

Bosentan

Judy W. M. Cheng, PHARM.D, BCPS

Abstract: Bosentan is the first endothelin (ET) receptor antagonist approved by the Food and Drug Administration for the management of pulmonary arterial hypertension (PAH). In patients with World Health Organization Class III and IV PAH, bosentan has demonstrated improvement in dyspnea and exercise tolerance. ET also plays an important role in the pathophysiology of different vascular diseases. Therefore, bosentan also may have the potential to alter the outcome of many other diseases, such as heart failure, hypertension, ischemic heart disease, and renal disease, as well as cerebrovascular disorders. Because of the rarity and the poor prognosis of patients with PAH, as well as the requirement of close monitoring of bosentan (due to its potential of causing liver dysfunction and its teratogenic effects), bosentan is currently available only through a special access program and is distributed by certain selected pharmacies. Patients who are receiving bosentan should be taught to recognize early signs and symptoms of liver dysfunction and possible pregnancy. In addition, bosentan is not only a substrate but also an inducer of CYP3A4 and CYP2C9. Therefore, it is anticipated that numerous drug interactions may occur. Patients should be advised to consult their physicians or pharmacists should they need to consume other prescription or nonprescription medications.

Key Words: Bosentan, pulmonary hypertension, heart failure, endothelin antagonist

(*Heart Dis* 2003;5: 161–169)

Bosentan (Tracleer™, Actelion Pharmaceuticals) is the first endothelin (ET) receptor antagonist approved for clinical use by the US Food and Drug Administration (FDA). The ET neurohormonal system is activated in several cardiovascular conditions including pulmonary arterial hypertension (PAH), congestive heart failure (CHF), essential hypertension, acute myocardial infarction (MI) and atherosclerosis.¹

From the Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, and Mount Sinai Medical Center, New York, NY.

Reprints: Judy W. M. Cheng, Pharm.D., BCPS, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1211, New York, NY 10029. jcheng@liu.edu.

Copyright © 2003 by Lippincott Williams & Wilkins
1521-737X/03/0502-0161

DOI: 10.1097/01.HDX.0000061696.83820.51

By antagonizing the effect of ET, ET receptor blockers may have the potential to augment the outcome of different cardiovascular diseases. Currently, bosentan is officially approved for PAH only. This article however, will review pertinent clinical trials related to the drug's approved and nonapproved indications, in addition to reviewing its clinical pharmacology, adverse effects, drug interactions, and contraindications.

THE ET NEUROHORMONAL SYSTEM

The ET family consists of a group of three 21-amino acid peptides with similar structures: ET-1, ET-2 and ET-3. ET-1 is the principal isoform in disease states. It is synthesized and secreted predominantly from the vascular endothelium in response to multiple stimuli, including hypoxia, ischemia, shear stress, growth factors, and other neurohormones, such as angiotensin II and norepinephrine.² The development of specific ET receptor agonists and antagonists has led to the identification of 2 receptor subtypes in mammalian cells, ET_A and ET_B. 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 of sustained elevation of intracellular calcium concentration. Nitric oxide (NO) shortens the duration of vasoconstriction by accelerating the decrease of intracellular calcium to its basal concentration.² ET_B receptors were first described on endothelial cells. They bind to ET-1 and ET-3 with similar affinity, and their stimulation leads to transient vasodilation, probably caused by increased production of NO and prostacyclin. However, ET_B receptors are also present on vascular smooth muscle cells, where their activation produces vasoconstriction.²

ET-1 is the most potent endogenous vasoconstrictor identified to-date, with its effects persisting for several hours.^{3,4} On a molar basis, it is 100 times more potent than norepinephrine and 10 times more potent than angiotensin II.^{2,5} Vasoconstrictive activity of ET-1 has been demonstrated in the pulmonary, coronary, renal and systemic vasculature. In addition, there are clinical and preclinical data available suggesting that ET-1 displays mitogenic, pro-inflammatory and pro-fibrotic activity at the vasculature and the myocardium.^{6–10} ET-1 also acts as a potent modulator of the

sympathetic nervous and renin-angiotensin-aldosterone systems.² These latter actions of ET-1 could have further deleterious effects in cardiopulmonary disease because of the hypertrophic effect of norepinephrine and angiotensin II and the potential profibrotic properties of aldosterone at both the myocardium and in the vasculature.^{7,11,12} The plasma level of ET-1 is also elevated in CHF, with the magnitude of the elevation associated with disease severity and prognosis.^{2,13}

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. Because of its potent vasoconstrictive effect and long-lasting action, the continuous release of small amounts of ET could contribute to the maintenance of elevated vascular tone. 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 and the potent endogenous vasodilator NO. An imbalance between the production of ET and NO could lead to a pathologically elevated vascular tone. Moreover, the vasoconstricting property of ET-1 is greatly enhanced in atherosclerotic vessels in which the opposing biologic effect of NO is lost. A role of the ET system has been postulated in various conditions of disturbed vascular homeostasis, such as hypertension, coronary artery disease, and CHF.^{2,13}

ET of either local or circulatory origin significantly contributes to the increased vascular resistance in the renal vasculature. The kidney is considered a major site of ET production and an important target organ of this peptide. The highest immunoreactive levels of ET in mammalian cells exist in the renal medulla. However, ET has also been localized in the renal cortex. The renal vasculature is preferentially sensitive to the vasoconstrictive effects of ET compared with other arteries or veins.¹⁴ In contrast to the consistent effects of ET on the renal hemodynamics, its effects on the excretion of sodium and water are variable. Systemic infusions of high doses of ET result 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 hypothesis that local ET acts in an autocrine/paracrine manner on the tubular epithelial cells where it inhibits sodium reabsorption, thereby enhancing salt and water excretion.^{14,15}

