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Review

Reevaluating the Role of Phosphodiesterase Inhibitors in the Treatment of Cardiovascular Disease

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Summary: First developed for clinical use in the late 1980s, the phosphodiesterase inhibitors were found to increase the levels of the ubiquitous second messenger cyclic adenosine monophosphate and could effect changes in vascular tone, cardiac function, and other cellular events. After several early studies using high doses of phosphodiesterase inhibitors in patients with severe heart failure suggested adverse consequences, they fell out of favor. However, recent investigations of phosphodiesterase inhibitors in patients with intermittent claudication have demonstrated profound benefits. Furthermore, these agents have proven useful in prevention of cerebral infarction and coronary restenosis, and their use in the treatment of heart failure is being reevaluated. The reemergence of phosphodiesterase inhibitors can be attributed to a better understanding of dosing and drug-specific pharmacology, the use of concomitant medications, and a recognition of unique ancillary properties; however, their use still requires caution.

Key words: phosphodiesterase inhibitors, cyclic adenosine monophosphate (AMP), cilostazol, peripheral arterial disease (PAD), pentoxifylline

Introduction

With the recognition that the cyclic nucleotide adenosine monophosphate (cAMP) is a ubiquitous second messenger in mammalian cells that participates in modulating function in a variety of human tissues, aggressive efforts were made to develop pharmacologic agents that could modify vascular tone, cardiac function, and other cellular events by increasing intracellular concentrations of cAMP. An effective means of increasing cellular levels of cAMP is to inhibit the metabolism of the nucleotide with phosphodiesterase inhibitors. After several early studies using high doses of phosphodiesterase inhibitors in patients with severe heart failure raised the possibility that these agents could do more harm than good, their development was largely discontinued. However, the development of new phosphodiesterase inhibitors, an improved understanding of human disease, the recognition of the importance of dosing and concomitant medications, and a better understanding of some of the ancillary properties of these agents have led to a reemergence of interest in these medications. The beneficial effect of cilostazol in the treatment of intermittent claudication is but one example of the reemergence of these compounds. Thus, it is important to review the development of phosphodiesterase inhibitors, their early history, their resurgence in the treatment of a variety of cardiovascular diseases, and cautions regarding their use.

The Receptor-G Protein—Adenylyl Cyclase System and Cellular Function

In the late 1960s, Earl Sutherland and his colleagues discovered the second messenger cAMP and its role in intracellular signaling. Synthesized from adenosine triphosphate (ATP) by the enzyme adenylate cyclase, cAMP modulates the biochemistry and physiology of the cell by activating a cAMP-dependent protein kinase with the subsequent phosphorylation of a variety of cellular proteins. Once synthesized, cAMP is metabolized by a family of phosphodiesterases to the chemically inactive byproduct—5'AMP. Alterations in the ability of specific cells and tissues for the appropriate regulation of the production of cAMP contributes to the pathophysiology of a

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variety of human diseases. On the other hand, modulation of intracellular levels of cAMP could have salutary effects by virtue of the ability of cAMP to affect a number of cellular processes, including dilatation of the coronary, pulmonary, and peripheral vasculature; inhibition of proinflammatory cytokine expression; attenuation of platelet aggregation; and augmentation of cardiac contractility.

The Development of Phosphodiesterase Inhibitors

In 1972, Alousi *et al.* developed the bipyridine derivative phosphodiesterase inhibitor amrinone.[1] This novel agent increased intracellular concentrations of cAMP by inhibiting its metabolism by phosphodiesterase and produced positive inotropic effects and concentration-dependent vasodilation.[1–4] Unfortunately, the use of amrinone was limited because of adverse effects, including gastrointestinal and central nervous system complaints as well as a suggestion of increased mortality in patients with heart failure.[5] However, a series of additional phosphodiesterase inhibitors, including milrinone, enoximone, vesnarinone, pentoxifylline, and cilostazol were developed, each having unique pharmacologic properties.

