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Review Article

Cardiovascular Effect of Pyridazine Derivative Pimobedan and Other Related Compounds

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ABSTRACT

The pyridazine ring is present in various biologically active compounds and some pyridazine compounds have been reported as valuable cardiovascular agents. Benzimidazole-pyridazinone compound, 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazole-5-yl]-5-methyl-3(*2H*)-pyridazinone (pimobedan or vetmedin) is a potent cardiovascular agent. It is a non adrenergic, non-glycoside inotropic drug with vasodilator activities and exerts a stimulatory myocardial activity by a dual mechanism of action with raise in calcium sensitivity of cardiac myofilaments and inhibition of phosphodiesterase. Pyridazine is an attractive compound for designing and development of novel pyridazine compounds as cardiotonic agents in future.

Keywords: Pimobendan, cardiovascular, vasodilatative, phosphodiesterase, calcium sensitiser.

INTRODUCTION

Nowadays cardiovascular diseases (CVD) are major public health problem wordwide, in this regards ischemic heart disease (IHD) or coronary heart disease (CHD) is more common.[1] The prevalence is increasingly occurs in the elderly population.[2] The common cause is coronary artery disease (CAD), either alone or in combination with hypertension. Other factors, likes hypercholesterolaemia, diabetes mellitus, obesity and smoking may raise the risk of rising this syndrome. Indications of heart failure (HF) contain fatigue, anorexia, limited exercise tolerance, and dyspnoea[3]. This results from myocardial ischaemia (MI), arrhythmias, non-compliance with treatment or intercurrent infections. Acute heart failure (AHF) may also arise suddenly following a cardiac insult in a patient without previous evidence of overt CVD. About 15% of worldwide mortality is attributable to heart disease (HD)[4]. It is estimated that HD will be the biggest cause of disease burden worldwide By 2020[5,6]. The IHD is the most important and most common contributor to the development of HF.[7,8] Treatment with positive inotropic agents is indicated for

patients with severe chronic or acute HF to recover the pump function of the heart.[9,10] The β-adrenergic agonists and phosphodiesterase (PDE) inhibitors improve cardiac contractility by increasing intracellular Ca^{2+} concentration. The mechanism, leads to increase in myocardial oxygen consumption (MOC) and increase in oxygen demand further leads to the increase of arrhythmic and ischaemic difficulties, which can occur in ischaemic patients, whose haemodynamics is unbalanced. These drugs have not been commonly used in patients with ischaemia.[11,12] Pimobendan and levosimendan drugs possesses a novel mechanism of positive inotropy. These are Ca^{2+} sensitizer agents, augments myocardial contractility by raising myofilament sensitivity to Ca^{2+} by binding to cardiac troponin C in a Ca^{2+}-dependent manner.[13-15] This mechanism allows the positive inotropic effect without increasing intracellular Ca^{2+} concentrations. Pimobendan and levosimendan also opens ATP-sensitive K^+ channels (K^+ ATP) in vascular and cardiac muscle, thereby generating vasodilator and also anti-ischaemic effects.[16-18] Pimobendan and levosimendan are inhibited cardiac and smooth muscle PDE.[19,20]

MANAGEMENT OF CHRONIC HEART FAILURE

The decline in the effective functioning of the heart as a pump characterises the syndrome of HF. It generally happens as a outcome of left ventricular systolic dysfunction (LVSD) (decreased contraction), although diastolic dysfunction (raise ventricular stiffness).[21] The complex reflex actions that are initiated to increase cardiac output (CO) in the failing heart eventually supply to additional cardiac dysfunction. Left ventricular (LV) pump failure results in reduced blood pressure (B.P) and reduced renal perfusion.[22,23] There are numerous essential objectives in the dealing of HF: enhancement of the force of cardiac contraction, decrease of the resistance to ejection of blood from the ventricles, decrease of the pre-load, i.e. the end-diastolic ventricular filling volume, reversal of the procedure of ventricular remodeling and restoration of the atrial involvement to ventricular filling. Optimization of therapy is of utmost value to improve signs and quality of life.

