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Review Article

Revefenacin: Drug review

Bhuvana K
Professor and Head of Department of Pharmacology, Sri Devaraj Urs Medical College, SDUAHER, Tamaka, Kolar, Karnataka, India.

Abstract

Revefenacin, a long-acting muscarinic receptor antagonist was approved by US Food and Drug Administration in November 2018 for the maintenance treatment of patients with Chronic Obstructive Pulmonary Disease (COPD). It is administered by inhalational route once-daily. Most common adverse reactions observed during the clinical trials were cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain. To be avoided in patients with hepatic impairment and history of hypersensitivity reaction to revefenacin.

Key-words: Revefenacin, Chronic Obstructive Pulmonary Disease, Muscarinic receptor antagonist

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease associated with high morbidity and mortality. Patient with COPD suffers from dyspnea, cough with expectoration of copious sputum. Smoking of tobacco is the most common cause of COPD and the other contributing factors are air pollution and occupational chemical hazards. The aim of drug treatment is to reduce the symptoms, improve the lung function and to prevent exacerbations.[1]

Current disease management guidelines developed by Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends maintenance treatment with either a long-acting muscarinic antagonist (LAMA, such as tiotropium and aclidinium) or a long-acting beta agonist (LABA, such as indacaterol, salmeterol, formoterol and olodaterol) in patients with moderate or severe COPD when short-acting muscarinic antagonists (SAMAs) fail to control symptoms. Combining LAMA with LABA or inhaled corticosteroids with LABA may help patients with persistent symptoms or exacerbations.[1,2]

Long-acting bronchodilators (e.g. LABAs or LAMAs) are delivered via hand-held devices, such as a dry powder inhaler (DPI) or a metered dose inhaler (MDI) but in some elderly, cognitively impaired or physically restricted COPD patients find it difficult to use such devices. This may result in inaccurate dosing, poor adherence, and poor clinical outcome. These may be reduced by using nebulized drug delivery device which may be easier to use and provide similar efficacy to hand-held inhalers. Revefenacin is a LAMA administered via a standard jet nebulizer. It was discovered and developed by Theravance Biopharma Ireland Limited and has been approved in the United States of America for use as maintenance treatment in patients with COPD since 9th November 2018.[3,4]

Chemistry

The chemical name for revefenacin is 1 -(2-{4-[(4–carbamoylpiperidin –1–yl) methyl] – N -methylbenzamido} ethyl)piperidin-4-yl N-({1,1'-biphenyl}-2-yl) carbamate. The molecu-

Corresponding Author

Dr. Bhuvana K
Professor & Head of Department of Pharmacology,
Sri Devaraj Urs Medical College, SDUAHER,
Tamaka, Kolar, Karnataka.
Mob No: 9900383738
E-mail: drbhuvana_k@yahoo.com
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lar weight is 597.76 and molecular formula is C35H43N5O4.[3]

Mechanism of action

Revefenacin is a long-acting muscarinic receptor antagonist with similar affinity to M1 to M5 muscarinic receptor subtypes. It competitively and reversibly inhibits M3 receptor at the smooth muscle of bronchioles leading to bronchodilatation.[1,3]

Pharmacokinetics

Bioavailability of revefenacin following oral administration is < 3%. In healthy volunteers and in COPD patients, peak plasma concentrations (Cmax) of revefenacin and its active metabolite was reached after 14–41 min following nebulization and steady state concentration was attained within 7 days following repeated inhalation. Intravenous administration of revefenacin in healthy volunteers showed that the mean steady-state volume of distribution was 218 L. Revefenacin, after inhalation in COPD patients was rapidly metabolized in the liver to its major active metabolite (THRX-195518), which has one third to one tenth the potency of revefenacin. [1,3,5]

Oral administration of a single dose of radiolabelled revefenacin revealed 88% radioactivity in faeces and < 5% in urine, suggesting poor oral absorption whereas minimal renal excretion (<1%) of revefenacin and its active metabolite was observed following inhaled administration in COPD patients. The elimination half-life of revefenacin and its active metabolite following once a day inhalation of revefenacin in COPD patients was 22–70 h.[1,3,5]

Indication and Dosage schedule

Revefenacin is used for maintenance treatment of patients with chronic obstructive pulmonary disease. It should be used for inhalation only and the drug should not be swallowed. The approved dosage of revefenacin inhalation solution is 175 mcg once daily, delivered via a standard jet nebulizer with a mouthpiece connected to an air compressor. It is available as inhalation solution in a unit-dose vial for nebulization and each vial contains 175 mcg/3 mL solution. A population pharmacokinetic analysis showed that age, gender, smoking status or weight does not significantly affect plasma levels of revefenacin and its active metabolite.[3,5]

Drug interactions

Concomitant use of revefenacin with other drugs having antimuscarinic activity is to be avoided in view of increased risk of antichoinergic side effects like acute narrow-angle glaucoma and urinary retention. Co-administration with rifampicin, cyclosporine may lead to an increase in exposure of the active metabolite and hence not recommended.[5]

Adverse effects

Revefenacin inhalation was generally well tolerated in patients with moderate to very severe COPD in clinical trials. Most common adverse reactions observed during the clinical trials were cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain and the incidence of these were ≥2%. If patient develops hypersensitivity reactions and paradoxical bronchospasm, the drug should be discontinued and bronchospasm to be treated with an inhaled, short-acting bronchodilator and resume treatment of COPD with an alternative drug.[5] Adverse events leading to treatment discontinuation occurred in 13% of patients receiving 175 mcg revefenacin and 19% of placebo recipients. The tolerability profile of revefenacin in patients with moderate to very severe COPD in the 52-week safety phase III study was similar to that observed in the two 12-week studies and revealed no new safety signals. Long-term use of inhaled revefenacin (up to 52 weeks) had no clinically relevant effect on QTc interval compared with placebo as well.[5,6,7]

Precautions and contraindications

Revefenacin should be used with caution in patients with narrow-angle glaucoma as the condition may worsen. Patients with prostatic hyperplasia or

bladder-neck obstruction may have urinary retention, hence to be avoided. Revefenacin is contraindicated in patients with hypersensitivity to revefenacin or any component of this product. It should not be prescribed to patients with hepatic impairment, acutely deteriorating COPD or to treat acute symptoms.[5]

Dosage adjustments are not required in patients with renal impairment but they have to be monitored for systemic antimuscarinic side effects as Cmax and Area Under the Curve(AUC) of revefenacin and its active metabolite increased up to 2.5-fold in patients with severe renal impairment. Information regarding use during pregnancy and lactation is not available. It should not be used in children as safety and efficacy is not established. [5]

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