Phosphodiesterase Inhibitors for Secondary Prevention of Cerebral Infarction

Agents that interfere with the formation of platelet fibrin thrombi have demonstrated long-term benefits by preventing strokes in high-risk patients, including those with a prior cerebral infarction. Ticlopidine and aspirin have been frequently used for secondary protection in high-risk patients; however, their use has been associated with neutropenia, diarrhea, and skin rash[6] in the case of ticlopidine, and frequent gastrointestinal side effects[7] in the case of aspirin. More recently, the benefit of clopidogrel has been described in the prevention of heart attack, stroke, and sudden death in patients with a history of heart attack, stroke, or peripheral arterial disease (as manifested by intermittent claudication).[8] A recent multicenter, randomized, placebo-controlled, and double-blind clinical trial demonstrated the effectiveness of the novel phosphodiesterase inhibitor cilostazol in the management of patients who are at high risk for the development of cerebral infarction because of a previous stroke.[9] Of importance is the fact that no clinically significant adverse drug reactions were encountered. In contrast to milrinone, cilostazol predominantly inhibits PDE3A and PDE3B, with far less effects on PDE4.

Phosphodiesterase Inhibitors for Intermittent Claudication

Peripheral arterial disease (PAD) is a common disorder most frequently found in elderly populations.[10] While many patients with PAD remain asymptomatic, nearly 40% have intermittent symptoms that limit their ability to perform their daily activities. Indeed, intermittent claudication, which is undiagnosed in as many as 75% of patients, has been found to affect as many as 5% of men and 3% of women > 60 years of age.[11] Symptoms routinely occur when patients are walking because the ability to increase vascular flow to the large muscle groups is limited, resulting in muscle ischemia and pain. Traditional therapy for intermittent claudication has included aggressive risk-factor modification, including smoking cessation, lipid modification, and treatment of hypertension and diabetes.[12] In addition, supervised exercise training has been shown to be of benefit and, for the prevention of atherosclerotic events, antiplatelet therapy, including aspirin, ticlopidine, and clopidogrel has been used extensively (see above).[12] However, some patients require surgical revascularization, percutaneous interventional procedures, or even amputation. Because of the role of cyclic nucleotides in the relaxation of vascular smooth muscle, it was hypothesized that agents that enhanced cAMP accumulation, that is, phosphodiesterase inhibitors, might be useful in the treatment of PAD, including intermittent claudication.

The first pharmacologic agent approved for the treatment of intermittent claudication in the U.S. was the nonspecific phosphodiesterase inhibitor, pentoxifylline (Fig. 1); however, the benefits of pentoxifylline have been somewhat controversial. In the Scandinavian Study Group trial, a large trial of pentoxifylline in patients with intermittent claudication, there was no statistically significant improvement in pain-free walking distance or maximal walking distance in pentoxifylline-treated patients compared with placebo-treated patients,[13] and a meta-analysis only "suggested" benefit.[14]

More recently, the phosphodiesterase inhibitor cilostazol has been approved by the Food and Drug Administration for the treatment of patients with intermittent claudication. The efficacy of cilostazol was demonstrated in seven U.S. and one U.K. placebo-controlled, multicenter studies. When cilostazol was evaluated in comparison with placebo in 81 subjects from three centers who had chronic lower-extremity arterial occlusive disease, active therapy effected a 35% improvement in initial claudication distance and a 41% improvement

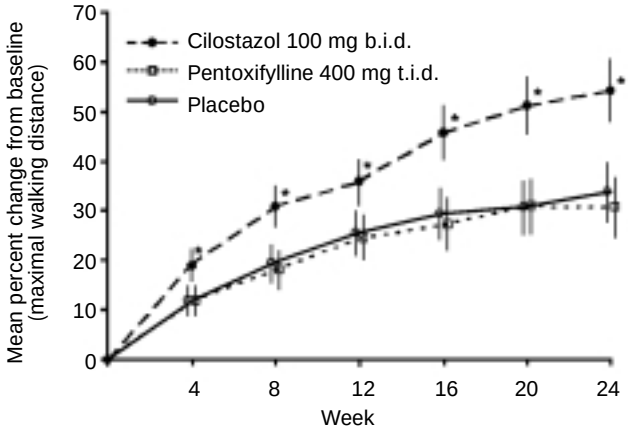

FIG. 1 Effects of the phosphodiesterase inhibitors cilostazol and pentoxifylline on functional capacity (maximal walking distance) in patients with intermittent claudication. Reprinted from Ref. No. 17 with permission.

in maximal walking distance without significant changes in resting or postexercise ankle/brachia indices. Furthermore, both patients' and physicians' subjective assessments were consistent with the measured improvements in walking performance.[11] More recently, the efficacy of cilostazol was also assessed in a multicenter, randomized, double-blind, placebo-controlled study at 37 centers in the U.S.[15] In this study, cilostazol effected an improvement in walking distance, quality of life, functional status, and global assessment. Similarly, in a different study, single-blind substitution of placebo for cilostazol was associated with a significant loss of treatment benefit.[16] Furthermore, survival was not different in any of the treatment groups during the course of the clinical trials.