Phosphodiesterase inhibitors

Phosphodiesterase(PDE)-3 inhibiting drugs (milrinone, amrinone and enoximone) raise contractility by decreasing the degradation of cyclic adenosine monophosphate (cAMP). They decreases both preload and afterload via vasodilation. The haemodynamic consequences of this action are reduced LV after load, increased cardiac output and reduced total peripheral resistance (PR). Distinct from sympathomimetic amines, PDE-3 inhibitors generate no tolerance and possess the distinct benefit of directly reducing pulmonary vascular resistance.[24-28] Low-dose oral enoximone has been evaluated in some clinical trials, mainly its effects during co-administration with β-blockers.[29,30] Other drug, vesnarinone, a mixed PDE inhibitor and ion-channel modifier has modest, dose-dependent, positive inotropic effects, but minimum negative chronotropic activity, has superior haemodynamics and quality of life.[31-33]

Calcium sensitizers

The positive inotropic agents act by increasing the sensitivity of troponin C or some other part of the myofibrillar Ca^{2+}–binding. There are several drugs with reported calcium sensitizing properties (eg. sulmazole, isomazole, adibendan, meribendan, etc), but most of the clinical data come from two compounds:

pimobendan and levosimendan. Pimobendan is a calcium sensitizer with PDE-3 inhibitor properties. Both intravenous and oral formulations have been studied in patients with HF. Intravenous bolus doses had clear inotropic, vasodilatory and chronotropic effects in patients with HF, increasing CO and reducing systemic vascular resistance (SVR) and LV end-diastolic pressure.[34,35] In comparison with captopril, pimobendan appeared to be a stronger arterio-venodilator.[36] The effects of oral pimobendan were similar to those seen after I.V administration.[37,38] Pimobendan increased exercise duration and peak oxygen uptake [39-41]. The efficacy and safety were similar to those seen with enalapril, although a some what higher incidence of arrhythmias was seen[42,43]. In contrast, pimobendan significantly less morbidity and better the physical activity of patients with stable HF without raise in adverse cardiac procedures. Therefore, the role of pimobendan in the treatment of HF remains to be clarified and adequately powered prospective long-term mortality/morbidity trials are warranted in that value.

BIOLOGICAL ACTIVITIES OF PYRIDAZINE ANALOGUES

Recently, a great attention has been focused on pyridazine analogues for their wide-spectrum pharmacological activities. Different structural alterations were carried out in pyridazine ring system. These structural modified compounds resulted in different type of fruitful biological activities. Large number of pyridazine analougues are well known as cardioactive agents.[44,45]

CARDIOVASCULAR ACTIVITIES

Intravenous (I.V) infusions of pimobendan, in pigs with normal coronary circulation caused dose-dependent changes in heart rate (10-35%), left ventricular systolic pressure (LVSP) (-5 to -45%), left ventricular filling pressure (LVFP) (-20 to -40%) but had only a slight effect on the highest rate of rise of left ventricular pressure (LVP) (10-20%). The decrease in mean arterial B.P was primarily due to systemic vasodilation; PR and CO decreased by up to 40 and 14%, respectively. Vasodilation occurred in several vascular beds, but was particularly pronounced in the adrenals, stomach, small intestine and myocardium. Although the increase in myocardial blood flow favoured the epicardium, vascular conductance in both the endo- and epicardial layers was significantly increased. Myocardial oxygen consumption (MOC) was not influences despite the raise in heart rate. However, in animals where max LVP and CO were reduced and pre- and/or after-load were increased by partial occlusion of the left anterior descending coronary artery, pimobendan clearly increased both max LVP and CO. Pretreatment with propranolol did not modify any of the cardiovascular responses to pimobendan, thereby excluding the involvement of a β-adrenoceptor mechanism. Pimobendan is thus a compound with vasodilator and positive inotropic properties that improves CO in animals with severe MI. The finding that the mild tachycardia caused by pimobendan was not accompanied by an increase in MOC warrants investigation to evaluate its usefulness in the treatment of HF.[46]

The pimobendan exhibited positive inotropic effect. The acute systemic hemodynamic effects of Ca^{+2} antagonist pimobendan, a PDE inhibitor with vasodilating as well as positive inotropic properties, were studied in awake pigs with chronic HF. Left ventricular (LV) dysfunction, manifested by a 25% decrease in cardiac output (CO), a 35% increase in SVR, and a doubling of the LVFP, was induced by a proximal ligation of the left