In PAH patients, the expression of ET-1 is substantially increased in the vascular endothelial cells, particularly in the endothelium of elastic and muscular pulmonary arteries

where medial hypertrophy and intimal fibrosis are present.¹⁶ The expression of ET-1 in patients is relatively low in the pulmonary capillaries, veins and bronchial arteries, and is not observed in the systemic vessels of the myocardium or kidneys, suggesting that much of the ET-1 synthesis is localized at the primary site of the disease pathology in these patients. In other studies, plasma ET-1 levels and selective up-regulation of ET_B-receptor gene expression are highly correlated with elevated right atrial pressure in patients with primary PAH.^{17,18}

PHARMACOLOGY/TOXICOLOGY

Bosentan is a specific and competitive antagonist of ET-1 receptors (ET_A and ET_B). The affinity of bosentan for the ET_A receptor is about 100 times greater than for the ET_B receptor in cultured cells. Thus, administration of bosentan causes vascular smooth muscle relaxation and vasodilation.

Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/d for 2 months in patients, without major adverse events.¹⁹ The most common side effect in these situations was headache of mild to moderate intensity. In the cyclosporin A interaction study, in which doses of 500 and 1000 mg twice daily of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased by 30-fold, resulting in severe headache, nausea, and vomiting, but no other serious adverse events.²⁰ A mild decrease in blood pressure and increases in heart rate were observed. There is currently no other experience of overdose with bosentan beyond these incidences. Because bosentan is a vasodilator, it is anticipated that massive overdose may result in pronounced hypotension requiring active cardiovascular support.¹⁹

BIOPHARMACEUTICS, PHARMACOKINETICS, PHARMACODYNAMICS

Biopharmaceutics

Bosentan is a highly substituted pyrimidine derivative, with no chiral centers (**Figure 1**). It has molecular weight of

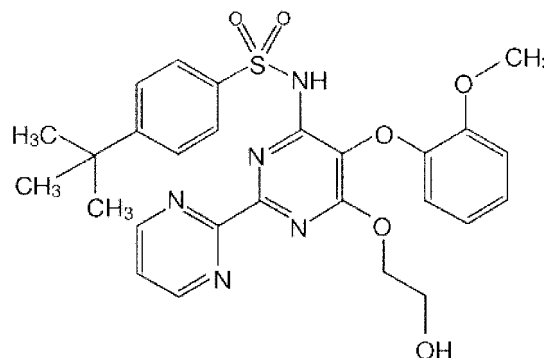


FIGURE 1.

569.64. Bosentan is stable in solid state and poorly soluble in water (1 mg/100 mL). It is not hygroscopic and not light sensitive.¹⁹

Pharmacokinetics

After oral administration, the maximum plasma drug concentration is achieved within 3-5 hours. The oral bioavailability in healthy subjects is about 50% and is unchanged at steady-state.²¹⁻²³ The bioavailability is unaffected by food.²⁴ Volume of distribution of bosentan is about 18 L after a single dose and 30 L after multiple dosing. Bosentan is also highly bound to plasma protein (98%), mainly to albumin.

In the liver, bosentan is metabolized by the cytochrome P-450 (CYP) isoenzymes, CYP3A4 and CYP2C9 to 3 metabolites, one of which is pharmacologically active. Although plasma levels of these metabolites are low, relative to the parent compound, the active metabolite may contribute up to 20% of the pharmacological effect. Steady-state drug levels are achieved within 3-5 days after multiple dosing, at which time plasma levels are approximately 50% lower than those observed after a single dose. This is caused by a 2-fold increase in clearance, which may be because of an induction of CYP3A4 and CYP2C9 isoenzymes. Bosentan is primarily eliminated by biliary excretion after metabolism in the liver, with less than 3% of an administered oral dose recovered in the urine. The terminal elimination half-life of bosentan is approximately 5 hours.²¹⁻²³

The influence of liver dysfunction on the pharmacokinetics of bosentan has not been evaluated. However, because bosentan is extensively metabolized by the liver, liver function impairment can significantly increase the systemic exposure of bosentan.²⁵ Caution should be exercised during the use of bosentan in patients with mild liver dysfunction. It should be avoided in patients with moderate or severe liver abnormalities and/or elevated aminotransferases of greater than 3 times the upper limit of normal range.

In patients with severe renal impairment (creatinine clearance 15 to 30 mL/min), plasma concentrations of bosentan were essentially unchanged, and plasma concentrations of the 3 metabolites were increased about 2-fold compared with people with normal renal function. Although one of the metabolites is active, the accumulation of the metabolite does not appear to produce clinically important differences in patient response or incidence of side effects.¹⁹

To date, it is not known if bosentan's pharmacokinetics are influenced by gender, body weight, race or age.

Pharmacodynamics

In healthy human subjects, the administration of a single oral dose of 600 mg or an intravenous dose of 250 mg of bosentan caused plasma ET-1 concentrations to increase maximally by 2-fold (oral) and 3-fold (intravenous). This increase with ET-1 was caused by the release of ET-1 from

the receptor sites and was directly related to bosentan plasma concentrations, according to an Emax model. Bosentan reversed the vasoconstrictor effect of ET-1 measured in skin microcirculation. There was a tendency toward decreased blood pressure (approximately 5 mm Hg) and increased pulse rate (approximately 5 beats/min). However, these changes did not appear to be dose-dependent. Bosentan is well tolerated orally. Its intravenous use, however, is limited because of local vein irritability.²³ The intravenous form of the drug did not receive FDA approval. Additional pharmacodynamics data in patients with different disease states are discussed in the clinical studies section.