The benefits of cilostazol appear to be substantially greater than those of pentoxifylline[17] when assessing both maximal and pain-free walking distances. Indeed, while mean maximal walking distance of cilostazol-treated patients was significantly greater at every post-baseline visit than that of patients who received either pentoxifylline or placebo, there was no statistically significant difference between exercise duration in the pentoxifylline and placebo treatment groups. The different efficacies of these two phosphodiesterase inhibitors might be explained by novel ancillary properties associated with cilostazol. For example, cilostazol appears to have beneficial effects on plasma lipoproteins in patients with intermittent claudication (Fig. 2).[18, 19] Cilostazol (100 mg b.i.d.) reduced plasma triglycerides by 15%, increased high-density lipoprotein (HDL) cholesterol by 10%, and increased apolipoprotein A1 by 5.7% compared with placebo in a group of patients with intermittent claudication.[19] Furthermore, both HDL-2 and HDL-3 subfractions of HDL cholesterol were increased, with the greatest percentage increase being observed in HDL-2, which is generally considered the more antiatherogenic of the HDL subfractions. The most robust effect on triglycerides, a 23% reduction, was observed in patients with baseline elevations in triglycerides (> 140 mg/dl).

Cilostazol has additional properties that may or may not be mediated through increased concentrations of intracellular cAMP, but which may play a role in the increased exercise tolerance seen in patients with intermittent claudication. For example, cilostazol significantly increased the accumulation of nitric oxide (NO) by cultured vascular smooth muscle cells. The cilostazol-induced nitrite production was accompanied by increased inducible NO synthase protein expression, but appeared to be mediated by activation of interleukin-1 beta and mediated at least in part through a cAMP-dependent pathway.[20] Cilostazol had a similar effect on NO production in a human neuroblastoma cell line; however, the effects of increasing cAMP and NO production in nerves appeared to be regulated by NO-dependent activation of Na, K-ATPase.[21] This improvement in Na, K-ATPase activity might explain the improvement in patients with diabetic neuropathy treated with cilostazol.[22, 23]

In contrast to the phosphodiesterase inhibitor milrinone, cilostazol also inhibits adenosine uptake into cardiac ventricular myocytes, coronary artery smooth muscle, and endothelial cells, resulting in increased cardiac interstitial adenosine levels.[24] An increase in extracellular adenosine concentrations effectively diminished the infarct zone after regional ischemia and reperfusion in rabbits and may be cardioprotective in patients with left ventricular dysfunction.[25] Thus, modification of adenosine concentrations in the peripheral muscles may positively influence exercise performance.

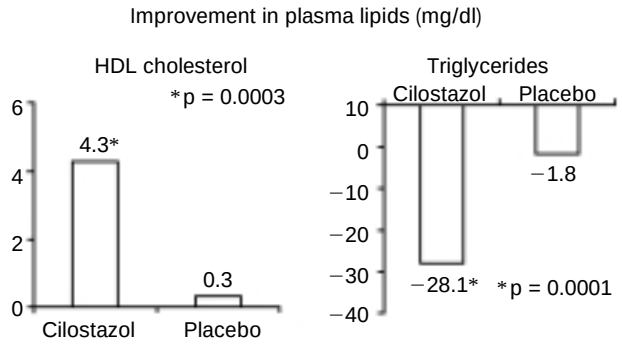

FIG. 2 Effects of the phosphodiesterase inhibitor cilostazol on plasma lipids. HDL = high-density lipoprotein. Adapted from Ref. No. 19.