circumflex coronary artery. Pimobendan normalized CO and exhibited a similar cardiac profile [systemic vasodilatation, reduction in LVFP, and an increase in heart rate (HR)] except for the appreciably larger raise in LVP with pimobendan (85%). The vasodilatory and positive inotropic activities are shifted more in support of the vasodilatory effects during HF.[47] A potent Ca^{2+}-sensitizer, was studied in human failing and non failing LV myocardium, the effects of the pimobendan, isoprenaline (Iso) as well as $CaCl_2$ were investigated. The positive inotropic reactions were observed in electrically motivated human LV papillary muscle strips. Pimobendan raised force of contraction (FOC) in a dose-dependent mode. In skinned fiber test, pimobendan augmented Ca^{2+}-sensitivity radically raises FOC in human myocardium through sensitizing of the contractile proteins towards Ca^{2+} and by inhibition of PDE-3 isoenzymes.[48] Ca^{2+} sensitizers, new class of cardiotonic drugs, have exert positive inotropic activities without raising intracellular Ca^{2+} ions transient. They evade Ca^{2+} overload that directed to arrhythmias and myocyte damage, and do not raise the energy utilization for handling Ca^{2+} ions. Therefore, Ca^{2+} sensitizers may be valuable for the therapy of HF. Though, most of the Ca^{2+} sensitizing drugs may impair cardiac diastolic role as a result of raised Ca^{2+} ion sensitivity of the myofilaments. The 6-[4-(4'-pyridylamino) phenyl]-4, 5-dihydro-3(2*H*)-pyridazinone hydrochloride trihydrate, MCI-154, is a new calcium sensitizing agents that has extra potent positive inotropic activity than pimobendan, adibendan and sulmazole.[49].

The safe and clinically effective inotropic drugs are use as adjunctive therapy in patients with advanced HF. Pimobendan raised myocardial contractile force without rising intracellular Ca^{+2} ions. The pimobendan exhibited significant progress in exercise capability and quality of life in HF patients. The clinical benefits of pimobendan found in these trials contrast with the adverse experience noted previously with milrinone and enoximone. This may be related to the different mechanism of action of pimobendan. The pimobendan may have a useful adjunctive role in HF and that further assessment of its effects on overall mortality is needed.[50-52] The Pimobendan (racemate) and its enantiomers were examined to their cardiotoxicity in adult female Beagle dogs. Fall of the B.P happened at low dosages of the racemate and the eutomer, but only in elevated dose distomer treated animals. An affinity to tachycardia grows only in elevated dose females getting the racemate. Racemate is comparable to the eutomer. The cardiotoxicity by Pimobendan in dogs resulted from the inflated pharmacodynamic effect but not from the chemical nature of the drug[53]

Pimobendan (Vetmedin)

The 4, 5-dihydro-6-[2-(4-methoxy-phenyl)-1H-benzimidazole-5-yl]-5-methyl-3(*2H*) pyridazinone (Pimobendan) is a benzimidazole-pyridazinone analogue and acts as ionotropic drug, mostly used for in dogs as chewable tablets contain 1.25 or 5 mg pimobendan/ tablet and used orally at a total daily dose of 0.5 mg/kg body weight. It is a non-sympathomimetic, non-glycoside inotropic drug with vasodilator activities. Pimobendan exerts a stimulatory myocardial effect by a dual mechanism of action consisting of an increase in Ca^{+2} ion sensitivity of cardiac myofilaments and inhibition of PDE-3. Pimobendan showed vasodilator effects by reducing PDE-3 activity.[54,55] Pimobendan is specified for the treatment of the signs of mild, moderate, or severe congestive heart failure (CHF) in dogs due to atrio-ventricular valvular insufficiency (AVVI) or dilated cardio-

myopathy (DCM). The total daily dose should be separated into two fractions. It should not be given in cases of hypertrophic cardio-myopathy, aorticstenosis, or any other conditions where an increase of cardiac output is unsuitable for functional or anatomical reasons. At 3 and 5 times commended dosage, used over a six month period, pimobendan caused an increased hemodynamic response in the normal dog heart, which was linked with cardiac pathology and not for use in humans.[56-58]

Adverse Reactions

The Pimobendan has the subsequent occurrence of common adverse reactions containing poor appetite, diarrhea, dyspnea, lethargy, azotemia, weakness and ataxia, pleural effusion, cough, syncope, sudden death, and heart murmur. Adverse reactions were seen and potentially related to CHF, therapy of CHF, or both. The following adverse reactions were reported not in order of prevalence, CHF death, chordate tendineae rupture, left atrial tear, sudden death, arrhythmias, tachycardia, weak pulses, syncope, irregular pulses, dyspnea, increased respiratory rate, increased pulmonary edema, pleural effusion, ascites, coughing, gagging, hepatic congestion, vomiting, diarrhea, melena, decreased appetite, weight loss, lethargy, depression, weakness, collapse, shaking, trembling, ataxia, seizures, restlessness, agitation, pruritus, increased urination, increased water consumption, urinary accidents, azotemia, dehydration, abnormal serum electrolyte, protein, and glucose values, mildincreases in serum hepatic enzyme levels, and mildly decreased platelet counts. The adverse reactions in the higher use study were consistent, with the following exception: A dog in the higher use study grows acute cholestatic liver failure after 140 days on Pimobendan and furosemide. Additional assumed adverse reactions were reported in dogs treated with pimobendan: hemorrhage, anemia, petechia, hyperactivity, excited behavior, erythema, drooling, rash, constipation, and diabetes mellitus.[55-60]