CLINICAL STUDIES

Pulmonary Arterial Hypertension

Primary PAH is a rare condition, with an estimated prevalence of 1-2 per million people.²⁶ Because the symptoms of PAH are nonspecific, and the physical findings can be subtle, the disease is often diagnosed in its later stages. The natural history of PAH is usually progressive and fatal. Current medical therapy for PAH include calcium channel blockers; however, only up to 20% of patients will respond.²⁶ Inotropic agents, such as milrinone, have also been used. However, there is a lack of data on the use of chronic inotropic therapy in patients with PAH, and the experience of increased mortality in patients with left heart failure is of concern.²⁷ Prostaglandins such as continuous intravenous prostacyclin have been evaluated and have been demonstrated to improve exercise tolerance, hemodynamics, and survival in patients who are in World Health Organization (WHO) Functional Class III and IV.^{28,29} However, its inconvenient delivery system (continuous IV infusion) and its severe rebound reaction that is observed if it is abruptly discontinued make it difficult to use clinically. Although there is considerable experience in the use of NO as a short-term treatment of PAH, the role of NO as a chronic therapy remains investigational.³⁰ Therefore, major efforts have been undertaken to explore new therapeutic agents for the management of this disease state, ET receptor antagonists being one of them. Two randomized, double-blind, multicenter, placebo-controlled trials were conducted to examine the effects of bosentan in PAH.

Channick and colleagues recruited 32 patients who had symptomatic, severe, primary PAH or PAH caused by scleroderma (WHO classes III and IV).³¹ Patients were double-blind randomized to 62.5 mg of bosentan twice daily (administered orally) for the first 4 weeks, followed by the target dose of 125 mg orally twice daily unless drug-related adverse events occurred (eg, hypotension), or matching doses of placebo. Patients were allowed to receive other treatment of PAH including digoxin, anticoagulants, diuretics and vasodilators (calcium channel blockers, angiotensin-converting en-

zyme inhibitors [ACEI]) but not epoprostenol (prostacyclin). The primary end point of the study was a change in exercise capacity, and the secondary endpoints included changes in cardiopulmonary hemodynamics, dyspnea index, WHO functional class, and withdrawal due to clinical worsening of symptoms. In patients who received bosentan, the 6-minute walk distance improved by 70 meters at 12 weeks as compared with base line, whereas in patients receiving placebo, it worsened by 6 meters (difference = 76 meters, 95% confidence interval [CI], 12-139; $P = 0.021$). This improvement was maintained for 20 weeks. The cardiac index in patients receiving bosentan was higher than the placebo group by 1 L/min/m² (95% CI, 0.6-1.4; $P < 0.0001$). Pulmonary vascular resistance decreased by 223 dyns/cm⁵ with bosentan, but increased by 191 dyns/cm⁵ in patients receiving placebo (difference = -415; [95% CI: -608 to -221]; $P = 0.0002$). Patients given bosentan also have a reduced Borg dyspnea index³² (1.6 lower than placebo; 95% CI, 0-3.1; $P = 0.05$) and an improved WHO functional class compared with those who received placebo. At base line, all patients were in functional class III ($P = 0.019$ between bosentan and placebo). At the end of 12 weeks, 9/21 (43%) patients in the bosentan group improved to class II, and none deteriorated to class IV ($P = 0.0039$ compared with base line within group). With placebo, only 1 of 11 patients (9%) improved to class II, and 2 (18%) deteriorated to class IV ($P = 1.00$ compared with base line within group). All 3 patients withdrawn from the study because of clinical worsening were in the placebo group ($P = 0.033$ withdraw rate between bosentan and placebo). The number and nature of adverse events did not differ between the 2 groups. No hypotension or clinically significant changes in hematological or biochemical measures were seen in either group. Increases in the concentration of hepatic aminotransferases were seen in 10 patients assigned to bosentan. But, these increases were not associated with symptoms, and the concentrations returned to normal without discontinuation or change of dose.

In the Bosentan Randomized Trial of Endothelin Antagonist Therapy Study Group (BREATH-1), 213 patients with PAH (primary or associated with connective tissue disease) were randomly assigned to receive bosentan 62.5 mg orally twice daily for 4 weeks, followed by 1 of 2 doses of bosentan (125 mg or 250 mg orally twice daily) for a minimum of 12 weeks, or placebo. The primary end point was the degree of change in exercise capacity. Secondary endpoints included change in WHO functional class, Borg dyspnea index, and increased in time to clinical worsening.³³ At week 16, patients treated with bosentan (both doses) had an improved 6-minute walking distance, 44 meters more than the placebo group (95% CI, 21 to 67; $P < 0.001$), whereas a deterioration of 8 meters occurred in the placebo group. Although both bosentan doses produced a significant treatment effect, the placebo-corrected improvement was more

pronounced for the dose of 250 mg twice daily than for the dose of 125 mg twice daily. However, no dose-response relation for efficacy could be confirmed. Bosentan also improved the Borg dyspnea index (-0.6 in favor of bosentan; 95% CI, -1.2 to -0.1). The placebo-corrected improvement was greater for patients receiving 250 mg twice daily (-0.9, $P = 0.012$) than for those receiving 125 mg (-0.4, $P = 0.42$). At base line, more than 90% of the patients were in WHO functional class III. At the end of the treatment period, in the groups receiving 125 mg and 250 mg twice daily of bosentan, 38% and 34% respectively of patients had improved to class II, and 3% and 1% had improved to class I, respectively. In contrast, in patients receiving placebo, only 28% improved to class II and none improved to class I. This resulted in a mean treatment effect of 12% in favor of bosentan (95% CI, -3 to 25%).