Phosphodiesterase Inhibitors for the Prevention of Coronary Restenosis

Percutaneous transluminal coronary angioplasty (PTCA) and newer percutaneous coronary interventions (PCI) have had a dramatic impact on the global burden of cardiovascular disease. Although the short-term success rate of PCI has been overwhelming,[26] the long-term impact of PCI has been limited by restenosis and the recurrence of clinically significant coronary artery occlusion within 6 months of the initial intervention. A variety of factors have been implicated in the development of restenosis, including elastic recoil, thrombosis, expression of vasoactive molecules such as growth factors and cytokines, smooth muscle cell migration, neointimal formation, extracellular matrix remodeling, and geometric remodeling.[26]

Although phosphodiesterase inhibitors have not been approved in the U.S. for patients post angioplasty, a group of interesting studies has suggested potential benefits of the phosphodiesterase inhibitor cilostazol in diminishing PTCA-induced restenosis in both animal models and human trials. In a rat model of carotid balloon injury, the local application of cilostazol at the time of injury halved the number of proliferating medial smooth muscle cells and inhibited neointimal formation.[26] When cilostazol and aspirin were administered to patients 2 days after PTCA, restenosis rates were not different from those in patients who had received ticlopidine and aspirin.[27] However, when patients undergoing rescue PTCA for an acute myocardial infarction received the combination of cilostazol and aspirin for 6 months, restenosis rates were significantly lower than those in a group of patients who were randomized to receive ticlopidine and aspirin.[28] Furthermore, cilostazol appeared to be as effective as ticlopidine when

combined with aspirin in inhibiting the development of thrombotic events during the first 30 days post PTCA.[29, 30] Recent studies have also demonstrated that cilostazol, when initiated immediately after PTCA or atherectomy, could substantially minimize coronary restenosis compared with aspirin or ticlopidine.[31–33] Cilostazol also reduced coronary artery restenosis by 55% and lesion area when administered prior to plaque removal in patients undergoing atherectomy.[33] Of importance is the fact that the salutary effects of cilostazol were not associated with adverse effects, whereas ticlopidine has a risk of neutropenia.

While the mechanism responsible for the salutary effects of cilostazol on coronary restenosis rate has not been definitively identified, investigators have hypothesized that its benefits are attributable to increased synthesis of NO within the coronary vasculature.[26] However, it is equally possible that the beneficial effects of cilostazol can be explained by cAMP-mediated inhibition of platelet aggregation, thrombus formation, and proinflammatory cytokine expression, promotion of vasodilation, or decreased smooth muscle cell proliferation and monocyte chemoattractant protein-1 synthesis. Additional studies will be required to assess the efficacy of phosphodiesterase inhibitors in patients undergoing stent placement and brachytherapy.

Phosphodiesterase Inhibitors in Patients with Heart Failure

Optimal therapy for patients with heart failure includes therapy with angiotensin-converting enzyme (ACE) inhibitors and beta blocker as they improve survival and decrease hospitalizations. Because of their ability to improve cardiac contractility independent of beta-adrenergic receptor activation, there was initial enthusiasm for using both intravenous and oral phosphodiesterase inhibitors in the treatment of patients with severe symptoms despite optimal therapy. Indeed, intravenous milrinone may be used as continuous therapy to bridge patients (especially those on beta blockade) to cardiac transplantation or to provide palliative treatment for patients with end-stage cardiac disease.

However, physicians' enthusiasm about using oral phosphodiesterase inhibitors in the therapy of patients with cardiovascular disease was diminished by two clinical studies performed in patients with severe heart failure. The Prospective Randomized Milrinone Survival Evaluation (PROMISE) study, a trial that randomized patients with severe congestive heart failure symptoms (class III–IV) and a left ventricular ejection fraction of < 35% to a relatively high dose of milrinone or to placebo,[34] was stopped by the data and safety monitoring board because of a 28% increase in mortality in the group receiving active therapy. VEST, begun in 1995, evaluated the effects of the phosphodiesterase inhibitor vesnarinone in a similar group of patients with similar results.[35]

Although these two early studies engendered great concern among physicians, subsequent investigations have highlighted several important points: (1) the doses used were chosen empirically without benefit of appropriate in vivo dose–response curves; (2) beta blockers, agents known to diminish the incidence of sudden death in patients with heart failure or post myocardial infarction, were excluded; and (3) patients were included only if they had severe symptoms.

Thus, an increasing number of interesting basic research and clinical findings suggested that phosphodiesterase inhibitors might have a role in the management of patients with heart failure when used at the appropriate doses/plasma concentrations, with concomitant heart failure medications (including ACE inhibitors and beta blockers), and in the correct patient population.

