



Pharmacy

January/February 1999

Update

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor

Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information
Service, and Clinical Specialist,
Endocrinology & Women's Health
kcalis@nih.gov

Associate Editor

Maryam R. Mohassel, Pharm.D.
Specialized Resident in Drug
Information Practice and
Pharmacotherapy
mmohassel@nih.gov

In This Issue

- **Bosentan and the Endothelin System**
- **Did You Know...**
- **Formulary Update**

Bosentan and the Endothelin System in Congestive Heart Failure

Congestive heart failure (CHF) is a progressive clinical syndrome characterized by signs and symptoms of intravascular and interstitial volume overload. Signs and symptoms include rales, edema, and shortness of breath, or manifestations of inadequate tissue perfusion, such as poor exercise tolerance or fatigue. CHF results primarily from the inability of the heart to properly fill or empty the left ventricle. In the United States, it is estimated that more than two million people have heart failure, and an additional 400,000 cases are diagnosed each year. The prevalence of CHF is increasing as the population continues to age. Mortality during the first five years from the time of diagnosis of CHF continues to be high, even among patients on the best available treatments. The last few years have brought significant advances in the understanding of the pathogenesis of CHF. Increasing evidence suggests a potential role of the endothelin system in the pathophysiology of CHF. With the recent discovery and development of endothelin receptor antagonists, the clinical potential of therapeutic agents that target the endothelin system is being actively evaluated. Bosentan, an orally active endothelin receptor antagonist, is to date the most well studied of these agents for the treatment of CHF.

The Endothelin System

The endothelin family includes a group of three 21-amino acid peptides with very similar structures: endothelin-1 (ET-1), ET-2 and ET-3.¹⁻⁴ ET-1 is the most important endothelin synthesized in the blood vessels, mainly in endothelial cells.¹ Almost 75 percent of ET-1 secreted by endothelial cells is directed toward the abluminal site, where it can bind to specific receptors on the smooth muscle cells.⁵ Therefore, plasma ET-1 concentrations do not necessarily reflect endothelial cell production or the biological effect of ET-1 on smooth muscle cells.

The development of specific ET receptor agonists and antagonists has led to the identification of two receptor subtypes in mammalian cells, ET_A and ET_B.^{6,7} ET_A receptors are present on smooth muscle cells and are responsible for the contractile response to ET-1. The vasoconstrictor effect persists even after ET-1 is removed from the receptor, probably because intracellular calcium concentrations remain elevated.⁸ Nitric oxide shortens the duration of this vasoconstriction by accelerating the decrease of intracellular calcium to its basal concentration.^{9,10} ET_B receptors were first described on endothelial cells.¹¹ They bind ET-1 and ET-3 with similar affinity, and their stimulation leads to a transient vasodilation, probably caused by increased production of nitric oxide and prostacyclin. However, ET_B receptors are also present on vascular smooth muscle cells, where their activation produces vasoconstriction.¹²⁻¹⁴ Besides short-term regulation of vascular tone, ET-1 exerts a long-term modulation of cell function by affecting nuclear signal transduction mechanisms. Via these mechanisms, ET-1 may participate in the pathogenesis of proliferative disorders, such as atherosclerosis, and also in adaptive changes leading to vascular remodeling and cardiac hypertrophy as observed in congestive heart failure.

ET-1 is the most potent endogenous vasoconstrictor. It is 100 times more potent than norepinephrine and ten times more potent than angiotensin II on a molar basis. ET-1-induced contraction in isolated blood vessels develops slowly, but is maintained for a longer time and is more resistant to removal than that evoked by any other vasoconstrictor. ET-1 also potentiates the vasoconstriction caused by norepinephrine and angiotensin II. The vascular

effect of ET-1 in healthy humans has been investigated by local infusion of the peptide into the brachial artery. ET-1 administration causes a dose-dependent vasoconstriction that is slow in onset and may be prevented by verapamil or nifedipine through blockade of voltage-operated calcium channels.⁸ Because of its high vasoconstrictor potency and long-lasting actions, the continuous release of small amounts of ET could contribute to the maintenance of vascular tone.^{15,16}

One postulated mechanism for the maintenance of basal tone is the production of vasoactive substances by endothelial cells. ET-induced vascular contraction is effectively antagonized by endothelium-derived vasorelaxant substances, such as prostacyclin (PGI₂) and the potent endogenous vasodilator nitric oxide (NO).^{9,10,17} An imbalance between the production of ET and NO could lead to a pathologically elevated vascular tone. Moreover, the vasoconstricting properties of ET-1 are greatly enhanced in atherosclerotic vessels in which the opposing biological effect of nitric oxide is lost.

