Phosphodiesterase Inhibitors

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Abstract

Phosphodiesterases (PDEs) comprise a superfamily with 11 subfamilies. Within these families, more than 40 isoforms are expressed. Phosphodiesterase-3 inhibitors (PDE3i) are used as inotrope/vasodilators for acute heart failure (HF), and PDE5i for pulmonary hypertension and erectile dysfunction. Despite being studied for chronic HF, none of the PDEis have been presently approved for such an indication itself. The PDE3i milrinone (the PROMISE trial and OPTIME-CHF), raised safety concerns. Although low-dose intravenous milrinone with a beta-blocker is still proposed by some. Enoximone failed to show significant benefits in patients with severe chronic HF in a series of phase 3 clinical trials (ESSENTIAL 1, ESSENTIAL II, EMOTE, EMPOWER). Of the PDE5is, Sildenafil is the most extensively investigated with proven efficacy in treating erectile dysfunction and pulmonary arterial hypertension, but it has only been tested in relatively small trials in the field of HFrEF, but shows some promise in HFpEF and in pulmonary hypertension complicating HF. Elucidation of the potential clinical role of PDEis on across the spectrum of HF phenotypes will require more definitive evidence from large-scale clinical trials.

Keywords: heart failure, PDE inhibitors, sildenafil, milrinone, enoximone

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Introduction

Phosphodiesterase (PDE) is a ubiquitous enzyme that catalyses the hydrolysis of phosphodiester bonds. Its homeostatic role was first described by Sutherland[1], who was awarded the Nobel Prize for Physiology and Medicine in 1971. It is responsible for the phosphodiester bond hydrolysis of cAMP and cGMP, both having an important role in the regulation of inotropic mechanisms in the myocardium, to form the inactive 5'-AMP and 5'-GMP. Cyclic AMP stimulates protein kinase A and exchange protein activated by cAMP, acutely enhancing excitation-contraction coupling and sarcomere function.[2] Cyclic GMP acts as a brake on this signaling by activating protein kinase G.[3] The inotropic effect is mediated through release of calcium from the sarcoplasmic reticulum and other sub-sarcolemmal sites, and the subsequent effectiveness of the interaction between released calcium ions and contractile proteins.

Phosphodiesterases (PDEs) comprise a superfamily with 11 subfamilies, which have been characterized on the basis of amino acid sequence, substrate specificity, pharmacological properties and allosteric regulation. Within these families, more than 40 isoforms are expressed either by different genes or as expression of the same gene through alternative splicing.[4] The importance of PDEs as regulators of signaling is evident from their development as drug targets in diseases that affect heart, lung, vasculature, platelet function and inflammatory mechanisms.

Several different agents will inhibit the specific types of enzyme within the superfamily, that could be differently expressed in tissues. As a result, PDE inhibitors (PDEis) can have a multiplicity of effects. Phosphodiesterase-3 inhibitors (PDE3i) are used as inotrope/vasodilators for acute heart failure (HF)[5], and PDE5i for pulmonary hypertension and erectile dysfunction, though cardiac indications have also been explored. PDE4i are used for forms of chronic pulmonary disease[6], while PDE9i have been tested for Alzheimer's disease, and recent data suggest they may hold promise for HF as well.[7] Despite being studied for chronic HF, none of the PDEis have been presently approved for such an indication itself.

Phosphodiesterase inhibitors and heart failure

Heart failure with reduced ejection fraction

PDE3i

Major interest in the cardiovascular effects of PDEi drugs for chronic HF dates from the early 1970s. A major factor underlying cardiac dysfunction in HF resides in second messenger signaling defects coupled to cAMP and cGMP. The demonstration of the positive inotropic actions of the PDE3i led to the development of clinical analogues, which triggered research on this field.

