Phosphodiesterase inhibitors and the cardiovascular system
Rob Feneck MB BS FESC FRCA

Phosphodiesterase is a ubiquitous enzyme that catalyses the hydrolysis of phosphodiester bonds. It is responsible for the hydrolysis of cyclic 3,5 adenosine monophosphate (cAMP) and 3,5 cyclic guanosine monophosphate (cGMP). Both cAMP, and to a lesser extent cGMP, have an important role in the regulation of inotropic mechanisms in the human myocardium. However, cAMP has numerous effects in other tissues, and different phosphodiesterase iso-enzymes are found in many other tissues (Table 1).

Drugs which inhibit the action of phosphodiesterase (thus reducing the breakdown of cAMP) have a therapeutic action on the heart, lung, and vasculature as well as on platelet function and inflammatory mechanisms. Many of these drugs affect more than one iso-enzyme, and many tissues have more than one iso-enzyme present. As a result, phosphodiesterase inhibitors (PDEI) can have a multiplicity of effects. For example, theophylline has effects on the lung, as well as cardiac and vascular effects; amrinone affects cardiac, vascular, and platelet functions. Sildenafil (Viagra) was originally studied as a possible anti-anginal agent.

This review will concentrate on the effects of PDEI in cardiac and vascular tissue, primarily on their usefulness in the management of acute and chronic heart failure.

Inotropic mechanisms
Figure 1 shows the interaction between the primary inotropic mechanisms in the human heart. 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. Conventional inotropic therapy has been directed to improving intracellular signaling resulting in the release of calcium from the sarcoplasmic reticulum. This may be achieved by mechanisms that are either independent or dependent on the activity of cAMP (Table 2); cAMP-independent mechanisms are generally less clinically effective than those dependent on cAMP. cAMP causes an increase in protein kinase A (PKA) activity which, in turn, promotes opening of the cell membrane L-type calcium channel resulting in calcium entry into the cell. Calcium entry provides the stimulus for calcium release via the ryanodine receptor in the sarcoplasmic reticulum. This process has been called calcium-induced calcium release (CICR).

PKA may also increase contraction by promoting calcium uptake into the sarcoplasmic reticulum as a result of phosphorylation of the regulatory protein phospholamban, and the calcium binding protein calmodulin. It has long been recognized that PKA, by promoting calcium entry via the L-type calcium channel and by phosphorylating these regulatory proteins, has a marked effect on promoting calcium release from the sarcoplasmic reticulum. However, recent work suggests that PKA may also affect sarcoplasmic reticulum calcium release independent of CICR by a voltage-sensitive release mechanism. This mechanism appears to promote sarcoplasmic reticulum calcium release independent of L-type calcium channel activity, and is more relevant for PDE III inhibitors than for catecholamines.

Increasing the concentration of cAMP (and hence activation of PKA) in cardiac tissue may have a significant inotropic effect. Until very recently, all the inotropic drugs commonly used in critical care patients utilized this mechanism, the exception being levosimendan which sensitizes the contractile proteins to the effects of calcium rather than directly affecting calcium release.

Concentrations of cAMP can be increased by two mechanisms. First, the concentration may be increased by active conversion of adenosine triphosphate (ATP) to cAMP via the enzyme adenylyl cyclase. This enzyme may be activated directly by forskolin but, in clinical practice, the process is facilitated by the interaction of drugs or ligands with a variety of receptors on the myocardium. These receptors

Key points
Drugs which inhibit the action of phosphodiesterase (PDE) promote a reduction in cAMP breakdown with a variety of tissue specific effects.

Increasing the concentration of cyclic 3,5 adenosine monophosphate and hence activation of protein kinase A in cardiac tissue may have a significant inotropic effect.

Drugs available in clinical practice for improving cardiac performance inhibit either phosphodiesterase isoenzyme III (milrinone) or IV (enoximone).

PDE inhibitors produce vasodilatation which may result in hypotension, particularly in the vasoconstricted or hypovolaemic patient.

PDE inhibitors have a useful role in the management of acute right ventricular failure.