A role of the endothelin system has been postulated in various conditions of disturbed vascular homeostasis, such as hypertension, coronary artery disease, and CHF.¹⁸⁻²⁴ The suspected role of ET-1 in the pathophysiology of CHF relies on several observations: 1) increased local production of the peptide by vascular tissues and/or increased circulating plasma levels due to its increased production or decreased degradation; 2) increased vasoconstrictor activity because of increased responsiveness of target cells or reduced counterbalancing mechanisms (reduced production or increased degradation of vasodilator substances); 3) beneficial effects of ET receptor antagonists in animal models and in humans; and 4) significant correlation between ET plasma levels and exercise capacity,²⁵ vascular resistance²⁶ and clinical prognosis in CHF.²⁷

ET of either local or circulatory origin significantly contributes to the increased vascular resistance in the renal vasculature.²⁸ The kidney is considered a major site of endothelin production and an important target organ of this peptide.²⁹ The highest immunoreactive levels of ET in mammalian cells exist in the renal medulla. However, ET has also been localized in the renal cortex.³⁰ The renal vasculature is preferentially sensitive to the vasoconstrictive effects of ET compared to other arteries or veins. In vitro studies utilizing isolated perfused kidney of either rat or rabbit demonstrated that ET is the most potent vasoconstrictor of renal arteries known to date, and its effects exceed those of other well known vasoconstricting agents such as angiotensin II and norepinephrine. Exogenous endothelin markedly decreases renal blood flow as a result of a severe and sustained increase in renal vascular resistance. In contrast to the consistent effects of ET on the renal hemodynamics, its effects on the excretion of sodium and water is variable. Systemic infusions of high doses of ET results in antinatriuretic and antidiuretic effects, probably as a result of the decrease in the renal blood flow and glomerular filtration rate. In contrast, administration of low doses of the peptide induces natriuresis and diuresis. Also, administration of big ET, the precursor of ET, has been shown to cause similar effects to low doses of ET. This finding supports the notion that local ET acts in an

autocrine/paracrine manner on the tubular epithelial cells where it inhibits sodium reabsorption, thereby inducing increased salt and water excretion.³¹⁻³⁹

Bosentan

Bosentan is the most studied endothelin receptor antagonist to date. Several other compounds with various affinities for endothelin receptors have been described and are currently under evaluation for various clinical indications, including CHF. Bosentan (Ro 47-0203) is a low-molecular weight, orally active, specific antagonist of the endothelin receptors, ET_A and ET_B.⁴⁰ The affinity of bosentan for the ET_A receptor is about 100 times greater than for the ET_B receptor in cultured cells.⁴⁰

Clinical Pharmacology

Following oral administration of an aqueous solution of bosentan, peak plasma concentrations were reached within two to three hours.⁴¹ Bosentan exhibits a strong binding to plasma proteins, especially albumin.⁴² This drug has a low systemic plasma clearance and a terminal half-life of approximately four hours. The clearance and volume of distribution of bosentan were 10 L/h and 0.2-0.3 L/kg, respectively after an intravenous dose of 250 mg (systemic exposure comparable to 500 mg of the oral solution). Both the clearance and volume of distribution of bosentan appear to decrease following higher intravenous doses. Bosentan is metabolized by the liver and undergoes some biliary excretion.

Animal Studies

Bosentan improves hemodynamics, left ventricular function, and cardiac remodeling in animal models of chronic heart failure. Several factors may account for the cardioprotective effects of bosentan, including reduced cardiac preload and afterload, improved coronary blood flow, inhibition of neurohormonal activation, and chronic structural effects (inhibition of cardiac remodeling, cardiac hypertrophy and cardiac fibrosis) by direct inhibition of the actions of ET-1 on myocardial cells. In animal experiments, treatment with bosentan has been associated with beneficial pharmacological effects, including vasodilation, prevention of cardiac remodeling, and improvement of ventricular performance. In several models of hypertension in rats, bosentan reduced blood pressure, and in the DOCA-salt model, decreased cardiac hypertrophy and fibrosis.⁴³⁻⁴⁵ These effects may result from the blockade of the cardiac actions of endothelins (i.e., myocardial hypertrophy,⁴⁶ smooth muscle cell⁴⁷ and fibroblast⁴⁸ proliferation, and protein [glycoproteins, thrombospondin, fibronectin] synthesis and secretion).⁴⁹ In a rat model of heart failure, following acute coronary ligation,⁵⁰ bosentan decreased the afterload. In another model, in which heart failure results from aorto-caval fistula, renal blood flow increased following treatment with bosentan suggesting that the vasodilatory properties of bosentan could be beneficial in the treatment of altered renal hemodynamics associated with heart failure. The long-term effects of oral bosentan treatment were studied in rats with heart failure following coronary artery ligation. Treatment with bosentan significantly improved survival at nine months to a similar extent as the ACE inhibitor cilazapril.⁵⁰ Bosentan treatment resulted in decreased preload and afterload;

