

Review Article

BOSENTAN - endothelin receptor antagonist

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Abstract

Activation of the endothelin system has been demonstrated in the plasma and lung tissue of PAH (Pulmonary Artery Hypertension) patients. Although it is not clear if the increases in endothelin plasma levels are a cause or a consequence of PH (Pulmonary Hypertension), the data supports a prominent role for the endothelin system in the pathogenesis of PAH. Bosentan is an endothelin receptor antagonist used in the treatment of Primary pulmonary hypertension (PPH) which is a progressive disease with high mortality and administration of the orally active, dual endothelin receptor antagonist bosentan improves exercise endurance, haemodynamics, and functional class over the short term. First-line bosentan therapy was found to improve survival in patients with advanced primary pulmonary hypertension.

Keywords: Pulmonary Artery Hypertension, Pulmonary Hypertension, bosentan, endothelin receptor antagonist

*International Journal of Human and Health Sciences Vol. 03 No. 01 January'19 Page : 10-13
DOI: <http://dx.doi.org/10.31344/ijhhs.v3i1.66>*

Introduction

Activation of the endothelin system has been demonstrated in the plasma and lung tissue of PAH patients.¹ Although it is not clear if the increases in endothelin plasma levels are a cause or a consequence of PH,² the data supports a prominent role for the endothelin system in the pathogenesis of PAH.³

Bosentan is an endothelin receptor antagonist used in the treatment of Primary pulmonary hypertension (PPH) which is a progressive disease with high mortality and administration of the orally active, dual (endothelin-A and B receptors) endothelin receptor antagonist bosentan, improves exercise endurance, haemodynamics, and functional class over the short term. First-line bosentan therapy was found to improve survival in patients with advanced primary pulmonary hypertension.^{4,5} In addition, a delay in time to clinical worsening

was demonstrated in bosentan-treated patients compared with placebo, with clinical benefits maintained for up to 28 weeks.⁵

Bosentan was investigated in six randomised controlled trials. Four of these (Channick 2001, BREATHE-1, BREATHE-5 and STRIDE-2) compared bosentan with. Another trial (BREATHE-2) compared the combination of epoprostenol plus bosentan with epoprostenol alone.⁶ The study reported data from a number of retrospective analyses and observational data to support their clinical findings. Bosentan plus supportive treatment showed significant improvement in exercise capacity (6MWD) and haemodynamic outcomes compared with placebo plus supportive treatment, both in PAH populations with mixed FC and specifically in FC III. There was also a significant increase in time to clinical worsening, improvement in FC and

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PAH symptom of dyspnoea, and reduced risk of serious adverse events in bosentan treated patients compared with placebo in PAH populations with mixed FC. Subgroup analysis of PAH/connective tissue disease (CTD) patients in Channick 2001 and BREATHE-1 showed similar results to those of the whole trial population (see pages 122–125 of the assessment report). It also used data from trials of lower quality to demonstrate that bosentan may be of benefit in patients with PAH associated with HIV, and that bosentan improves patient's quality of life. Methods of randomisation and allocation concealment were not clearly described in some bosentan trials. Intention-to-treat analysis was used in most trials except in STRIDE-2. The Assessment Group stated that the potential bias from non-intention-to-treat analysis was expected to be small in STRIDE-2 as the number excluded from analysis in each treatment group was very small. However, outcomes were not blindly assessed (such as clinical worsening, treatment withdrawal and adverse events) in the study, so interpretation requires greater caution, particularly in light of its open label design. BREATHE-2 compared the initiation of epoprostenol plus bosentan with epoprostenol alone in mixed PAH populations with mixed FC (III and IV). No significant difference was observed between both the groups for any of the outcomes assessed in the trial.⁶

Absorption

In healthy subjects, the absolute bioavailability of bosentan is approximately 50% and is not affected by food. The maximum plasma concentrations are attained within 3–5 hours.⁷ After a single intravenous dose of 250 mg, the clearance was 8.2 L/h. The terminal elimination half-life ($t_{1/2}$) is 5.4 hours. Upon multiple dosing, plasma concentrations of bosentan decrease gradually to 50%–65% of those seen after single dose administration. This decrease is probably due to auto-induction of metabolising liver enzymes. Steady-state conditions are reached within 3–5 days.⁸