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are all heterotrimeric seven stranded membrane linked receptors, linked to G-proteins. Following receptor activation, stimulatory G-proteins activate adenyl cyclase leading to an increase in myocardial 3,5 cAMP. Although there are a number of receptors that activate stimulatory G-proteins (vasointestinal peptide, histamine, 5 hydroxy-tryptamine), the beta-adrenoceptors are by far the most effective. Drugs which activate these receptors, notably the catecholamines, are used primarily for this purpose. Other receptors (M2 muscarinic cholinergic, somatostatin, adenosine) will, when stimulated, activate an inhibitory G protein which will inhibit adenyl cyclase activity and thereby reduce inotropic activity. Blockade of these receptors, for example by a muscarinic cholinergic blocker such as atropine, may reduce this negative inotropic effect and potentiate the effects of catecholamines.

The breakdown of cAMP is under the control of the enzyme phosphodiesterase, which catalyses the hydrolysis of phosphodiester bonds in cAMP leading to the production of a monophosphate and a free hydroxyl group. Numerous drugs have been identified which will inhibit specific types of enzyme within the superfamily. Currently, drugs which are available in clinical practice for improving cardiac performance are those known to inhibit either phosphodiesterase isoenzyme III or IV. These compounds are the biguanides amrinone and milrinone, and the imidazolone derivative enoximone.

**Phosphodiesterase inhibitors in clinical use**

**Milrinone**

Milrinone largely replaced amrinone in the 1980s; the latter is no longer widely available worldwide and has never been available in the UK. It has very similar pharmacodynamics to milrinone. Milrinone is a biguanide compound with a chemical structure

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### Table 1

Caffeine, theophylline, and papaverine are examples of non-specific PDEI. Other PDE subtypes, their tissue origin and effective inhibitors are shown below.

<table>
<thead>
<tr>
<th>Human phosphodiesterases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PDE isoenzyme</strong></td>
<td><strong>Tissue</strong></td>
</tr>
<tr>
<td>1</td>
<td>Heart, brain, kidney, liver, skeletal muscle, smooth muscle</td>
</tr>
<tr>
<td>2</td>
<td>Adrenal cortex, brain, corpus cavernosum, heart, liver, airway smooth muscle, platelets</td>
</tr>
<tr>
<td>3</td>
<td>Heart, corpus cavernosum, platelets, smooth muscle, liver, kidney T-lymphocyte, B lymphocyte, basophil, mast cell, monocyte, macrophage, endothelial cell</td>
</tr>
<tr>
<td>4</td>
<td>Kidney, lung, heart, skeletal muscle, smooth muscle (vascular, visceral, airway), platelet most inflammatory cells (T-lymphocyte, B-lymphocyte, basophil, mast cell, monocyte, macrophage, endothelial cell, eosinophil, neutrophil)</td>
</tr>
<tr>
<td>5</td>
<td>Corpora cavernosa, platelets, skeletal muscle, smooth muscle kidney, platelets</td>
</tr>
<tr>
<td>6</td>
<td>Retina</td>
</tr>
<tr>
<td>7</td>
<td>Skeletal muscle, heart, kidney, airways, T-lymphocyte, B lymphocyte, monocyte, eosinophil</td>
</tr>
<tr>
<td>8</td>
<td>8A: testis, ovary, ileum, colon; also heart, brain, kidney, pancreas, airways, monocyte, BB: thryoid</td>
</tr>
<tr>
<td>9</td>
<td>Spleen, small intestine, and brain</td>
</tr>
<tr>
<td>10</td>
<td>Brain (putamen, caudate nucleus)</td>
</tr>
<tr>
<td>11</td>
<td>Skeletal muscle, prostate, kidney, liver, pituitary, salivary glands and testis</td>
</tr>
</tbody>
</table>

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### Table 2

Mechanisms of inotropic action

<table>
<thead>
<tr>
<th>Cyclic AMP dependent mechanisms</th>
<th>Cyclic AMP independent mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catecholamines</strong></td>
<td>Direct activation of Ca channels</td>
</tr>
<tr>
<td><strong>Phosphodiesterase inhibitors</strong></td>
<td>Alpha-1-adrenoceptor stimulation</td>
</tr>
<tr>
<td></td>
<td>Direct inhibition of Na/Ca exchange</td>
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<td></td>
<td>Alpha-1-adrenoceptor stimulation</td>
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<td></td>
<td>Direct inhibition of Na/Ca exchange</td>
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<td></td>
<td>K-channel inhibition</td>
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<tr>
<td></td>
<td>Ca salts</td>
</tr>
<tr>
<td></td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>Glucose/K/insulin</td>
</tr>
<tr>
<td></td>
<td>Inhibition of ATPase dependent Na/K pump</td>
</tr>
<tr>
<td></td>
<td>Myofilament Ca sensitizer e.g. Levosimendan</td>
</tr>
</tbody>
</table>