Another small open-label, dose-ranging study was performed in 7 female patients with primary PAH ($n = 5$) or PAH associated with scleroderma ($n = 2$).³⁴ Four of these patients were resistant to inhaled-NO therapy. Infusions of 50, 150 and 300 mg of bosentan were administered at 2-hour intervals, and the hemodynamic responses were measured. Bosentan induced dose-dependent reduction in total pulmonary resistance ($-20 \pm 11\%$, $P = 0.01$) and mean pulmonary arterial pressure ($-10.6 \pm 11\%$, $P > 0.05$) compared with base line. Systemic vascular resistance was also reduced ($-26.2 \pm 12.8\%$, $P < 0.005$) as well as mean arterial pressure ($-19.8 \pm 14.4\%$, $P < 0.001$). There was a slight but nonsignificant increase in cardiac index ($15 \pm 12\%$, $P > 0.05$) and a dose-dependent increase in ET-1 level. This study demonstrated that intravenous bosentan is a potent pulmonary vasodilator at the doses tested, even in patients resistant to inhaled NO. However, systemic hypotension and local venous irritation may limit its intravenous use.

Currently, there is no direct comparative trial of bosentan to epoprostenol therapy.

Heart Failure

In the United States, prevalence of heart failure is increasing as the population continues to age. Mortality during the first 5 years from the time of diagnosis of CHF continues to be high, even among patients on the best available treatments (digoxin, diuretics, ACEI and β -blockers).³⁵ The last few years have brought significant advances in the understanding of the pathogenesis of heart failure. Increasing evidence suggests a potential role of the ET system in the pathophysiology of heart failure. The clinical potential of therapeutic agents that target the ET system is being actively evaluated. Five clinical studies using bosentan have been reported to date, including patients with moderate to severe chronic heart failure.

In the study performed by Kiowski and colleagues,³⁶ there were 24 patients with CHF (New York Heart Associa-

tion [NYHA] functional class III), in whom therapy for heart failure had been discontinued. Patients were randomized to placebo or bosentan intravenously (100 mg, followed by 200 mg 1 hour later). Cardiac, pulmonary, and systemic hemodynamic parameters were measured repeatedly for 2 hours. Infusion of bosentan resulted in pronounced systemic, pulmonary, and venous vasodilation accompanied by an improvement in cardiac performance without reflex tachycardia. These effects were submaximal at the first 100-mg dose. Plasma concentrations of norepinephrine, angiotensin II, and renin remained unchanged, suggesting an absence of neurohormonal stimulation.

The second study in patients with heart failure was conducted in 2 phases. In Phase I, 7 patients with CHF NYHA functional class III received bosentan 500 mg twice daily for 14 days in an open-label fashion.³⁷ 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 heart failure medications (digoxin, diuretics, and ACEI in all patients). Bosentan therapy was well tolerated and was associated with a marked improvement in cardiac performance, decreased pulmonary resistance and systemic vascular resistance. Heart rate increased slightly at the initiation of therapy but was difficult to evaluate because of the absence of a control group. In Phase II,³⁸ the same protocol was followed as in Phase I, but 24 patients received 1000 mg bosentan twice daily, and 12 patients received placebo twice daily for 14 days in a double-blind fashion. The administration of the ACEI was delayed by 3 hours on the days of repeated hemodynamic assessments. Hemodynamic and hormonal measurements were obtained before and repeatedly for 24 hours after administration of bosentan on days 1 and 14. Bosentan was discontinued in 1 patient because of symptomatic hypotension. Compared with placebo, bosentan on day 1 significantly decreased mean arterial pressure, pulmonary artery mean and capillary wedge pressures. Cardiac output increased, but heart rate was unchanged. Both systemic and pulmonary vascular resistance were reduced. After 2 weeks, cardiac output had increased further by 15.2%, and systemic and pulmonary vascular resistance decreased further compared with day 1. Plasma ET-1 levels increased after bosentan, but levels of the other hormones were unchanged.

The next trial using bosentan in patients with CHF was the Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) trial.³⁹ Three hundred and seventy patients with NYHA Class III and IV heart failure were randomized to receive placebo or bosentan, given in 1 of 2 dosing regimens (125 mg twice daily or 250 mg twice daily), in addition to full conventional therapy. The primary end point was clinical status at 6 months. The study was stopped early after the decision to conduct future trials at a lower dose (because of elevations in hepatic transaminases at the higher

dose group); only 50% of patients had reached the intended end point of 6 months. In the proportion of patients who received bosentan for 6 months, there was a significant clinical improvement (19 versus 27%, bosentan versus placebo; $P = 0.045$). This study led to the launching of a larger scale study using the lower dose regimen.

The latest study, Endothelin Antagonist Bosentan for Lowering Cardiac Events (ENABLE) trial was a phase 3 investigation that included 2 trials (ENABLE 2 in North America and ENABLE 1 in Europe and Australia).⁴⁰ A total of 1613 patients with NYHA Class III or IV (mean left ventricular ejection fraction was about 25%; 2/3 of patients had ischemic heart failure, whereas the remaining 1/3 had nonischemic heart failure) were randomized to receive bosentan at a dose of 125 mg twice a day or placebo, in addition to optimal therapy with diuretics, β -blockers and ACE inhibitors. The primary end point was the combined risk of death and hospitalization for heart failure, with a secondary end point of all-cause mortality. The primary end point was observed in 321 of 808 patients receiving bosentan and 312 of 805 patients receiving placebo (hazard ratio 1.01, $P = 0.9$). Similarly, the hazard ratio was one for all-cause mortality. Kaplan-Meier curves indicated that the initiation of bosentan was associated with early risk of an event within the first 2-4 weeks of the start of treatment that persisted for over 1 year. This was primarily related to an increase in the risk of hospitalizations for heart failure.