Metabolism

Its pharmacokinetic profile in humans is characterized by a low systemic plasma clearance of 17 l/h, a volume of distribution of about 30 l.⁷ Therapy with bosentan is initiated at 62.5 mg bid for the first month and increased to 125 mg bid thereafter.⁹ At the maintenance dose of 125 mg bid, bosentan trough concentrations decrease during the first days of treatment as a result of autoinduction of metabolizing enzymes, leading to an about 40% lower exposure at steady state. Bosentan is metabolized in the liver (Fig.1), mediated to a similar extent by CYP2C9 and CYP3A4, followed by subsequent biliary

excretion. Hydroxylation at the t-butyl group by CYP2C9 and CYP3A4 yields metabolite Ro 48-5033, a metabolite that retains pharmacological activity and is present in human plasma at levels of about 10% compared with parent bosentan. Ro 47-8634 is formed by oxidative demethylation of the guaiacol ether, catalyzed by CYP3A4, to the corresponding phenol, whereas metabolite Ro 64-1056 is formed as a minor product from both primary metabolites. Renal clearance of bosentan is negligible.^{10,11} Bosentan is neither a substrate nor an inhibitor of the intestinal efflux pump MDR1 (P-glycoprotein, ABCB1).¹²

Bosentan is a human OATP (organic anion transporting polypeptides) substrate. The elimination process of the endothelin receptor antagonist bosentan in humans is entirely dependent on metabolism mediated by two cytochrome P450 (P450) enzymes, i.e., CYP3A4 and CYP2C9. It has been shown that the hepatic uptake of the endothelin receptor antagonist bosentan and its metabolite Ro 48-5033 in humans is mediated by OATP1B1 and OATP1B3, which are responsible for its drug-drug interaction with rifampicin, cyclosporin A, and, to a minor extent, sildenafil and clearly show that inhibition of hepatic uptake may become the rate-limiting step in the overall elimination process even for drugs whose elimination is mainly dependent on metabolism.¹³

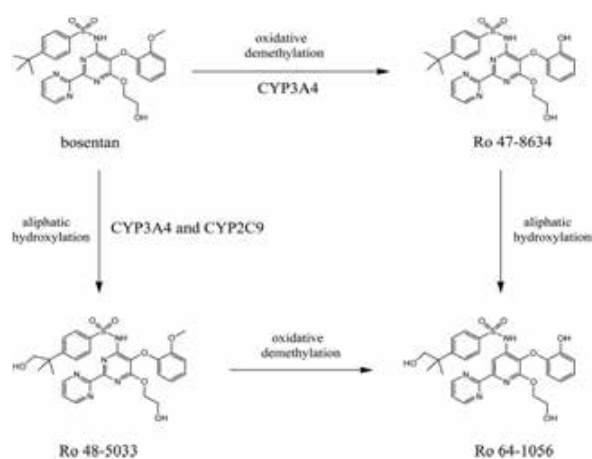


Figure 1: Ro 48-5033, 4-(2-hydroxy-1,1-dimethyl-ethyl)-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2_]bipyrimidinyl-4-yl]-benzenesulfonamide;

Ro 47-8634, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-hydroxy-phenoxy)-[2,2_]bipyrimidinyl-4-yl]-benzenesulfonamide;

Ro 64-1056, 4-(2-hydroxy-1,1-dimethyl-ethyl)-N-[6-(2-hydroxy-ethoxy)-5-(2-hydroxy-phenoxy)-[2,2_]bipyrimidinyl-4-yl]-benzenesulfonamide; **CYP3A4**, **CYP2C9**, Cytochrome P450 enzymes.

Indications

Treatment of pulmonary arterial hypertension (WHO group 1) in functional class (mainly FC III and IV) to improve exercise ability and decrease the rate of clinical worsening.