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**Fig. 1** Mechanisms of inotropic action (see text for details).
similar to amrinone. It is presented as a clear liquid in a 10 mg vial as milrinone lactate. Dose finding studies following cardiac surgery recommended a dosing schedule of 50 mcg kg\(^{-1}\) over 30 min as an intravenous loading dose, followed by a maintenance infusion in 0.5mcg kg\(^{-1}\) min\(^{-1}\). Variations in the loading and maintenance regimens have been described, including a prolongation of the time for the loading dose, repeating the loading dose over 1 h if little or no effect is seen, and omitting the maintenance dose following an efficacious response to the original loading dose.\(^1\)

Following intravenous loading infusions in congestive heart failure patients, milrinone had a volume of distribution of ~0.41 kg\(^{-1}\), a mean terminal elimination half-life of 2.3 h, and a clearance of 0.131 kg\(^{-1}\) h\(^{-1}\). The steady-state milrinone plasma levels after ~6–12 h of unchanging maintenance infusion of 0.5 µg kg\(^{-1}\) min\(^{-1}\) are approximately 200 ng ml\(^{-1}\). Milrinone has been shown to be over 70% bound to human plasma proteins at plasma concentrations of 70–400 ng ml\(^{-1}\). The primary route of excretion of milrinone is via the urine. The major excretion products in man are milrinone (83%) and its glucuronide metabolite (12%). Urinary elimination in normal subjects via the urine is rapid. Following administration, approximately 60% is recovered within 2 h and approximately 90% is recovered within 8 h. The mean renal clearance of milrinone is approximately 0.3 l min\(^{-1}\) while that of the metabolites is even greater, suggesting active secretion. The half-life of milrinone increased from 0.94 h in subjects with normal renal function to 1.71 h in patients with moderate renal impairment and to 3.09 h in patients with severe renal impairment. Therefore, accumulation may be relevant, particularly in patients with severe renal impairment during prolonged infusions.

**Enoximone**

Enoximone, a substituted imidazoline derivative, is the other PDEI in current clinical usage. It acts by competitive inhibition of the sub-type PDE IV and possibly PDE III. It is presented as a clear yellow liquid and administered usually as 100 mg diluted to 40 or 50 ml. It has an elimination half-life of 20 h and administered as a loading infusion of 0.5–1.0 mg kg\(^{-1}\) over 10–30 min, followed by a maintenance infusion of 5–20 mcg kg\(^{-1}\) min\(^{-1}\).

Enoximone is metabolized mainly by oxidation to enoximone sulphone. In congestive heart failure, approximately 75% of a rapidly administered intravenous dose is excreted in the urine over 24 h as the sulphone metabolite. Enoximone sulphone has the same inotropic and vasodilator activities as enoximone but is 0.13–0.14 times as potent and has a greater than 10 times duration of action. Rather than reaching a steady state as predicted by their terminal exponential half-lives, plasma concentrations of both enoximone and enoximone sulphone continue to rise following prolonged infusion. This is suggestive of non-linear pharmacokinetics and indicates a potential for excessive accumulation of enoximone and its metabolite during prolonged infusion. Thus, the metabolite may contribute significantly to some of the effects that follow enoximone administration.