Clinical Pharmacology

Pimobendan is oxidatively demethylated to a active metabolite which is conjugated with sulfate or glucuronic acid and excreted mainly through feces. The mean extent of protein binding of pimobendan and active metabolite in dog plasma is more than 90%. Single oral use of 0.25 mg/kg Pimobendan , the maximal mean plasmacon centrations (Cmax) of pimobendan and the active metabolite were 3.09 ng/ml and 3.66 ng/ml, respectively. The total body clearance of pimobendan was about 90 ml/min/kg, and the terminal eradication half-lives of pimobendan and the active metabolite were about 0.5 hrs and 2 hrs, respectively. Food reduced the bioavailability of aqueous solution of pimobendan. In dogs with LV pressure transducers, pimobendan raised LV dP/dtmax (measure of contractility of the heart) in a dose-dependent mode between 0.1 and 0.5 mg/kg orally. Repeated oral use of pimobendan did not result in support of tachyphylaxis (decreased inotropic action) or drug accumulation (increased inotropic action). The inotropic action of pimobendan may be attenuated by the simultaneous use of ß-adrenergic blockers or calcium channel blockers.[55-60]

Effectiveness

Pimobendan is used safely in dogs along with receiving furosemide, digoxin, atenolol, enalapril, spironolactone, hydralazine, nitroglycerin, diltiazem, antiparasitic substances, antibiotics, topical ophthalmic and otic drugs, theophylline, levothyroxine sodium, famotidine, metoclopramide, diphenhydramine, hydro-

codone, and butorphanol, and in dogs on sodium-restricted diets.[55-60]

PYRIDAZINE ANALOGUES AS CARDIOVASCULAR AGENTS

The inotropic and vasodilatory activities of pyridazinone derivatives are well reported.[61] Pyridazine derivatives like Pimobedan and levosimendan have emerged as potent cardiotonic agents with dual inotropic and vasodilatory properties in higher animals.[62] These pyridazine compounds have shown good activity against CHF. Pyridazinone derivatives, SK&F-93741, its nor-methyl derivative and levosimendan possess a substituted amino group at *para*-position of 6-phenyl ring and have potent inotropic drugs with dual inotropic and vasodilatory activities in animals. The 4, 5-dihydro-3(2H)-pyridazinone derivatives showed positive inotropic activity and PDE inhibitory activity.[63] Some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-di-hydro-3(2H)-pyridazinone were showed vasodilatory activity. The 6-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy) phenyl]-2-(4-fluorophenyl)-4,5-dihydropyridazin-3(2H)-one was showed vasodilator effect in nanomolar range.[64] Pyridazinone-dinitrile derivative, levosimendan enhances myocardial contractility by stabilizing the Ca^{+2} bound conformation of troponin C. It is also showed pulmonary and systemic vasodilator effects. The positive inotropic and vasodilator activity has shown increasing cardiac output and reducing LV end-diastolic pressure, right atrial pressure, pulmonary wedge pressure, and SVR in CHF patients.[65] A analogues of (E)-4,5-dihydro-6-[2-[4-(1H-imidazol-1-yl)phenyl] ethenyl]-3(*2H*)-pyridazinone were showed hemodynamic activity, cAMP-PDE inhibitory effects in human platelets and guinea pig heart tissue, and antiplatelet effects.[66] The 6-[4-[[(aryloxy) acyl] amino] phenyl]-4,5-dihydro pyridazinones were showed combined vasodilator and β-adrenoceptor antagonists and potential antihypertensive activities.[67] Some substituted pyridazinones are act as PDE-inhibitors and actas cardiac stimulants.[68] The cardiovascular activities of 6-[4-[2-[3-(5-chloro-2-cyano-phenoxy)-2-hydroxy-propylamino]-2-methyl propylamino] phenyl]-4,5-dihydro-5-methyl-3(*2H*) pyridazinone monoethyl maleate (TZC-5665) and its main metabolite in human, M-2. The TZC-5665 showed negative chronotropic and inotropic activities, whereas M-2 exhibited potent positive inotropic action with a slight positive chronotropic activity in guinea pigs and dogs. The TZC-5665 was showed a non-selective β-adrenoceptor antagonist effects comparable to propranolol in guinea-pig. The TZC-5665 and M-2 were more effects and selective inhibitors of PDE-III than milrinone. Combination of β-adrenoceptor blocking effect of TZC-5665 and positive inotropic effect of M-2 could be useful in the treatment of CHF by mutual prevention of undesirable effects.[69,70] Pyridazinone derivatives having a phenoxy propanolamine moiety showed hypotensive and β-blocking activities in rats. The 5-chloro-2-cyanophenoxy derivative showed the promising dual activities.[71] The Ca^{2+} sensitizers agents have shown to exert positive inotropic effects without raising intracellular Ca^{2+} transient. They avoid Ca^{2+} overload that leads to arrhythmias and myocyte injury, and do not enhance the energy utilization for handling Ca^{2+}. The Ca^{2+} sensitizers are useful for the therapy of CHF. The 6-[4-(4'-pyridylamino) phenyl]-4,5-dihydro-3(2*H*)-pyridazinone hydro-chloride trihydrate MCI-154 has showed for hemodynamic, inotropic, mechanoenergetic and oxidative metabolic effects. The MCI-154 has minimal inotropic action, induces a significant "oxygen waste", and decreases vascular resistance in intact pigs.[72] The