Side effects^{4, 8, 14, 15}

More common

- Blurred vision
- confusion
- dizziness
- dark urine
- faintness or light-headedness when getting up from a lying or sitting position
- fever with or without chills
- light-coloured stools
- loss of appetite
- nausea and vomiting
- stomach pain
- sudden sweating
- unusual tiredness or weakness
- yellow eyes or skin

Less common

- Swelling

Incidence not known

- Black, tarry stools
- bleeding gums
- blood in the urine or stools
- blue lips and fingernails
- chest pain
- chills
- clay-coloured stools
- coughing that sometimes produces a pink frothy sputum
- coughing up blood
- dark urine
- decrease in the amount of urine
- difficult, fast, or noisy breathing, sometimes with wheezing
- fainting
- fast heartbeat
- fatigue on exertion
- fever
- headache
- hives
- hoarseness
- increased sweating
- irritation
- itching
- joint pain, stiffness, or swelling
- large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs
- noisy, rattling breathing
- pale skin
- pinpoint red spots on the skin
- rash
- redness of the skin
- shortness of breath

- swelling of the eyelids, face, lips, hands, fingers, legs, ankles, or feet
- tightness in the chest
- troubled breathing at rest
- troubled breathing or swallowing
- troubled breathing with exertion
- unpleasant breath odour
- unusual bleeding or bruising
- vomiting of blood
- weight gain
- wheezing

Drug interactions^{4, 8, 14, 15}

Some products that may interact with this drug include: cyclosporine, glyburide. Other medications can affect the removal of bosentan from your body, which may affect how bosentan works. Examples include anti-seizure drugs including carbamazepine, azole antifungals including itraconazole/ketoconazole, macrolide antibiotics including erythromycin, HIV protease inhibitors including ritonavir, rifamycins including rifabutin, amiodarone, cimetidine, tacrolimus, St. John's wort, among others. This drug can speed up the removal of other drugs from your body, which may affect how they work. Examples of affected drugs include "statin" cholesterol medications (such as simvastatin, lovastatin), warfarin, among others. This medication may decrease the effectiveness of combination-type hormonal birth control (e.g., pills, patch). This effect can result in pregnancy. You may need to use an additional form of reliable, non-hormonal birth control (e.g., condom, diaphragm with spermicide) while using this medication.

Contraindications^{4, 8, 14, 15}

- Hypersensitivity to the active substance.
- Moderate to severe hepatic impairment, i.e., Child-Pugh class B or C. Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal.
- Concomitant use of cyclosporine A.
- Pregnancy.
- Women of child-bearing potential who are not using reliable methods of contraception.

Method of administration

Tablets are to be taken orally morning and evening, with or without food. The film-coated tablets are to be swallowed with water.

Overdose

Bosentan has been administered as a single dose of up to 2400 mg to healthy subjects and up to 2000 mg/day for 2 months in patients with a disease other than pulmonary hypertension. The most common adverse reaction was headache of mild to moderate intensity.

Massive overdose may result in pronounced

hypotension requiring active cardiovascular support.

Note: bosentan is not removed through dialysis.

Cost effectiveness¹⁴

Independent economic evaluation suggests that bosentan, sitaxentan and sildenafil may be cost effective by standard thresholds and that iloprost and epoprostenol may not be cost effective.

Summary

Bosentan is a dual endothelin receptor antagonist with affinity for both endothelin A and B (ETA and ETB). It is licensed to treat people with PAH in FC III to improve exercise capacity and symptoms. Two tablet sizes are available: 62.5 mg and 125 mg. Bosentan is contraindicated in people with a known hypersensitivity to the drug, hepatic impairment (including aminotransferases of more than three times the upper limit of normal) and those taking cyclosporin. Bosentan is contraindicated in pregnancy as it is assumed to be teratogenic, and women with child-bearing potential should not receive bosentan unless

they are using a reliable contraceptive (bosentan may interact with and lessen the effectiveness of hormonal contraception). Patients are usually admitted to hospital as day cases under specialist care for the initiation of treatment. Patients return home and drugs are usually delivered to them at regular intervals.

Conflict of Interest

No Conflict of interest has been disclosed by the authors.

Funds

This study did not receive any special funding.

Authors Contributions

Conception and design: NS, RM, KKS
 Analysis and interpretation of data: NA
 Critical revision of the article for important Intellectual content: NS, RM, AB, NM
 Final approval of article: NS, RM, AB, NM
 Statistical expertise: NA
 Collection and assembly of data: NA

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