**Clinical use and haemodynamic effects**

**Chronic heart failure**

Major interest in the cardiovascular effects of PDEI drugs for chronic heart failure dates from the early 1970s. The drawbacks of digoxin were well known and the potential for another type of orally acting positive inotrope was viewed with interest. Initial studies were encouraging, but a randomized controlled trial of milrinone vs placebo (PROMIS) was abandoned due to excess early mortality in the treatment group.\(^2\)

More recently, interest has focused on enoximone as an orally active inotropic agent. Despite initial promise, enoximone failed to show significant benefit in patients with chronic severe heart failure in a series of phase 3 clinical trials (ESSENTIAL, ESSENTIAL II, EMOTE, EMPOWER).\(^3\)\(^,\)\(^4\)

**Acute heart failure**

Although milrinone and enoximone are chemically unrelated compounds affecting different PDE sub-types, their clinical effects (particularly haemodynamic) are similar. Both have been studied extensively in patients following cardiac surgery and, more recently, in a critical care setting.

A dose-finding study in cardiac surgery patients found that all three dosage regimens of milrinone caused a mean increase in cardiac index of 25–30%, despite a reduction in pulmonary capillary wedge pressure (PCWP) of approximately 20%. Systemic vascular resistance (SVR) was significantly reduced, mean arterial pressure (MAP) was also reduced, and heart rate increased by 10–15%.\(^5\) Analysis of the effects of milrinone in subgroups of patients revealed that the proportional increase in cardiac index was greatest in those patients with low treatment values, and that blood pressure falls were greatest in those patients with high pretreatment values.\(^6\) This suggested a good efficacy and safety profile, particularly for relatively short term (<24 h) administration.

Intravenous enoximone is also associated with an increase in cardiac index and a fall in PCWP.\(^7\) The effects on arterial blood pressure and heart rate are variable; however, most studies have shown little change or modest falls in blood pressure, little change in heart rate, and a reduction in pulmonary artery and central venous pressure. The major drawback to the use of enoximone and milrinone lies in their vasodilator effects which may result in hypotension, particularly in the vasoconstricted or hypovolaemic patient. Both drugs are effective at treating and reversing a low cardiac output state. However, it is worth reflecting that, in the acute intra-operative setting, diagnosing a low cardiac output state is particularly difficult without some means of directly measuring cardiac output, since the clinical stigmata of a low output state take some time to develop and may be masked by other factors. Therefore, patients may demonstrate not simply a low cardiac output, but also a low output state complicated by systemic...
hypotension before they are treated. The following practice points may be valuable:

- Before starting a PDEI, hypovolaemia must be corrected to prevent a further significant fall in blood pressure. Preloading the circulation may be necessary, although volume loading may be given at the same time as starting treatment with a PDEI. Volume loading should be undertaken with care in patients recently weaned from cardiopulmonary bypass since left ventricular compliance is usually abnormal, and rapid transfusion resulting in excessive left ventricular volume may cause a precipitate rise in left ventricular pressure, subendocardial compression, and myocardial ischaemia.
- Vasopressors may be needed and should be prepared for use at the same time as PDEI administration. A norepinephrine infusion is commonly used; vasopressin has been described as an alternative. For those patients already on a vasopressor, an increase in dosage requirements should be expected.

Comparison with catecholamines

There have been numerous small studies comparing the efficacy and safety of PDEI with catecholamines, usually following cardiac surgery. The most common clinical settings are in patients with a cardiac index of \(<2.2\) \text{L/min}\cdot\text{m}^2, or those following valve surgery. Milrinone or enoximone have been compared with either dobutamine or dopamine. Occasionally, a combination of catecholamine and a vasodilator has been used as the comparative treatment.

As might be predicted, most of these studies are relatively underpowered to show differences between treatments, establishing only that each drug is capable of improving haemodynamics within each group compared with baseline, with few differences between the groups at each time point. In general, the catecholamines show a greater increase in heart rate and MAP, whereas the PDEI show a greater reduction in PCWP and a greater increase in stroke index (SI). The change in cardiac index is often comparable, although many studies are designed with efficacy criteria set to achieve a 25–30% increase. Most studies conclude that either treatment is acceptable.

One study comparing milrinone with dobutamine has compared patients in severe low output states to those who were severely hypotensive at the time of treatment.9 The results are similar to other studies; milrinone was more effective at increasing stroke index and reducing PCWP, whereas dobutamine was more effective at reversing hypotension and increasing heart rate.