Hypertension

Endothelin is a potent vasoconstrictor. Therefore, an ET-1 receptor antagonist may be used as a potential alternative class of agent for hypertension management. In a study by Krum and colleagues,⁴¹ 293 patients with mild to moderate hypertension were randomized to receive treatment with placebo, enalapril 20 mg once daily, or bosentan (100, 500, or 1000 mg once daily, or 1000 mg twice daily). Patients receiving bosentan exhibited blood pressure reductions similar to those receiving 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% from base line. Bosentan was well tolerated overall, with only a few reports of adverse effects. These adverse effects were those commonly seen with other vasodilators and included headache, leg edema, and dizziness. Fewer than 5% of the patients receiving bosentan developed increases in hepatic transaminases that were asymptomatic and reversible.

Ischemic Heart Disease

High plasma ET levels have been reported in an experimental ischemia model, and ET-1 concentrations in plasma have been demonstrated to predict 1-year mortality.^{13,42} The use of ET-1 receptor antagonists, therefore, may have the

potential to alter patient outcomes. In a double-blind, randomized controlled study, Wenzel and colleagues examined the effects of bosentan on systemic and coronary hemodynamics in 28 patients with angiographically documented stable coronary artery disease.⁴³ Bosentan 200 mg or placebo was administered intravenously over 15 minutes. Forty minutes after the infusion, hemodynamic measurements were repeated, and an angiogram was performed. All other medications consumed by the patients were discontinued for at least 3 to 4 half-lives prior to the study. Bosentan significantly reduced patients' systolic blood pressure (-10 mm Hg; $P < 0.05$) and slightly increased their heart rate ($+2$ beats per minute; $P < 0.05$). Coronary diameter also increased, particularly in vessels with minimal angiographic changes ($P < 0.01$). Nitrates did not dilate these segments further. In contrast, nitrates increased coronary diameter significantly in the placebo patients ($P < 0.01$). Bosentan was well tolerated in this study.

ADVERSE EFFECTS, DRUG INTERACTION, PRECAUTION AND CONTRAINDICATIONS

Adverse effects

Safety data on bosentan were obtained from 777 patients in various clinical studies. Doses up to 8 times the FDA approved doses were administered for a variety of durations. The use of bosentan in these trials ranged from 1 day to 4.1 years.¹⁹ In patients using bosentan for PAH, common adverse events that occurred in $\geq 3\%$ of patients were headache, nasopharyngitis, flushing, liver function abnormality, lower limb edema, hypotension, palpitation, dyspnea, edema, fatigue and pruritis. In patients using bosentan in clinical trials other than PAH (primarily chronic heart failure), the adverse events that occurred in $\geq 3\%$ of patients were headache, flushing, abnormal hepatic function, leg edema and anemia.¹⁹ Of these reported side effects, it is particularly important to pay close attention to hepatic function abnormalities. In clinical studies, the use of bosentan has caused at least a 3-fold upper limit of normal elevation of liver aminotransferases in approximately 11% of patients, accompanied by elevated bilirubin in a small number of cases. The manufacturer currently recommends measurement of liver function test prior to initiation of therapy, and then monthly thereafter. To-date, in clinical trial settings, where close monitoring occurs, elevations of liver function tests have all been reversible, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae.¹⁹ Bosentan should be avoided in patients with base line abnormal liver function tests.

Drug Interactions

Bosentan is highly bound to albumin ($>98\%$, mainly to albumin). In vitro displacement studies were undertaken with

digoxin,⁴⁴ glyburide,⁴⁵ phenytoin, tobutamide and warfarin.⁴⁶ No relevant interactions between bosentan and these agents were observed at the level of protein binding.¹⁹

Bosentan is extensively metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Ketoconazole, a potent inhibitor of CYP3A4, increases maximum concentration and area under the curve of bosentan by 1.6- and 1.8-fold, respectively.⁴⁷ No drug interaction study has been performed to date with a pure CYP2C9 inhibitor. In addition, medications that are also metabolized by CYP2C9 and CYP3A4 may compete with bosentan for the isoenzymes and alter each other's plasma concentration. In a study looking at interaction between bosentan and cyclosporin A, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporin A.²⁰ On the other hand, the concentration of cyclosporin A is decreased by approximately 50%. The manufacturer currently states the coadministration of bosentan and cyclosporin as a contraindication. Bosentan is also an inducer of CYP3A4 and CYP2C9. Therefore, plasma concentrations of drugs metabolized by these 2 isoenzymes will be decreased when bosentan is coadministered. For example, coadministration of bosentan and glyburide decreased the plasma concentrations of glyburide by approximately 40%.⁴⁵ The bosentan concentrations were also decreased by approximately 30%. In addition, an increased risk of elevated liver aminotransferases was observed. Therefore, the manufacturer also states that the use of bosentan and glyburide is contraindicated.¹⁹

Warfarin is extensively metabolized by the liver. In addition, patients with PAH or chronic severe heart failure oftentimes receive warfarin for anticoagulation purpose. Therefore, it is anticipated that bosentan and warfarin may be commonly coadministered in clinical practice. In a drug interaction study between bosentan and warfarin, coadministration of bosentan 500 mg twice daily for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29-38%, respectively.⁴⁶ Clinical experience with concomitant administration of bosentan and warfarin in patients with PAH, however, did not show any clinically important changes in the International Normalized Ratio or the warfarin dose used.¹⁹

Coadministration of bosentan has also been observed to decrease the plasma concentration of simvastatin (a CYP3A substrate) by approximately 50%.⁴⁸ The plasma concentrations of bosentan were not affected. It is also anticipated that similar interactions will exist with other statins that have significant metabolism by CYP3A4, such as lovastatin and atorvastatin.

