BOSENTAN –AN ENDOTHELIN RECEPTOR BLOCKER

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Introduction

The pulmonary vascular bed is influenced by local vascular mediators much more than the adrenergic [1]nervous system, though α, β receptors are present on pulmonary vascular smooth muscle. The normal pulmonary vasculature is in a state of relaxation. Pulmonary vasoconstriction is mediated by hypoxia and by endothelin and angiotensin II. Vasodilation can be effected by prostacyclins, endothelin receptor blockers, smooth muscle relaxants, and by nitric oxide.

BOSENTAN has been evaluated in pulmonary arterial hypertension – of idiopathic, hereditary origin and in cases of collagen vascular disease.[2,3]

Mechanism of action

Endothelin-1 released by endothelial cells binds to endothelin receptors A&B in the endothelium and vascular smooth muscle causing vaso-constriction.Endothelin-1 levels are raised in pulmonary arterial hypertension. With this milieu in mind, Bosentan has been tried in treatment of PAH.[2,3,5] Bosentan is a specific& competitive antagonist at both endothelin A&B receptors[2];thus it prevents endothelin-1 mediated vaso-constriction.

Pharmacodynamics

Bosentan is well absorbed orally. It has a half-life of 5 hours. Its bioavailability is 50% and is unaffected by food. It is highly protein-bound[>98%],mainly to albumin and does not enter RBC's. Bosentan is a cytochrome inducer and is metabolized in the liver; it is predominantly excreted in bile.[4]

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Dosage

Bosentan is available as 62.5mg and 125mg tablet. It is started at 62.5mg b.d for 4 weeks and then increased to 125mg b.d. No significant benefits have been noted at higher doses; can be stored at room temperature. The dose is not increased beyond 62.5 m.g. in patients of weight< 40 kg.

Adverse effects

Hepatotoxicity is a major adverse effect; ALT, AST monitoring is done and medication is stopped if they rise 5 times the normal. Peripheral edema, nasal congestion, flushing, dizziness itching/rash, anemia, neutropenia, thrombocytopenia have also been observed. It is not safe in pregnancy. As the drug is a cytochrome inducer and is highly protein-bound, abundant drug interactions occur; cyclosporine, carbamazepine, ketoconazole, amiodarone, erythromycin levels are affected; statins, warfarin binding to albumin is altered.[4]

13 clinical studies [9 placebo controlled & 4 open label] have been conducted till date. A total of 870 patients of PAH were included in these studies.

Two randomized double-blinded multicentric placebo controlled studies-BREATHE-1 [2]and STUDY 351 included a total of 245 PAH patients of stage WHO class III&IV. A significant increase in exercise capacity on 6-minute walk test was observed. Angiographic studies revealed significant increase in cardiac index, decrease in pulm. art. pressure and mean right atrial pressure.

Another study of 185 patients [4] of WHO class II has revealed a significant delay in time to clinical worsening after diagnosis; these patients tolerated Bosentan at a dose of 125m.g.b.d.

Thus the treatment options available for pulmonary arterial hypertension [idopathic, collagen vascular

related, HIV related, recurrent thrombo-embolic] are wide:[4,5]

* calcium channel blockers
* endothelin receptor antagonists like Bosentan
* nitric oxide generators /phosphodiesterase inhibitors like sildenafil
* prostacyclin analogs. These drugs are used singly or in combination based on the functional class of the patient.

References

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