Long acting beta agonists – where are we at with safety?

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For the last twelve years, long acting beta agonists (LABAs) have been commonly prescribed for moderate to severe asthma. They were first introduced in Europe in the late 1980s. At that time the controversy about regular short acting beta agonists (SABAs) was raging and there were concerns about the safety of the long acting variety.[1] Clinical and epidemiological data from New Zealand had shown an association between the regular use of SABAs and the instability of asthma and increased mortality.[2] Recently in the US, the Food and Drug Administration (FDA) has issued a stern public health advisory alerting *'health care professionals and patients that these medicines (LABAs) may increase the chance of severe asthma episodes, and death when those episodes occur'.* Similar warnings have been made in the UK and New Zealand[3] (www.fda.gov/cder/drug/advisory/LABA.htm).

Inhaled corticosteroids (IHCs) are the cornerstone of effective treatment for persistent asthma and focus on treating the inflammatory nature of the condition. However, in patients with more severe disease, corticosteroids in appropriate dose may fail to control the symptoms adequately, necessitating additional treatment with inhaled bronchodilators. Until the early late 80s, the only available bronchodilators available were short-acting beta$_2$-adrenergic agonists such as salbutamol or terbutaline. Long acting beta agonists were seen as a solution to the regular and possible overuse of SABAs.

Paradoxically after the LABAs were introduced in the US, researchers in the UK published a large double-blinded study[4] comparing salmeterol with salbutamol used as bronchodilator supplements. It was a large study (25 000 patients) and was of 16 weeks duration. Patients receiving salmeterol had a higher mortality than those on salbutamol. However it must be emphasised that the mortalities were rare and were not of statistical significance. There were confusing factors – a higher proportion of patients in the salbutemol arm were withdrawn, and those on salmeterol may have had more severe asthma. Following this the Salmeterol Multicentre Asthma Research Trial (SMART) study was conducted, which produced similar results to the UK study. However, increased morbity was more prevalent among the Afro-American cohort, and the study also suggests that risk is increased among those patients not on IHCs. There are no studies of a similar nature with formoterol. There is evidence that LABAs may be prescribed to more severe asthmatics and some studies show there is no difference in morbidity or mortality with the use of LABAs when subjects are matched for age, severity, and hospitalisation history.[5]

Nonetheless, it appears that, internationally, deaths from asthma have decreased since the introduction of LABAs.[6] It may well be that the increased primary use of IHCs may have influenced this decrease. There is now suggestion to use long action bronchdilators as sole therapy in COPD[7] and in the light of current evidence this should be viewed with caution. There is also discussion of paradoxical bronchospasm, increased bronchial responsiveness and tachyphylaxis occurring with LABAs.[8] No paradoxical bronchospasm was noted, however, when us-

ing a powder device, suggesting a reaction to the propellant. Nonetheless prescribers should be aware of this rare phenomenon. In addition there is no evidence that tachyphylaxis occurs with LABAs.[9]

There are important differences in the two products available in New Zealand. Formoterol is a total agonist and its effect increases with dose. It is rapid acting – of the same magnitude as SABAs. Salmeterol is a partial agonist, and is at the top of its dose response curve at a dose of 50mcg. It takes longer to act – about 30 minutes. The duration for both is about twelve hours, but it is the author's personal experience that effects of both medications can be elicited for up to 36 hours.

So where does that leave us in the current state of our knowledge? It is fair to say that the jury is still out with respect to safety of LABAs, but they are very useful agents to use when control of asthma cannot be gained with ICCs alone with the addition of no more that two puffs of SABAs/day. Adverse events are rare but real. LABAs should ALWAYS be monitored by a doctor especially for the first few weeks of therapy and they should ALWAYS be used in conjunction with IHCs. They alone are not a substitute for IHCs. Patients should be monitored in the early stages of treatment, and patients should be instructed not to stop their therapy.

Competing interests

Assoc Prof Reid has received lecture fees from Astra Zeneca and Pfizer. He is an executive member of the International Primary Care Respiratory Group, and a director of BPACNZ.

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