Overactivity of Renin may perpetuate congestive heart failure by increasing circulatory angiotension II, which disturb peripheral circulatory dynamics and cause secondary hyperaldosteronism leading to body fluid retention and possible attenuation of the response to vasodilator therapy and is a more physiological approach to the relief of chronic heart failure by the utilization of oral angiotension II converting enzyme inhibitors rather than standard vasodilators.

The search of a new inotropic agent to stimulate failing myocardium is a major pharmacological challenge in the treatment of heart failure. Phosphodiesterase inhibitors has the combination of vasodilator and positive inotropic effect hence known as "Inodilators". Their potential advantages are a limited increase in heart rate and a relatively remote risk of inducing myocardial ischemia. As these agents may decrease arterial pressure, they should be used in heart failure only in absence of arterial hypotension. The combined inotropic and vasodilator action of PDE inhibitors, mediated by a mechanism which by passes the adrenergic receptors, may be of particular clinical significance in patients whose adreno receptors are losing as a result of high circulating catecholamines so characteristics of patient in heart failure. In severe heart failure, PDE inhibitors can be used in combination with adrenergic agents. Biochemically, beta adrenergic stimulation results in an increase in myocardial CAMP levels and the concurrent PDE inhibition can maintain these high levels. As PDE inhibitors do not require the availability of myocardial receptor to be effective, there is a lesser problem of tolerance in these agents[45].

Although PDE inhibitors can stimulate the failing ventricle and improve hemodynamics, their influence on the natural history of heart failure is less clear. Much of the trials are conducted for observing acute hemodynamic over a short period. From the point of view of patient the essential end point of inotropic therapy is prolonged survival and/or improvement of symptoms. Hence there is a need to demonstrate the long term benefits from phosphodiesterase inhibitors as it is important to determine that these agents do not exert deleterious effects on myocardial function or patient survival during long term use.

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