The manufacturer has also studied the interactions between bosentan and digoxin, nimodipine (a CYP3A4 sub-

strate), and losartan (a CYP2C9 substrate). No significant interactions have been observed.¹⁹

Precaution and Contraindications

Bosentan is contraindicated in pregnancy. Animal data suggest that bosentan is likely to produce major birth defects.⁴⁹ Bosentan was teratogenic in rats given oral doses ≥ 60 mg/kg/d (twice the maximum recommended for human use in mg/kg basis). Teratogenic effects observed included malformations of the head, mouth, face and large blood vessels. Bosentan also increased stillbirths and pup mortality. Pregnancy must be excluded before the initiation of bosentan therapy and prevented after the beginning of therapy. Hormonal contraceptives, including oral, injectable, and implantable contraceptives, may not be reliable in the presence of bosentan. Although there is no drug interaction study to date between bosentan and hormonal contraceptives, there is a possibility of reduction of plasma concentration with the coadministration of bosentan, because many of these drugs are metabolized by CYP3A4. Therefore, hormonal contraceptives should not be used as the sole contraceptive method in patients receiving bosentan. Follow-up urine or serum pregnancy tests should be obtained monthly in women of child-bearing age receiving bosentan. It is not known whether bosentan is excreted in human breast milk; therefore, the use of bosentan while breastfeeding is not recommended.

Coadministration of cyclosporin A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of bosentan and cyclosporin A is contraindicated. An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore, concurrent use of these 2 drugs is also contraindicated. Bosentan is also contraindicated in patients who are hypersensitive to bosentan or any component of the medications.

Treatment with bosentan has been observed to cause a dose-related decrease in hemoglobin and hematocrit. In clinical studies, marked decreased in hemoglobin ($>15\%$ decrease from base line resulting in values <11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. Most of these decreases were detected during the first few weeks of bosentan treatment and stabilized at 4-12 weeks of treatment.¹⁹ The explanation for the change in hemoglobin is not known, but it does not appear to be related to hemorrhage or hemolysis. The manufacturer recommends that hemoglobin be checked at base line, 1 and 3 months, and every 3 months post initiation of therapy.

PEDIATRICS AND GERIATRICS CONSIDERATION

The efficacy and safety of bosentan use in pediatric patients have not been established. Experience with bosentan

in subjects older than 65 is not adequate to identify a difference in response between elderly and younger patients.

THERAPEUTIC AND ECONOMIC ISSUES AND CONTROVERSIES

The average wholesale price of bosentan in the US is \$49.50 per tablet, without regard to dosage strength. This translates to a monthly cost of US \$2,970.00 and annual cost of US \$35,640.00 for patients. This is considerably less than epoprostenol therapy, another treatment of patients in WHO Class III and IV PAH (up to US \$75,000 per year). To-date, pharmacoeconomic studies have not been performed with bosentan in PAH. Bosentan has also not been studied for its impact on PAH mortality. However, in view of the rarity of the disease, the poor prognosis of PAH, the less than optimal response to other therapy (only approximately 20% of patients with PAH will respond to oral calcium channel blockers) and the inconvenience of other therapeutic alternatives (epoprostenol therapy requires continuous infusion, and abrupt withdrawal causes severe rebound; NO is a continuous inhalation therapy), bosentan represents a convenient (oral dosing) and effective alternative form of treatment.

APPROVED LABELING AND POSSIBLE OFF-LABEL USES

Bosentan is approved by the FDA for the treatment of PAH in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. In recent years, significant progress has been made in our understanding of ET receptors and their role in the pathophysiology of many vascular disease states (cardiovascular, cerebrovascular and renal vascular).¹⁵ Therefore, ET receptor antagonists may have a potential role in the management of these different disease states as well. In addition to PAH, bosentan has been tested for other clinical conditions including heart failure, hypertension and ischemic heart disease. The results of clinical trials of heart failure are not conclusive at this point, in terms of both morbidity and mortality. The one study done for the treatment of hypertension demonstrated that bosentan is as effective as ACEI in reducing blood pressure, which makes bosentan a potential new class of antihypertensive agent. However, its risk of causing liver dysfunction needs to be investigated further before it can be used long term. Similarly, bosentan has been demonstrated in a small sample of patients to dilate the coronary artery, which may make it potentially useful in patients with ischemic heart disease. Long-term studies looking at its effect on morbidity and mortality in patients with ischemic heart disease, especially those with acute coronary syndromes, need to be investigated before it can be recommended for routine use.

DOSAGE AND ADMINISTRATION

Bosentan is available for clinical use in tablet form. The intravenous formulation in premarketing clinical trials have demonstrated excessive local venous irritation and hypotension, and therefore it is not suitable for clinical use.^{23,34} For the treatment of PAH, bosentan should be initiated at a dose of 62.5 mg orally twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily do not appear to confer additional benefit. In patients with a body weight below 40 kg but who are over 12 years of age, the recommended initial and maintenance dose is 62.5 mg orally twice daily. Tablets should be administered in the morning and evening with or without food.¹⁹ Liver function tests should be performed at base line, 1 month, 3 month, and every 3 months afterward. If at any point aminotransferase is >3 but ≤ 5 times of upper limit of normal, daily dose should be reduced or treatment should be interrupted. A liver function test should be repeated at least every 2 weeks. If liver function tests return to normal, one may consider continuing or reintroducing the treatment as appropriate. If aminotransferase is >5 to ≤ 8 times the upper limit of normal, treatment should be stopped, and a liver function test should be performed at least every 2 weeks. Once the liver function test returns to normal, one may consider reintroducing treatment. If aminotransferase is >8 times the upper limit of normal, treatment should be stopped and reintroduction of treatment should not be considered.

No dosage adjustment is required in renally impaired patients. There is no specific data to guide dosing in hepatically impaired patients. Because bosentan may cause liver injury, caution should be exercised in patients with mildly impaired liver function and generally should be avoided in patients with moderate or severe liver impairment.

