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Long-acting beta agonists—prescribe with care

According to a recent consultation document, PHARMAC plans to increase the availability of the higher-strength long-acting beta agonists (LABAs), and to fund the salmeterol/fluticasone combination. Thus we are likely to see increased high-strength LABA use and increased prescribing of combination long-acting beta agonists and inhaled corticosteroids (ICS).

In many ways this is a positive move. The combination of long-acting beta agonists and inhaled corticosteroids have been shown in many studies to significantly improve day-to-day asthma management in mild to moderately severe asthma.[1] Prescribing combinations of LABAs and ICS for suitable patients, is now a major component of asthma management around the World and firmly incorporated in evidence-based asthma management guidelines.[2] But despite their advantages and widespread acceptance, there is a need for caution. Long-acting beta agonists are associated with a small but significant increased risk of life-threatening asthma attacks and asthma death.

While this has led to strong label warnings on all LABA containing medication in the US, it has received little publicity in New Zealand while both salmeterol and the formoterol/budesonide combination have been heavily promoted directly to patients on television.

Salmeterol was launched in the aftermath of the fenoterol controversy[3] in the early 1990s and amid concerns about the use of beta agonists in asthma.[4] Glaxo conducted a post-marketing safety study in the UK, published in 1993.[5] The study (n=25,000) randomised patients 2 to 1 to salmeterol 50 µg twice daily or salbutamol 200 µg four times daily.

Asthma severity and concomitant therapy were well balanced between the treatment groups and 70% of patients were prescribed inhaled corticosteroids at entry to the study. There were 14 deaths due to asthma (12 in the salmeterol group, and 2 in the salbutamol group), a non-significant relative risk of 3.0 (95%CI 0.7–20). All deaths were in patients with severe asthma in the opinion of their GP or the independent consultants to the study, and 5 were on oral corticosteroids.

In the opinion of the consultants, 10 of the 14 patients who died might have been more appropriately treated with earlier or higher doses of inhaled corticosteroid. The authors concluded that severe or unstable asthma patients: “require stabilisation of their asthma with appropriate doses of inhaled or oral glucocorticosteroids (>1 mg per day of beclomethasone dipropionate or equivalent) as their main treatment.”

At the time of approval in the US, the Food and Drug Administration (FDA) asked GlaxoSmithKline to provide more safety data on salmeterol which led to a further randomised trial in the United States—the Salmeterol Multicenter Asthma Research Trial (SMART).[6] This study commenced in 1996, consisting of 28 weeks of salmeterol 50 µg twice daily or placebo added to usual asthma care in subjects >12 years of age.

Unfortunately the warnings of the previous UK safety study were not followed, and there was no attempt to make sure that patients were stabilised before commencing salmeterol or even that they were using ICS. Following an interim analysis in 2003 with enrolment at just over 26,000 subjects, the study was terminated due to increased mortality in the salmeterol group. The full findings from this study were finally published earlier this year. There were 13 asthma deaths in the salmeterol group and 3 in the placebo group, a significant relative risk (RR) of 4.4 (CI 1.2–15.3).

For African Americans who had more severe asthma at baseline (twice the frequency of hospital admission and ED attendance for asthma and lower percent predicted peak expiratory flow rate [PEFR] than Caucasians) and were less likely to be receiving ICS at enrolment, the non-significant increased RR was 7.3 (CI 0.89–58.9).

For asthma deaths and life-threatening experiences, the increased relative risk was significant for the total study population RR 1.71 (1.0–2.9), and for African Americans RR 4.9 (CI 1.7–14.5). The number needed to harm for the total population and the African American sub group were 879 (CI 438–∞) and 158 (CI 97–429) respectively. Importantly, most of these adverse effects appeared to be reduced if ICS were prescribed at baseline, although the study was not powered to specifically answer this question.

The evidence that salmeterol increases the risk of death is now convincing; it has recently been further supported in a meta-analysis of studies of both salmeterol and formoterol with the authors concluding that both agents were associated with increased asthma hospitalisations, life-threatening asthma attacks, and asthma deaths in both adults and children and that ICS did not adequately protect against these effects.[7] Indeed, in the US, these studies have led the FDA to place black box warnings (the strongest warning that the FDA issue) on all LABAS whether sold on their own or in combination with ICS.

However, despite widespread introduction and uptake around the World, there have not been any reported recent increases in asthma mortality. This is reassuring but perhaps surprising until one considers the unique way in which LABAs are generally prescribed and used, as twice daily regular treatment. Thus, there is little potential for LABAs to be used excessively in worsening asthma as happened during the fenoterol epidemic.[8] The corollary of course is that LABAs increase the risk of death and life-threatening asthma at prescribed doses.

There have been recent calls for formoterol, which has a rapid onset of action, or the formoterol/budesonide combination to be used as a ‘one stop shop’ for maintenance and relief of acute asthma attacks.[9] While these studies demonstrate improved asthma control, the benefits to the majority may well come at the cost of increased life-threatening attacks and deaths for a small minority.

What are the implications for New Zealand?

Firstly, long-acting beta agonists should not be used unless adequate doses of ICS are being taken regularly. Compliance with ICS is notoriously poor, being as low as 15% in some studies.[10] The combination products will of course ensure this and for this reason should be encouraged. Secondly, LABAs should not be introduced when a patient’s asthma is deteriorating or poorly controlled. Particular care should be taken with patients who are using excessive amounts of short-acting beta agonists, who

have recently been admitted to hospital with acute asthma or have received frequent courses of oral corticosteroids all of which may indicate poorly controlled and severe disease.[11] Thirdly, the lowest effective dose should always be used.

It is unfortunate that we still do not know how some short-acting beta agonists such as isoprenaline and fenoterol or the long-acting beta agonists increase the risk of death in severe asthma, but in the case of LABAs it appears to happen without excessive use.

New Zealand is a particularly sensitive barometer for the adverse effects of bronchodilator treatment. For carefully selected asthmatic patients to reap the symptomatic benefits of long-acting beta agonists combined with inhaled corticosteroids (without a small but significant proportion of patients incurring serious or fatal asthma attacks), they need to be prescribed judiciously and not be seen as a panacea for asthma.

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