increased cardiac output; and decreased left ventricular hypertrophy, left ventricular dilatation, and cardiac fibrosis. Heart rate was slightly decreased, and neurohormonal activation was reduced. In dogs with heart failure due to repeated coronary embolization, acute injection of bosentan had no significant effect on mean aortic blood pressure but reduced left ventricular end-diastolic pressure and systemic and pulmonary vascular resistance. Furthermore, bosentan increased cardiac output.⁵¹ Given these pharmacologic effects, bosentan could potentially reduce the pulmonary hypertension which occurs in congestive heart failure.

By blocking both ET_A and ET_B receptors, bosentan may be of particular benefit in heart failure. Indeed, stimulation of ET_A receptors contributes to renal and systemic vasoconstriction as well as cardiac hypertrophy. On the other hand, ET_B receptors are upregulated in the media of coronary arteries from patients with ischemic heart failure.⁵² The ET_B receptors contribute to vasoconstriction in dogs and in man with heart failure.^{52,53} Additionally, ET_B receptors are important mediators of cardiac fibrosis⁵⁴ and of aldosterone secretion.⁵⁵ Oral administration of bosentan is associated with an increase in the levels of circulating ET-1 in various animal species.⁴⁰ The mechanism leading to this reactive increase in ET-1 remains unknown, although it has been suggested that it may result from blockade of ET_B receptors involved in the clearance of endothelins from the circulation. The apparent absence of functional consequences of increased ET-1 concentrations may be due to complete inhibition of the endothelin system as result of bosentan's blockade of both both ET_A and ET_B.

Human Studies

Two clinical studies have been reported to date in patients with moderate to severe chronic heart failure. Additionally, one large dose-ranging study has been completed in patients with mild to moderate essential hypertension. All three studies were placebo-controlled, double-blind trials which provide the first clinical evidence of the potential clinical benefits of bosentan.

In the study by Krum et al.,⁵⁶ 293 patients with mild to moderate hypertension were randomized to receive treatment with placebo, enalapril 20 mg once daily, or bosentan (100 mg, 500 mg or 1000 mg once daily or 1000 mg twice daily). Patients receiving bosentan exhibited blood pressure reductions similar to those receiving the ACE-inhibitor enalapril. Heart rate, angiotensin II, renin, norepinephrine and epinephrine plasma concentrations remained unchanged during therapy with bosentan, whereas ET-1 plasma levels increased by approximately 50 percent from baseline. Bosentan was generally well tolerated. Adverse effects included headache, leg edema, and dizziness. Transient elevations in hepatic transaminases were reported in fewer than five percent of the patients.

In the study by Kiowski et al.,⁵⁷ 24 patients with CHF (New York Heart Association [NYHA] functional class III) in whom therapy for heart failure had been discontinued were studied. Patients received placebo or bosentan intravenously (100 mg followed by 200 mg one hour later). Cardiac, pulmonary, and systemic hemodynamic parameters were

assessed repeatedly for two hours. Infusion of bosentan resulted in pronounced systemic, pulmonary, and venous vasodilation accompanied by an improvement in cardiac performance without reflex tachycardia. Plasma concentrations of norepinephrine, angiotensin II, and renin remained unchanged, suggesting an absence of neurohormonal stimulation.

The second study in patients with CHF was conducted in two phases. In Phase I, seven patients with CHF NYHA functional class III received bosentan 500 mg twice daily in an open-label fashion for 14 days.⁵⁸ Hemodynamic and neurohormonal parameters were measured repeatedly after the first dose and after 14 days of therapy. All patients continued to receive their pre-study CHF medications. These included digoxin, diuretics, and ACE-inhibitors in all of the patients. Bosentan therapy was well tolerated and was associated with a marked improvement in cardiac performance and decreased pulmonary resistance and systemic vascular resistance. Heart rate increased slightly at the initiation of therapy but was difficult to evaluate due to the absence of a control group. In Phase II,⁵⁹ the same protocol was followed as in Phase I, but 24 patients received bosentan 1000 mg twice daily, and 12 patients received placebo twice daily for 14 days in a double-blind fashion. The administration of the ACE inhibitor was delayed by three hours on the days of repeated hemodynamic assessments. Statistically significant hemodynamic improvements were observed with the 1000 mg dose of bosentan compared to the placebo. As with the 500 mg dose used in Phase I, a slight increase in heart rate was observed during the first hours following administration of bosentan. However, a similar increase in heart rate was observed in patients receiving placebo, suggesting that this effect was related to the study protocol rather than a true effect of bosentan. Norepinephrine, epinephrine, renin and angiotensin II remained unchanged, and ET-1 increased in patients treated with bosentan.