There is limited experience with abrupt discontinuation of bosentan. No evidence for acute rebound has been observed. However, to avoid the potential for clinical deterioration, a gradual dose reduction (from 125 mg twice daily to 62.5 mg twice daily for 3 to 7 days before total discontinuation) should be considered.

PATIENT COUNSELING

Patients receiving bosentan therapy should be counseled to follow up with their physicians for regular liver function test monitoring every 3 months (all patients) and pregnancy test monthly (for female patients). In addition, patients should be educated to watch out for signs and symptoms of potential liver injury (right upper quadrant discomfort, jaundice) and pregnancy (late menses). If these symptoms occur, they should contact their physicians immediately. To prevent pregnancy, women of childbearing age should also be counseled to use additional means of contraception in addition to hormonal contraceptive. Because

bosentan may have potential drug interaction with any other medications that are substrates, inhibitors or inducers of CYP3A4 and CYP2C9, patients should be advised to consult their physicians or pharmacists if they are taking any other prescription or nonprescription medications.

SUMMARY

Bosentan (Tracleer™, Actelion) is the first ET receptor antagonist approved by the FDA for the management of PAH. In patients with WHO Class III and IV PAH, bosentan has demonstrated improvement of dyspnea and exercise tolerance. ET is a neurohormone that plays an important role in the pathophysiology of different vascular diseases. Although bosentan is currently approved for use in only one disease state, it has the potential to alter the outcome of many other diseases such as heart failure, hypertension, ischemic heart disease and renal disease, as well as cerebrovascular disorders. Because of the rarity and poor prognosis of PAH, as well as the requirement of close monitoring of bosentan (because of its potential of causing liver dysfunction and its teratogenic effects), bosentan is currently available only through a special access program and distributed by certain selected pharmacies. Patients who are receiving bosentan should be encouraged to recognize early signs and symptoms of liver dysfunction and possible pregnancy. In addition, bosentan is not only a substrate but also an inducer of CYP3A4 and CYP2C9. Therefore, it is anticipated that numerous drug interactions may occur. Patients should be advised to consult their physicians or pharmacists should they require other prescription or nonprescription medications.

REFERENCES

1. Frishman WH, Kaur S, Singh I, Tamirisa P. Endothelin as a therapeutic target in the treatment of cardiovascular disease. In: Frishman WH, Sonnenblick EH, Sica D, eds. *Cardiovascular Pharm-Acotherapeutics*. 2nd ed. New York, NY: McGraw-Hill; 2003;527–543.
2. Levin E. Endothelins. *N Engl J Med*. 1995;333:356–63.
3. Parker JD, Thiessen JJ, Reilly R, et al. Human endothelin-1 clearance kinetics revealed by a radiotracer technique. *J Pharmacology Experimental Therapeutics*. 1999;289:261–265.
4. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*. 1988;332:411–415.
5. Ellahham SH, Charlon V, Abassi Z, et al. Bosentan and the endothelin system in congestive heart failure. *Clin Cardiol*. 2000;23:803–807.
6. Battistini B, Chailler P, D'Orleans-Juste P, et al. Growth regulatory properties of endothelins. *Peptides*. 1993;14(2):385–99.
7. Kaddoura S, Firth JD, Boheler KR, et al. Endothelin-1 is involved in norepinephrine-induced ventricular hypertrophy in vivo. *Circulation*. 1996;93:2068–2079.
8. Muller DN, Mervaala EM, Schmidt F, et al. Effect of bosentan on NF-kb, inflammation, and tissue factor in angiotensin II-induced end organ damage. *Hypertension*. 2000;36:282–290.
9. Mansoor AM, Honda M, Saida K, et al. Endothelin induced collagen remodeling in experimental pulmonary hypertension. *Biochem Biophys Res Commun*. 1995;215(4):981–986.
10. Piacentini L, Honda M, Saida K, et al. Endothelin-1 stimulates cardiac fibroblast proliferation through activation of protein kinase C. *J Mol Cell Cardiol*. 2000;32(4):565–576.

