

# RGH Pharmacy E-Bulletin

Volume 40 (3): November 1, 2010

A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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## Phosphodiesterase 4 inhibitors in COPD

Patients affected by Chronic Obstructive Pulmonary Disease (COPD) experience chronic symptoms and exacerbations with reduced quality of life despite treatment. Current treatment options for COPD include inhaled short-acting and long-acting bronchodilators (either  $\beta_2$ -agonists and/or anticholinergic drugs). Inhaled corticosteroids are added to reduce frequent exacerbations but, among other side effects, there is concern about increased pneumonia risk when inhaled corticosteroids are used in COPD.

Phosphodiesterases (PDE) are the superfamily of enzymes that inactivate the intracellular second messengers cAMP and cGAMP. The known enzymes in the family have different tissue distribution and substrate specificity, and hence are targets for drug design and research. A range of specific PDE isoenzymes have been studied in a range of diseases, notably, erectile dysfunction.

PDE<sub>4</sub> is the main cAMP metabolising enzyme in immune and inflammatory cells, airway smooth muscle and pulmonary nerves. Inhibition of PDE<sub>4</sub> suppresses recruitment and activation of several inflammatory cells that are considered important in airway diseases.

Roflumilast, a PDE<sub>4</sub> inhibitor, inhibits chemotaxis, leucocyte activation and cytokine production in vitro and in animal models of COPD. In patients with COPD roflumilast reduces the number of neutrophils and eosinophils in the sputum. The drug has no direct effect on smooth muscle in most animal models and no appreciable acute bronchodilator effect in people.

Trials have looked at roflumilast (for up to one year) as add-on therapy to short acting inhaled anticholinergics and salbutamol in moderate to severe COPD. Roflumilast has been studied as add-on to long acting bronchodilators (either salmeterol or tiotropium). Compared to placebo there was improvement in lung function and reduced number of exacerbations. There has been no direct comparison of roflumilast plus tiotropium against roflumilast plus salmeterol. The most effective combination is not known. Data are not available about efficacy compared to, or if added to, inhaled corticosteroids.

The known side effects of Roflumilast include gastrointestinal disturbance (nausea and diarrhoea) headache and weight loss. There will be interest in how this adverse effect profile balances against the increased pneumonia risk when inhaled corticosteroids are used in COPD.

Marketed PDE<sub>4</sub> inhibitors in COPD include cilomilast (approved by the FDA) and roflumilast (approved for use in the EU for maintenance treatment of COPD in patients with frequent exacerbations as add-on to bronchodilator treatment). Theophylline is a non selective PDE inhibitor acting on multiple additional targets. Theophylline also has effects on other pharmacological pathways, has a narrow therapeutic index and clinically significant drug interactions, hence its diminished use.

To date, in Australia, PDE<sub>4</sub> inhibitors for COPD are not available.

This E-Bulletin is based on work by Nicky Gordon, Senior Pharmacist, RGH

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