These preliminary studies suggest that the inhibition of the vascular effects of endothelin may have beneficial effects in patients with CHF who remain symptomatic despite optimal therapy with currently available pharmacological treatments.

Conclusions

In recent years, significant progress has been made in our understanding of the endothelin receptors and the role of the endothelin system in the pathophysiology of CHF. This research has led to the development of several selective and highly specific ET receptor antagonists. Bosentan is the most studied orally active endothelin receptor antagonist currently in clinical trials for the treatment of CHF. Early clinical experience with this compound has confirmed its short-term benefits, especially in terms of hemodynamic improvement in patients with CHF. However, long-term trials to investigate the effects of chronic inhibition of the endothelin system are needed. It is hoped that endothelin receptor antagonists such as bosentan will slow the progression of CHF and improve survival of patients with the disease.

References available upon request.

Did You Know . . .

- ❖ Atovaquone (Mepron[®], GlaxoWellcome) was recently approved for the prevention of *pneumocystis carinii* pneumonia (PCP). This product was previously approved for acute treatment of mild-to-moderate PCP in patients who are unable tolerate trimethoprim-sulfamethoxazole.
- ❖ The FDA recently approved celecoxib (Celebrex[®], Searle/Pfizer) for the management of pain and inflammation associated with osteoarthritis or adult rheumatoid arthritis. The product is believed to cause significantly fewer gastrointestinal adverse effects than conventional non-steroidal anti-inflammatory drugs.
- ❖ Modafinil (Provigil[®], Cephalon) has been approved for the treatment of excessive daytime sleepiness associated with narcolepsy. This agent is a non-amphetamine drug which is classified as a Schedule IV controlled substance. The most common adverse effects associated with the use of modafinil include headache, nausea, nervousness, anxiety, and insomnia.
- ❖ LYMERix (Lyme disease vaccine), manufactured by SmithKline Beecham, has been approved for active immunization against Lyme disease in patients between the ages of 15 and 70 years.
- ❖ The first oral micronized progesterone (Prometrium[®], Solvay) has been approved for use with estrogen therapy in postmenopausal women who have not had a hysterectomy. This product was originally approved for the treatment of secondary amenorrhea.
- ❖ The FDA has approved abacavir (Ziagen[®], Glaxo-Wellcome) for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and children over three months of age. The drug is known to cause a potentially fatal hypersensitivity reaction.
- ❖ The ribavirin and interferon alfa-2b combination therapy (Rebetron[®], Schering-Plough) has been approved for use in interferon-naive patients diagnosed with hepatitis C. The product is contraindicated in pregnant women, women of child-bearing age, and male partners of such women.

Formulary Update:

The Pharmacy and Therapeutics Committee recently approved the following formulary actions:

Additions:

- ❖ Lepirudin (Refludan[®]), an anticoagulant for use in patients with heparin-induced thrombocytopenia and associated thromboembolic events

Deletions:

- ❖ Diamox[®] Ophthalmic Solution
- ❖ Betoptic-S[®] Ophthalmic Suspension
- ❖ Chloroptic[®] Ophthalmic Ointment
- ❖ Miostat[®] Ophthalmic Solution
- ❖ Phospholine Iodide[®] Ophthalmic Solution
- ❖ Polysporin[®] Ophthalmic Ointment
- ❖ Econopred[®] Ophthalmic Suspension
- ❖ Neosporin[®] Ophthalmic Solution

Editors' Note

We wish to thank Samer Ellahham, M.D. for his contribution to this issue of *Pharmacy Update*.

Drug Information Service

- ↪ Patient-specific pharmacotherapy evaluations and recommendations
- ↪ Comprehensive information about medications, biologics, and nutrients
- ↪ Critical evaluation of drug therapy literature
- ↪ Assistance with study design and protocol development
- ↪ Clinical trial drug safety monitoring
- ↪ Investigational drug information
- ↪ Parenteral nutrition assessment and monitoring

301-496-2407

Pager #104-2619-7 or 104-5264

Building 10, Room 1S-259



Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196