When high doses of enoximone, a selective type III sarcoplasmic reticulum-associated phosphodiesterase inhibitor, were initially evaluated in patients with heart failure (4–6 mg/kg/day), their use was associated with an increase in mortality.[36] However, early studies suggested that < 3.0 mg/kg/day could be used successfully to bridge patients from heart failure to heart transplantation without an apparent increase in mortality.[37] These results led investigators to hypothesize that low doses of enoximone might preclude the increased toxicity associated with higher doses of a phosphodiesterase inhibitor. Furthermore, the advent of beta-blocker therapy for patients in class II and III heart failure also led clinicians to propose that the combination of a phosphodiesterase inhibitor and a beta blocker could result in additive efficacy while their adverse effects could be subtractive, that is, the arrhythmogenic effects of phosphodiesterase inhibitors could be attenuated by beta blockade while the negative inotropic effects of beta blockers could be abrogated by the phosphodiesterase inhibitor.[38] This hypothesis was first tested in 1998 by Shakar *et al.*, who used beta blockers and low-dose therapy with enoximone to treat patients with severe heart failure.[39] Of the patients who received the combination therapy, 48% were weaned off of enoximone over the long term. Furthermore, there was a significant improvement in left ventricular ejection fraction and in functional classification.

More recently, Lowes *et al.* used low-dose enoximone (25 and 50 mg t.i.d.) to treat patients in class II to III heart failure[38] (Fig. 3). When compared with placebo, both doses improved exercise capacity after 12 weeks. Significant improvements in heart failure symptoms and left ventricular function were also seen when patients receiving baseline therapy with digoxin, ACE inhibitors, and the beta blocker carvedilol were randomized to receive a low dose (400 mg t.i.d.) of the nonspecific phosphodiesterase inhibitor pentoxifylline for up to 6 months.[40] Based on the success of these initial studies, the use of low-dose enoximone to wean patients from intravenous inotropic therapy or to bridge patients to beta blockade is now being evaluated in two large multicenter clinical trials (Oral Enoximone in Intravenous Inotrope-Dependent Subjects [EMOTE] and Enoximone Plus Metoprolol in Subjects with Advanced Chronic Heart Failure [EMPOWER]).

The efficacy of low doses of phosphodiesterase inhibitors in patients with heart failure without arrhythmogenic and cardiotoxic effects may be attributable to the low doses or to their combination with beta blockers. However, it should also be recognized that virtually all of the phosphodiesterase inhibitors that are now utilized for the treatment of intermittent clau-

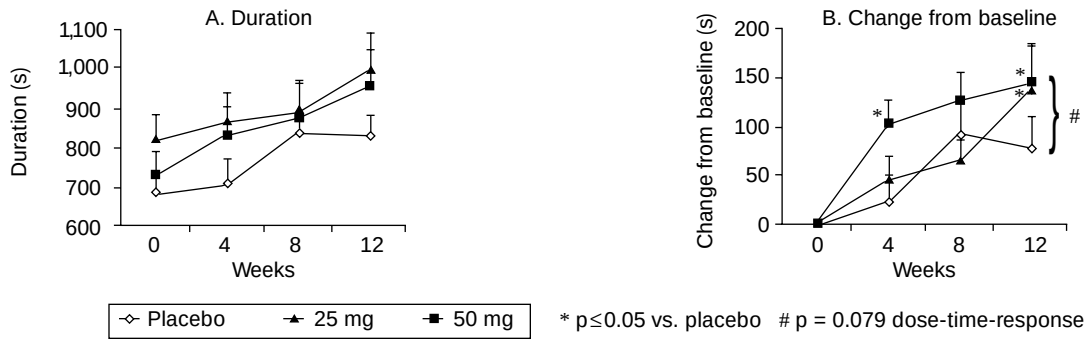

FIG. 3 Effects of the various doses of the phosphodiesterase inhibitor enoximone on exercise in patients in New York Heart Association class II and III heart failure. Adapted from Ref. No. 38.

dication (pentoxifylline and cilostazol) or are under evaluation for the treatment of heart failure (pentoxifylline and enoximone) are potent inhibitors of myocardial expression of proinflammatory cytokines, and in particular of tumor necrosis factor alpha (TNF-α), a peptide strongly implicated in the development of heart failure.[41]

Safety of Phosphodiesterase Inhibitors in the Treatment of Heart and Vascular Disease

