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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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Safety of inhaled bronchodilators in COPD

Inhaled bronchodilators are the mainstay of therapy in chronic obstructive pulmonary disease (COPD). Earlier studies have suggested that long-acting beta agonists (LABAs) and ipratropium may be associated with increased mortality, and the U.S. Food and Drug Administration has an ongoing safety review of tiotropium in relation to stroke risk. However COPD itself is associated with significant morbidity and mortality due to cardiovascular disease, which makes it difficult to assess the possible contribution of medications. Several studies published during 2008 have investigated this issue.

In a large nested case control study of U.S. veteran patients with newly diagnosed COPD, 32,130 case patients who died were matched with 320,501 control patients, and mortality risk was adjusted for co-morbid conditions, healthcare use and markers of COPD severity. Inhaled corticosteroids (ICS) and LABAs were associated with a decreased risk of all cause mortality (OR 0.80 and 0.92 respectively), whilst ipratropium was associated with an increased risk (OR 1.11). Ipratropium was used by 50% of patients and was associated with an increased risk of cardiovascular death (OR 1.34; 95% CI 1.22 to 1.47). A similar trend has also been observed in the prospective Lung Health Study. The authors speculate that in clinical practice use of an ICS may attenuate possible risk associated with ipratropium.

Earlier studies have suggested an association between LABAs and an increased risk of respiratory deaths in patients with COPD, although these studies have a number of limitations. This year researchers conducted a systematic review of 27 studies comparing LABAs with placebo or inhaled anticholinergics over a minimum of four weeks. There was no significant difference between LABA and placebo groups for respiratory deaths. The combination of a LABA with an ICS reduced the risk of respiratory death compared with LABA alone (RR 0.35; 95% CI 0.14 to 0.93), although this result was based on only two studies.

Another systematic review and meta analysis studied the safety of inhaled anticholinergic drugs. 17 randomised controlled trials (n = 14783) were included, with 12 trials evaluating tiotropium and 5 ipratropium. Most were short term studies ranging over 6-26 weeks, with five studies of 2 to 5 years duration. Inhaled anticholinergics significantly increased the composite risk of non-fatal MI, non-fatal stroke and cardiovascular (CV) death (1.8% vs 1.2%; RR 1.58, P <.001). Most of the excess risk came from studies where therapy continued for at least six months. In these long-term trials tiotropium was associated with a higher risk than ipratropium (RR 2.12 vs 1.57 respectively). None of the trials were designed to monitor CV risk and events were not adjudicated, so the results require confirmation in prospective studies. The authors recommend that individual CV risk should be evaluated to determine whether symptomatic and other benefits outweigh potential long-term CV risk. They speculate that an increased risk of CV events may be mediated by inflammatory cytokines.

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