11. Peifley KA, Winkles JA. Angiotensin II and endothelin-1 increase fibroblast growth factor-2 mRNA expression in vascular smooth muscle cells. *Biochem Biophys Res Commun*. 1998;242(1):202–208.
12. Mizuno Y, Yoshimura M, Yasue H, et al. Aldosterone production is activated in failing ventricle in humans. *Circulation*. 2000;103:72–77.
13. Pacher R, Stanek B, Hulsmann M, et al. Prognostic impact of big endothelin-1 plasma concentrations compared with invasive hemodynamic evaluation in severe heart failure. *J Am Coll Cardiol*. 1996;27:633–641.
14. Benigni A, Zoja C, Corna D, et al. A specific endothelin subtype A receptor antagonist protects against injury in renal disease progression. *Kidney Int*. 1993;44:440–444.
15. Benigni A, Remuzzi G. Endothelin antagonists. *Lancet*. 1999;353:133–138.
16. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in lungs of patients with pulmonary hypertension. *N Engl J Med*. 1993;328:1732–1739.
17. Nootens M, Kaufmann E, Rector T, et al. Neurohormonal activation in patients with right ventricular failure from pulmonary hypertension: relation to hemodynamic variables and endothelin levels. *J Am Coll Cardiol*. 1995;26(7):1581–1585.
18. Bauer M, Wilkens H, Langer F, et al. Selective upregulation of endothelin B receptor gene expression in severe pulmonary hypertension. *Circulation*. 2002;105:1034–1036.
19. Actelion Pharmaceuticals US, Inc. Tracleer™, Bosentan Tablets. South San Francisco, CA: Actelion Pharmaceuticals; 2001.
20. Binet I, Wallnofer A, Weber C, et al. Renal hemodynamics and pharmacokinetics of bosentan with and without cyclosporin A. *Kidney Int*. 2000;57:224–231.
21. Weber C, Gasser R, Hopfgartner G. Absorption, excretion, and metabolism of the endothelin receptor antagonist bosentan in healthy male subjects. *Drug Metab Dispos*. 1999;27:810–815.
22. Weber C, Schmitt R, Birnboeck H, et al. Multiple-dose pharmacokinetics, safety, and tolerability of bosentan, an endothelin receptor antagonist, in healthy male volunteers. *J Clin Pharmacol*. 1999;39:703–714.
23. Weber C, Schmitt R, Birnboeck H, et al. Pharmacokinetics and pharmacodynamics of the endothelin-receptor antagonist bosentan in healthy human subjects. *Clin Pharmacol Ther*. 1996;60:124–137.
24. Dingemans J, Bodin F, Weidekamm E, et al. Influence of food intake and formulation on the pharmacokinetics and metabolism of bosentan, a dual endothelin receptor antagonist. *J Clin Pharmacol*. 2002;42:283–289.
25. Fattinger K, Funk C, Pantze M, et al. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. *Clin Pharmacol Ther*. 2001;69:223–231.
26. Rashid A, Lehrman S, Romano P, et al. Primary pulmonary hypertension. *Heart Disease*. 2000;2:422–430.
27. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med*. 1991;325(21):1468–1475.
28. McLaughlin VV, Genthner DE, Panella MM, et al. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med*. 1998;338:273–277.
29. Frishman WH, Azizad M, Agarwal Y, Kang DW. Use of prostacyclin and its analogues in the treatment of pulmonary hypertension and other cardiovascular diseases. In: Frishman WH, Sonnenblick EH, Sica D, eds. *Cardiovascular Pharmacotherapeutics*. 2nd ed. New York, NY: McGraw-Hill; 2003:429–442.
30. Perez-Penate G, Julia-Serda G, Pulido-Duque JM, et al. One-year continuous inhaled nitric oxide for primary pulmonary hypertension. *Chest*. 2001;119:970–973.
31. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo controlled study. *Lancet*. 2001;358:1119–1123.
32. Sorenson HM. Dyspnea assessment. *Respir Care*. 2000;45:1331–1338.
33. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:896–903.
34. Williamson DJ, Wallman LL, Jones E, et al. Hemodynamic effects of bosentan, an endothelin receptor antagonist, in patients with pulmonary hypertension. *Circulation*. 2000;102:411–418.
35. LeJemtel TH, Sonnenblick EH, Frishman WH. Diagnosis and management of heart failure. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart*. 10th ed. New York, NY: McGraw-Hill; 2001:687–724.
36. Kiowski W, Sutsch G, Hunziker P, et al. Evidence for endothelin-1 mediated vasoconstriction in severe heart failure. *Lancet*. 1995;346:732–736.
37. Sutsch G, Bertel O, Kiowski W. Acute and short-term effects of the nonpeptide endothelin-1 receptor antagonist bosentan in humans. *Cardiovasc Drugs Ther*. 1997;10:717–725.
38. Sutsch G, Kiowski W, Yan XW, et al. Short-term oral endothelin receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. *Circulation*. 1998;98:2262–2268.
39. Packer M. Multicenter, double-blind, placebo-controlled study of long term endothelin blockade with bosentan in chronic heart failure—results of the REACH-1 trial [abstract]. *Circulation*. 1998;98(suppl 17):1–3.
40. Packer M. ENABLE – the role of bosentan in CHF. *American College of Cardiology Meeting, Atlanta, GA*, March 17–20, 2002. Available at: http://www.acc.org/2002ann_meeting/ssnews/enable.htm. Accessed on June 8, 2002.
41. Krum H, Viskoper RJ, Lacourciere Y, et al., for the Bosentan Hypertension Investigators. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *N Engl J Med*. 1998;338:784–790.
42. Miyauchi T, Yanagisawa M, Tomizawa T, et al. Increased plasma concentrations in endothelin-1 and big endothelin-1 in acute myocardial infarction. *Lancet*. 1989;1:53–54.
43. Wenzel RR, Fleisch M, Shaw S, et al. Hemodynamic and coronary effects of the endothelin antagonist bosentan in patients with coronary artery disease. *Circulation*. 1998;98:2235–2240.
44. Weber C, Banken L, Birnboeck H, et al. The effect of bosentan on the pharmacokinetics of digoxin in healthy male subjects. *Br J Clin Pharmacol*. 1999;47:701–706.
45. van Giersbergen PL, Treiber A, Clozel M, et al. In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide. *Clin Pharmacol Ther*. 2002;71(4):253–262.
46. Weber C, Banken L, Birnboeck H, et al. Effect of the endothelin-receptor antagonist bosentan on the pharmacokinetics and pharmacodynamics of warfarin. *J Clin Pharmacol*. 1999;39:847–854.
47. Van Giersbergen PL, Halabi A, Dingemans J. Single- and multiple-dose pharmacokinetics of bosentan and its interaction with ketoconazole. *Br J Clin Pharmacol*. 2002;53:589–595.
48. Dingemans J, Schaarschmidt D, Van Giersbergen PL. Investigation of the mutual pharmacokinetic interactions between bosentan, a dual endothelin receptor antagonist, and simvastatin. *Br J Clin Pharmacol*. 2002;53:547P.
49. Wight E, Kung CF, Moreau P, et al. Chronic blockade of nitric oxide-synthetase and endothelin receptors during pregnancy in the rat: effect on pregnancy outcome. *J Soc Gynecol Invest*. 1998;5:132–139.