Currently, phosphodiesterase inhibitors are approved for only two treatment indications in the U.S. The intravenous form of milrinone is approved for the treatment of patients with acute exacerbations of congestive heart failure and the oral phosphodiesterase inhibitors cilostazol and pentoxifylline are approved for the treatment of intermittent claudication. Although cilostazol remains contraindicated in patients with heart failure, it is important to recognize that differences exist between the various phosphodiesterase inhibitors in terms of their selectivity for specific phosphodiesterase isoforms as well as in their ancillary properties. For example, they have varying inhibitory effects on proinflammatory cytokine expression and different inotropic properties. Furthermore, although cilostazol and milrinone effect similar increases in cAMP levels in platelets, milrinone elevated cAMP levels significantly more than did cilostazol in cardiac myocytes and coronary artery smooth muscle cells.[42]

Patients with exercise-limiting heart failure were excluded from the clinical trials of cilostazol since this condition could have masked the effect of the drug on intermittent claudication. In the Phase III trial, patients with a prior history of heart failure, only 2 of 42 patients on placebo (4.8%) and 3 of 55 patients on cilostazol (5.5%) experienced worsening heart failure; thus, cilostazol does not appear to exacerbate heart failure. On the other hand, patients with heart failure were more likely to withdraw from the trials if they were on cilostazol than if they were on placebo. Furthermore, cilostazol does not appear to precipitate heart failure.

Thus, while regulatory guidelines currently preclude the use of cilostazol in patients with heart failure, additional studies will be needed to assess the safety of cilostazol in patients with intermittent claudication and symptomatic heart failure. It would also be of interest to test the hypothesis that cilostazol will have an even greater safety margin in heart failure patients when used in combination with beta blockade. While awaiting the results of these additional studies, physicians should exercise prudence in defining which patients can safely receive cilostazol therapy.

The presence of classical signs and symptoms should alert the physician to the possibility of heart failure and warrant further evaluation, including an echocardiogram. However, in the absence of signs and symptoms, the practitioner should feel comfortable in treating patients with intermittent claudication with a phosphodiesterase inhibitor. Two additional caveats, though, warrant mention. First, the term "heart failure" implies left ventricular dysfunction secondary to diminished systolic performance. However, many patients have signs and symptoms of heart failure secondary to hypertrophic cardiomyopathy and diastolic dysfunction. These patients will routinely present with signs and symptoms of heart failure, but, unlike patients with heart failure secondary to systolic dysfunction, should not receive a phosphodiesterase inhibitor or digoxin as increased inotropy is counterproductive in this group of patients. Furthermore, it is important to note that the patients enrolled in the clinical studies that reported poor outcomes in patients randomized to oral phosphodiesterase inhibitors had "severe" heart failure symptoms. Thus, these patients were easily recognized by a relatively simple but careful history and physical examination. Furthermore, recent studies have shown that measurement of brain natriuretic peptide levels may also be useful in diagnosing the presence of left ventricular dysfunction.[43] Therefore, withholding therapy with phosphodiesterase inhibitors from patients with the possibility of heart failure but without accompanying signs or symptoms may not be warranted.

Conclusion

Although phosphodiesterase inhibitors lost favor in the early 1990s, recent studies have restored them to investigational and clinical focus. First and foremost, the phosphodiesterase

inhibitor cilostazol has been found to have highly beneficial effects in patients with intermittent claudication. Indeed, the recent approval of cilostazol has provided a new weapon in our therapeutic armamentarium for the treatment of this common and debilitating disease. In addition, a study demonstrating that cilostazol was effective in secondary prevention of cerebral infarction[11] and other studies indicating its effectiveness in prevention of restenosis after PCI encourage additional investigation of this compound.

As noted, the "black box" contraindication of heart failure for cilostazol is based solely on the experience with other PDE III inhibitors in patients in class III–IV heart failure. However, the early investigational support for the hypothesis that the combination of a beta blocker and a phosphodiesterase inhibitor could have a greater impact than the use of either drug alone by obviating the potential adverse effects of either agent has led to new and interesting clinical studies assessing the role of phosphodiesterase inhibitors in heart failure. Furthermore, the demonstration that phosphodiesterase inhibitors are potent inhibitors of the expression of proinflammatory cytokines and the recognition that cytokines participate in pathobiology of many human diseases including heart failure, rheumatoid arthritis, and Crohn's disease also opens up new treatment arenas for these interesting compounds. Thus, it is possible that we will see additional uses of phosphodiesterase inhibitors in a variety of human diseases in the future.

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