In randomized placebo-controlled clinical trials, amrinone was found to be of no significant benefit over placebo. This led to the development of more potent PDE3i inhibitors, e.g. milrinone and enoximone. Initial studies were encouraging, but a randomized placebo-controlled trial with oral milrinone (the PROMISE trial[8]) in 1088 HF patients with NYHA functional classes III-IV showed a 28% higher mortality at 6 months in the milrinone group as compared to a placebo group. However, at that time, patients did not receive defibrillator therapy, those requiring beta-blockers were excluded and haemodynamic evaluations at enrollment were not available. In a more recent trial[9], OPTIME-CHF, a neutral to beneficial effect of milrinone on 60 days cardiovascular hospitalizations and composite of death and readmission in non-ischaemic cardiomyopathy was demonstrated, but with harmful effects in ischaemic cardiomyopathy. In patients with advanced HF, the use of the combination therapy of low-dose intravenous milrinone with a beta-blocker offers an appealing strategy. Some authors propose chronic milrinone infusion as a “bridge to beta-blockade” in addition to the recommended bridge to advanced options.[10]

Latterly, interest has focused on enoximone as an orally active inotropic agent. Nonetheless, enoximone failed to show significant benefits in patients with severe chronic HF in a series of phase 3 clinical trials (ESSENTIAL 1, ESSENTIAL II, EMOTE, EMPOWER).[11,12] Although milrinone and enoximone are chemically unrelated compounds affecting different PDE3 sub-types, their clinical effects (particularly haemodynamic) are similar. Both have been studied extensively in patients following cardiac surgery and in a critical care setting.

PDE5i

Among all PDEs, PDE5 has been the most widely investigated. Three PDE5 isoforms have been described – A1, A2, and A3. PDE5 A1 and A2 isoforms are expressed in several tissues, including heart, lung, brain, kidney, bladder, prostate, urethra, penis, uterus, and skeletal muscle. The A3 isoform is located in tissues having a cardiac or smooth muscle constituent.

PDE5i have proven efficacy in treating erectile dysfunction and pulmonary arterial hypertension.[13] Clinical safety and epidemiological studies have established proven safety profiles for PDE5i. The biggest concern relates to a co-administration with nitrates resulting in severe hypotension. Sildenafil is the agent most extensively investigated in experimental and clinical cardiology. It must be noted that while sildenafil preferentially inhibits PDE5i, it is not truly selective, especially at high doses.

Within the pulmonary and systemic vasculature its actions are well-defined, leading to the relaxation of vascular smooth muscle and vasodilatation through the enhancement of cGMP derived from nitric oxide (NO). Furthermore, stimulation of the cGMP-protein kinase-G (PKG) axis reduces stress responses, and its activation can attenuate pathological hypertrophy and protect against ischaemic injury within cardiomyocytes.[14] With the discovery that PDE5 is also expressed in cardiac muscle and upregulated in hypertrophy and HF[15], attention has shifted towards the direct myocardial effects of PDE5i. While PDE5i theoretically could elevate cAMP through cGMP-inhibition of PDE3, the vast majority of studies find that cGMP-PKG effects predominate,

with a corresponding negative inotropic action.[16] However, it should be noted that PDE5 actions and its inhibition in the normal myocardium are unclear, and may depend on whether effects are assessed under the basal conditions or with the adrenergic stimulation. Growing evidence from animal models supports a cardioprotective action of PDE5i, including improving contractile function[17] and left ventricular hypertrophy regression.[18]

Vasoconstriction is a pathophysiological hallmark of chronic HF, one that involves both the systemic and pulmonary circulations, and results in an increased impedance to the ejection of both left and right ventricles. The possibility that selective inhibition of PDE5 might be helpful in HF through NO release, promoting NO-dependent vasodilatation, is receiving more attention in recent years. An additional reason why PDE5 inhibition may be beneficial in chronic HF is that resistance to natriuretic peptide in the syndrome is partially related to an increased PDE5 activity.

Small single-centre studies have shown that PDE5i reduces pulmonary vascular resistance[19] and improves patient exercise capacity and ventricular function in HFrEF.[20-22] A meta-analysis of 6 randomized clinical trials (RCTs) investigating the efficacy and safety of PDE5i in patients with HFrEF revealed that the additional use of a PDE5i reduced clinical symptoms and hospitalizations when compared with placebo.[23] Nevertheless, such data should be interpreted with great caution, as they were obtained in highly selected patients, and data from larger RCTs are lacking. Currently, targeted therapies with pulmonary vasodilatory properties, including PDE5i, are not approved for the treatment of HFrEF itself.

