Safety of β_2-agonists: a 50-year debate closed?

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Can current evidence close the debate on the safety of beta-2 agonists? http://ow.ly/qJrCt

The safety of β_2-agonists has been questioned since their introduction in the late 1950s. Hundreds of papers have been published on short- and long-acting inhaled products, and the debate still persists. Is it time to close the debate with current evidence?

The early debate with short-acting β_2-agonists

The introduction of isoproterenol forte, a poorly selective inhaled short-acting β_2-agonist (SABA), was associated with an epidemic of asthma deaths in the UK, Australia and the USA [1]. Trends in deaths were parallel to the increased consumption of this SABA and many concluded that SABAs had a cardiac toxicity or induced an acquired resistance [2]. In fact, most deaths occurred in patients who stopped oral corticosteroids and this was further associated with asthma deaths.

M. Sears and co-workers were at the forefront of the second debate on deaths of asthmatic children [3, 4]. This was initially attributed to fenoterol (SABA) [5], and then to an inappropriate management of patients, including the lack of inhaled corticosteroid (ICS) use [6]. Moreover, fenoterol was used more often by severe asthma patients and, after adjusting for differences in baseline risk, it did not increase the risk of severe exacerbations [7].

A new debate when long-acting β_2-agonists were introduced

Due to the concerns regarding SABA safety, a UK nationwide surveillance study compared the safety of salmeterol with salbutamol in asthmatic patients [8]. In 16 787 patients treated with salmeterol for 16 weeks, 54 deaths and 12 deaths from asthma occurred (0.07%). The interpretation of the study was questioned by Sears and Taylor [9]. The complete study of 15 407 patients observed for over 1 year did not find that salmeterol was associated with asthma deaths [10].

The Food and Drug Administration (FDA) requested a confirmation of the Castle *et al.* [8] study. The Salmeterol Multicenter Asthma Research Trial (SMART) compared usual pharmacotherapy for asthma with or without salmeterol [11]. Following an interim analysis of 26 355 subjects, the study was terminated due to findings in African Americans and difficulties in enrolment. The occurrence of the primary outcome, respiratory-related deaths or life-threatening experiences, was low and not significantly different between groups. There was a small but significant increase in asthma-related deaths (13 *versus* three; RR 4.37, 95% CI 1.25–15.34), and in combined asthma-related deaths or life-threatening experiences (37 *versus* 22; RR 1.71, 95% CI 1.01–2.89) in subjects receiving salmeterol *versus* placebo. The imbalance occurred largely in the

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African American subpopulation. This population is known for poor management [12] and the vast majority of deaths occurred in patients who did not receive ICS [13].

A new meta-analysis confirming previous ones

The impact of ICS on LABA safety was then considered in meta-analyses of randomised controlled trials (RCTs) on salmeterol [14] or formoterol [15].

Data from 66 GlaxoSmithKline trials involving a total of 20 966 participants with asthma were analysed [14]. Asthma-related hospitalisations were very low (35 events in patients receiving ICS plus salmeterol, *versus* 34 events in those receiving ICS alone). One asthma-related death occurred among participants receiving ICS with salmeterol. A subset of 24 trials showed a decreased risk for severe asthma-related exacerbations for ICS plus salmeterol *versus* ICS alone (risk difference -0.025, confidence interval -0.036– -0.014); $p<0.001$).

A study examined whether asthma, cardiac or all-cause mortality and morbidity were increased with formoterol use. The analysis included all AstraZeneca randomised controlled parallel-group asthma trials of 3–12-month duration involving formoterol [15]. The study of SEARS and RADNER [16] published in this issue of the journal expands the previous study completed in December 2006 and reports the results of around 100 000 patients followed up by AstraZeneca [15]. The relative risk of asthma-related deaths was 1.13 with formoterol (eight *versus* two; RR 1.13, 95% CI 0.19–1.22). However, non-fatal asthma-related serious adverse events were significantly reduced with formoterol (RR 0.63). The authors conclude that ''this enlarged dataset indicates no increased risk for asthma-related deaths due to formoterol although the wide confidence interval precludes certainty.''