Combinations of PDEI and catecholamines

As previously described, 3,5 cAMP is highly effective in promoting an inotropic effect. Since catecholamines activate adenylyl cyclase leading to an increase in intracellular cAMP, and PDEI prevent the breakdown of cAMP, one would predict that a combination of both catecholamine and PDEI would have an additive effect. Royster et al.10 have demonstrated this using amrinone and epinephrine in patients recovering from cardiac surgery. Other studies have drawn similar conclusions, usually combining amrinone or milrinone with dobutamine. In clinical practice, PDEI and catecholamines are frequently combined in order to maximize the inotropic effect, while at the same time limiting the vasodilator effects of PDEI.

Right ventricular function and pulmonary hypertension

The pulmonary circulation represents a high flow low-pressure circuit. In the adult, the right ventricular muscle mass is significantly less than the left. The pulmonary vasculature is relatively poorly endowed with smooth muscle. Either an acute reduction in right ventricular contractility or an acute increase in right ventricular afterload may precipitate right ventricular failure.

PDEI have a useful role in the management of acute right ventricular failure, although it should be understood that the condition is notoriously difficult to treat effectively. Studies following cardiac surgery show a reduction in pulmonary artery pressure and pulmonary vascular resistance. Right ventricular stroke work index is increased and marked improvements in right ventricular ejection fraction have also been noted. However, a reduction in pulmonary artery pressure relies on vasorelaxation of smooth muscle which will be significantly more difficult to achieve in advanced pulmonary hypertension when hyalinization of the pulmonary arterioles may occur.

Milrinone has also been combined with other drugs to achieve pulmonary vasodilation. Experimental studies have been reported combining milrinone with a PDE type V inhibitor (sildenafil, zaprinast) and also with prostacyclin and inhaled NO.11, 12 Overall, combination of milrinone with a type V inhibitor appears to be effective. Inhaled milrinone seems also to be effective and associated with a reduced incidence of systemic hypotension compared with intravenous administration. The vasodilator effects of inhaled prostacyclin and NO are potentiated with inhaled milrinone.

Vascular effects

Both milrinone and enoximone have been shown to reduce systemic, pulmonary, and coronary vascular resistance when administered in inotropic doses. Since both drugs are considered to be inotropic agents, they are assumed to have adverse effects on myocardial oxygen balance. In fact, previous studies have established that myocardial oxygen balance is not impaired with milrinone13 and that ischaemic cardiac damage following CABG is less with milrinone than nifedipine.14 Studies in cardiac patients have even shown that exercise tolerance is improved with milrinone. While it may be inappropriate to suggest using milrinone as an acute anti-anginal agent, it clearly does not have the stress provoking properties of the catecholamines, including dobutamine.
The vasorelaxant properties of enoximone and milrinone are clearly associated with improvements in right and left ventricular function. However, splanchnic blood flow is not selectively increased with PDEI therapy, and levosimendan has been shown to be superior at increasing gastric mucosal oxygenation selectively.15

Sildenafil (Viagra), tadalafil, and vardenafil are selective inhibitors of type V phosphodiesterase (PDE5), which is cGMP-specific and responsible for the degradation of cGMP in the corpus cavernosum. These PDEI are used as remedies for erectile dysfunction. However, the vascular effects of PDE V inhibitors are more widespread and studies have described their use either alone or with PDE III inhibitors in patients with pulmonary hypertension.

Effects on inflammation

Patients with decompensated heart failure show marked systemic inflammation and increased production of oxygen free radicals. Short-term inotropic support not only improves functional status but has also been shown to reduce indices of inflammation and oxidative stress.

PDE IV inhibitors have greater effects on inflammation when compared with PDE III inhibitors. In particular, roflumilast, cilomilast, and rolipram have been associated with significant anti-inflammatory effects, including the inhibition of neutrophil degranulation.16 PDE IV inhibitors have been studied extensively in patients with asthma, and they have received considerable attention due to their attenuating effects on activated inflammatory cells which are involved in the pathophysiology of a wide range of allergic and inflammatory diseases. However, the side-effects of the PDE IV inhibition (including nausea, vomiting, and headache) have limited the development of this class of compound. Nonetheless, there is speculation that the anti-inflammatory properties of PDEI may be relevant in reducing the pro-inflammatory response to cardiopulmonary bypass, and there may be a role for phosphodiesterase i.v. inhibitors in sub-inotropic doses in this setting.

References


Please see multiple choice questions 21–25