PDE1i

ITI-214 is the only potent and selective PDE1i yet developed and tested in humans, as it has successfully completed several phase I clinical trials. These studies have not focused on the cardiovascular system, but on important nervous system functions that are impacted in neurodegenerative and neuropsychiatric disease. These early studies provided safety data in support of a current phase Ib/IIa dosing, safety, and tolerance study of ITI-214 in stable, NYHA classes II-III HF patients. This study will assess for the first time the impact of ITI-214 on cardiovascular function in humans, and help determine if the observations made by Hashimoto et al.[24] in mammalian models (dog and rabbit) are indeed translatable to the human disease state. These authors described that PDE1 inhibition by ITI-214 in vivo confers acute inotropic, lusitropic, and arterial vasodilatory effects in PDE1C-expressing mammals with and without HF. The effects appear to be related to a cAMP signaling that is different from that provided via beta-adrenergic receptors or the PDE3 modulation.

Heart failure with preserved ejection fraction

Recently proposed HF with preserved ejection fraction (HFpEF) paradigms implicate a contribution of multiple co-morbidities including type-2 diabetes mellitus, obesity, hypertension and vasculopathy, causing a systemic proinflammatory state, coronary microvascular inflammation and compromised NO availability.[25] These favour hypertrophy and titin hyperphosphorylation, increasing myocyte stiffness and promoting left ventricular diastolic dysfunction. Longstanding elevation of the left-sided filling pressures associated with neurohormonal and other

mediator activation, as well as neurogenic effects, may cause an excessive vasoconstriction with or without vascular remodelling, leading to a 'disproportionate' increase in pulmonary arterial pressure with RV involvement, which becomes predominant in the pathophysiological scenario and may determine the clinical consequences.

PDE5i

The largest study on PDE5i in HFpEF (RELAX trial[26]) failed to demonstrate clinical benefits. It has shown that sildenafil did not improve peak oxygen consumption (primary endpoint) and exercise capacity in patients with HFpEF in the absence of PH.[26] In a recent single-centre RCT, sildenafil also failed to improve either haemodynamics or exercise capacity in 53 patients with HFpEF and isolated post-capillary PH.[27]

Two factors are proposed to explain the differential efficacy of PDE5i according to HF phenotypes. First, PDE5i exerts an effect on left ventricular remodelling in HFrEF, which was not observed in HFpEF. Secondly, PDE5i acutely reduces contractile function, which may further limit their use in HFpEF.

Pulmonary hypertension in the course of heart failure PDE5i

Dysfunction of the vascular endothelium and a reduction in NO bioavailability are involved in the development of pulmonary vascular remodeling, pre-capillary pulmonary hypertension and right HF in both HFrEF and HFpEF [28], with a significant prognostic impact. Given the high selectivity of PDE5 for the pulmonary microvessels, lung haemodynamics should reasonably be regarded as a primary target of PDE5 inhibition in this setting.

PDE5i also offers the double advantage of selectively dilating the pulmonary vessels without producing tachyphylaxis.[29] In patients with predominantly RV dysfunction, cardiac output increases more with sildenafil in comparison with inhaled NO at comparable reductions of pulmonary vascular resistance. [30] An important investigation on PDE5i effects in abnormal human myocardium demonstrated that although PDE5 was not found in normal human RV myocardium, it was found in diseased, hypertrophied RV myocardium, and it was possible to show an inotropic effect of PDE5 inhibition in this tissue.[31] The proposed mechanism is indirect inhibition of PDE5 as a result of increased guanosine monophosphate signaling, with subsequent cyclic adenosine monophosphate mediated effects as would be expected.[32]

An additional effect of sildenafil on the lung is an improvement of carbon monoxide diffusion capacity of more than 10% in patients with chronic HF. This appears to be achieved through a selective increase of the alveolar-capillary membrane gas conductance, without affecting the pulmonary capillary volume of blood available for gas exchange.

Conclusions

A number of theoretical considerations support the usefulness of NO potentiating compounds in HF. Increases in output and reductions in the afterload to ventricular ejection are potentially useful ways to treat the HF syndrome in patients with prominent pulmonary vasoconstriction and pulmonary hypertension.

Elucidation of the potential clinical role of PDEi on these processes across the spectrum of HF phenotypes will require more definitive evidence from large-scale clinical trials.

Declarations of interest

The authors declare no conflict of interest.

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