EDITORIAL

Are long-acting β_2-agonists safe in the treatment of asthma?

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Ever since the epidemic of asthma deaths linked to high dose inhaled isoprenaline use in the United Kingdom, Australia and New Zealand in the seventies and the more recent one linked to fenoterol prescribing in New Zealand in the 1990s, there remains a lingering doubt over this class of bronchodilator drug used in the relief of asthma symptoms.[1] Although no clear mechanisms could account for these deaths, suspicion was cast on the cardiac toxic effects of the propellants, lack of cardiac selectivity, overdependence on the use of short acting β_2-agonists to chronic therapy and resistance of the airways to the bronchodilator effect. The recognition that asthma was an inflammatory disease led to the regular use of inhaled corticosteroids as controller therapy with strong recommendations that short-acting β_2-agonists should only be used for as required breakthrough symptom relief. Thus, the introduction of inhaled long-acting β_2-agonists (LABAs) created a conundrum in that on the one hand they produced prolonged bronchodilatation, but on the other, when used alone, they could mask an underlying in asthma exacerbation and, therefore, put the patient at risk of a catastrophic event.[2] While acknowledging the value of LABAs to the asthma treatment armamentarium, asthma management guidelines insisted that these drugs should only be used alongside inhaled corticosteroids either as separate inhalers or as combination products in the same inhaler.[3] Such treatment is now advocated as first line in the management of moderate-severe asthma or where there is a need for corticosteroid sparing.[4] Although a case has been made for LABAs exerting enhancing effects on the anti-inflammatory actions of inhaled corticosteroids[5], the clinical significance of this remains controversial.

Set against this background of advancement in treatment options came the Salmeterol Multicenter Asthma Research Trial (SMART) that, in 26,000 asthmatic patients, revealed an excess of asthma deaths and severe asthma-related events with salmeterol use especially when used alone and in African Americans.[6] This was followed by a composite meta-analysis of a series of post-marketing pharmacovigilance studies of LABAs that include both salmeterol and formoterol (the majority of which still comprised the SMART patients) and reinforced concerns over excess mortality associated with this drug class especially when used alone.[7] While a case-control study of 532 asthma deaths has failed to identify LABA use as a risk factor[8] there remains lingering concern over the safety of this drug class.[9]

One key issue arising from these studies is whether LABAs prescribed with inhaled corticosteroids reveals increased risk of severe asthma-related exacerbation events and increased risk of death.[10] To address this question, Bateman et al. reviewed all salmeterol inhaled corticosteroid studies versus inhaled corticosteroids alones that had been entered onto the GSK Clinical Trials Registry up to September 2007.[11] In a detailed appraisal of 66 eligible trials totalling almost 21,000 patients equally divided between the 2 treatment options, no difference was found in asthma-related hospitalisations, -deaths or -severe exacerbations requiring systemic corticosteroids. Clearly, this well powered study that uses both the published and the grey literature, as the source of data is reassuring.

However, this meta-analysis leaves unanswered the tricky question of why there was a statistically significant increase in asthma deaths in the SMART and the Salpeter studies. Most likely this is due to the excess deaths occurring in these patients not receiving concomitant inhaled corticosteroids with a LABA and the masking of deteriorating airway inflammation. Patients selected for clinical trials can represent only a minority of asthmatic subjects in the real word (4%)[12], raising the question over whether the outcomes

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derived from company-sponsored efficacy drug trials can truly be representative of real world patients. Other possible explanations include pharmacogenetic influences where polymorphism of the β_2-adrenoreceptor, which have been shown to predict greater asthma severity and impaired bronchodilator responses[13], some of which are more prevalent in American Africans[14]. In detailed studies looking at β_2-adrenoreceptor polymorphism in relation to the efficacy of salmeterol, there remains conflicting findings in different studies.[15,16]

Although a little residual uncertainty still prevails over the long-term safety of LABAs in asthma[17], the Bateman study[11] would indicate that there use with corticosteroids can be regarded as safe but under no circumstances should LABAs be used in isolation in either asthmatic adults or children.

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