MCI-154 has more potent positive inotropic activity than pimobendan, adibendan and sulmazole. The MCI-154 has to improve not only cardiac systolic function but also diastolic relaxation in chronic HF.[73,74] The zardaverine is a selective inhibitor of PDE-III and PDE-IV isozymes. The zardaverine is a selective inhibitor of PDE isoenzyme act as potent bronchodilator. The zardaverine exerts a positive inotropic effect on heart muscle. The Zardaverine inhibited the cGMP-inhibitable PDE-III from human platelets and affected the calmodulin-stimulated PDE-I, the cGMP-stimulated PDE-II and the cGMP-specific PDE-V. the Zardaverine inhibits the ADP-induced aggregation of human platelets. This inhibition was synergistically augmented by activators of adenylate cyclase such as PGE1 and forskolin.[75] Traditional inotropic drugs containing β-adrenergic agonists such as adrenaline, dobutamine, dopexamine, dopamine and phosphodiestrase (PDE) inhibitors such as milrinone and enoximone. Stimulation of β-adrenoreceptors results in increased activity of adenylate cyclase, thus increasing production of cyclic adenosinemonophosphate (cAMP). Alternatively, PDE inhibition reduces pre-existing cAMP breakdown. Both classes of inotrope exert their effects via increased levels of cAMP. The results increased levels of Ca^{+2} within the cardiac myocyte hence increased cardiac contractility.[76,77] Although β-agonists and PDE inhibitors contain positive effects on cardiac muscle contractility, the harmful effects of raised intracellular Ca^{+2} on the failing myocardium edge their use. Thus, myocardial oxygen demand is increased, ischaemia potentially exacerbated, diastolic relaxation is impaired, and tachycardia and malignant arrhythmias may occur. The effect of β-agonists is attenuated by the use of β-blockers: this is clinically relevant since the use of beta blockers as an effective evidence-based therapy in HF is more extensive. The β-agonists is also showed tachyphylaxis (drug tolerance). The positive inotropic drugs have produced short-term haemodynamic advance in AHF. The use of inotrope agents have frequently linked with adverse outcomes and increased mortality.[78-79]

CONCLUSION

The management and medical treatment of AHF, focusing on the emerging role of pimobedan for the treatment of AHF. The new inotropic drug with a dual mechanism of action: sensitisation ofthe cardiac myofilament to Ca^{+2}, thus enhancing cardiac contractility, and vasodilation of vascular smooth muscle. The literature reveals that pyridazine derivative has diverse biological potential, and has taken attention of the researchers. The diversity in pharmacological response profile has attracted the attention of many researchers to discover this moiety to its manifold potential against different activities. The pyridazinone derivatives have studied extensively with diverse chemical entities and broad spectrum of biological activities. The biological profile of these generations of pyridazines represents much progress with regards. By the present development it can be concluded that pyridazine have a great potential which remain to be disclosed till date. Pyridazines drew attention because it makes attractive synthetic compounds for designing and development of novel pyridazinone based cardiotonic compounds.

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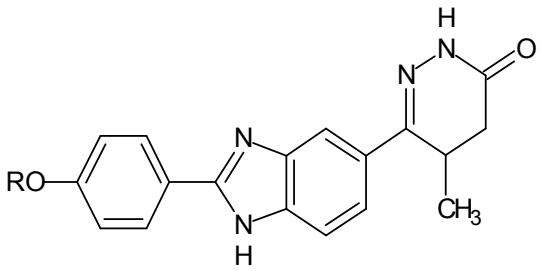

Figure No. 1: Pimobedan.