But this study cannot close the debate

These RCTs had limitations, as they involved selected patients who received careful follow-up, and some trials were of short duration (12 weeks). One death in the salmeterol trials and eight in the formoterol trials limited the ability to measure risk for this outcome. In the study of SEARS and RADNER [16], statistical issues prevent the proposition of a definite conclusion. Finally, there are pitfalls in meta-analyses of RCTs [17].

Two recent Cochrane meta-analyses assessed the safety of salmeterol and formoterol. In adults, by comparison with placebo, an increased risk of serious adverse events was found with regular formoterol, and this was not abolished in patients taking ICS [18]. The authors conclude that data on all-cause serious adverse events should be more fully reported in journal articles, and not combined with all severities of adverse events or limited to those events that are thought by the investigator to be drug-related [18]. The discrepancies between the SEARS and RADNER [16] study and the meta-analysis of CATES *et al.* [18, 19] are unclear since results are not similar. The outcomes studied may not be identical but it is surprising that SEARS and RADNER [16] did not compare their results with those of CATES *et al.* [18, 19].

The effect on serious adverse events of regular formoterol in children was greater than the effect in adults [18], but the difference between age groups was not significant. No definite conclusion could be made on the risk of dying from asthma from regular combination therapy [19]. Regular ICS+LABA combination therapy is likely to be less risky than LABA alone, but may not be risk free. The results of large on-going surveillance studies are needed to further clarify the risks of combination therapy in children and adolescents with asthma. The relative safety of formoterol in comparison to salmeterol remains unclear [19].

The cardiovascular safety of LABAs does not appear to cause any problem [20]. However, ECG may not be sufficient to identify patients at risk of cardiovascular events.

Randomised controlled trials are insufficient to appraise the safety of medications which induce rare but serious side-effects

Although recently debated, RCTs are vital for the assessment of the efficacy of a new intervention but are not well designed to assess safety. The number of patients is probably too low to find rare but serious side-effects and a number of drugs have notoriously been withdrawn after commercialisation because these rare events were not sufficiently accounted for in RCTs or, possibly, also because of a lack of patient stratification. Moreover, there may be an underestimation of side-effects in some company-funded studies [21].

Real-life trials and observational studies are needed

The Brussels Declaration requested a need for change in asthma management and specifically that the European Medicines Agency guidance note on asthma should be updated: "real-world" studies should be funded and results used to inform guidelines [22]. The SMART study of NELSON *et al.* [11] was stopped partly because of the difficulty of randomising patients. Observational studies are also of interest [23].

The Food and Drug Administration safety concerns

In 2010, the FDA conducted a comprehensive review of the benefits and risks of using LABAs to treat asthma. ''The agency has concluded that the benefits of LABAs continue to outweigh the risks when the drugs are used appropriately and that the agents should remain available for the treatment of asthma. However, because of their serious risks, the FDA recommends that LABAs be reserved for patients whose asthma cannot be adequately managed with asthma-controller medication such as an inhaled corticosteroid. Furthermore, until additional data are available from large, randomised, controlled trials evaluating the safety of LABAs when administered with an ICS, the FDA believes that long-term use of LABAs should be limited to patients who require prolonged use of these drugs'' [24].

However, common sense is probably most important

With current studies, LABAs cannot be replaced by other drugs in moderate–severe asthmatic patients. Appropriate management and asthma plans are highly effective in the control of asthma [25]. Considerable reductions in asthma deaths and hospitalisations have been consistently demonstrated in developed and developing countries where an appropriate management of asthma is available, affordable and acceptable [26]. This was first demonstrated in the New Zealand epidemic for ICS [6] and confirmed further. The availability of LABAs increased these trends. It appears that most asthma-related deaths occur in untreated patients; however, ICS must be given with LABAs in asthma.

Is this debate closed? Not completely, since some high-risk subgroups (children, ethnicity) may present more toxic effects than others and cannot yet be excluded. More sufficiently powered studies (RCTs, real-life and observational studies) in well phenotyped and stratified patients are therefore required. Moreover, there is a need for studies with new molecules. Further studies are therefore needed to determine whether the addition of LABAs to ICS increases the risk of serious asthma outcomes. RCTs initiated by the FDA began in 2011 and results are expected in 2017 [27].

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