Preventing asthma deaths: above all, do no harm

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Lancet Respir Med 2019
Published Online
June 25, 2019
http://dx.doi.org/10.1016/S2213-2600(19)30197-3

Two truths, universally acknowledged, are that asthma outcomes in the UK are among the worst in Europe, and that the overuse of short-acting β_2 agonists (SABA) is a risk factor for asthma deaths.[1]

The first step in evidence-based asthma guidelines around the world is intermittent administration of SABA, progressing to prophylactic inhaled corticosteroids (ICS) if SABA are being used more than an arbitrary number of times per week. The evidence against this approach has been mounting, culminating in a real-life study by Beasley and colleagues,[2] in which the conventional approach was compared with low-dose ICS plus as-needed SABA, and with combined ICS (budesonide) plus a long-acting β_2 agonist (LABA; formoterol) taken as needed. The results were clear-cut: SABA alone was inferior to the other approaches in terms of asthma attacks, and as-needed budesonide-formoterol was better than either of the other approaches at preventing severe attacks. The mean inhaled dose per day of corticosteroid was less in the as-needed budesonide-formoterol regimen (107 µg [SD 109]) than in the regular ICS regimen (222 µg [113]).

The Beasley and colleagues study[2] adds to the mounting evidence that intermittent, as-needed regimens are more effective than are conventional regimens based on regular ICS. Two rigorous randomised controlled trials,[3,4] both in adults, showed the superiority of the as-needed budesonide-formoterol approach, with no maintenance therapy, in mild asthma. A meta-analysis[5] in adults and children older than 12 years, and a single study[6] in children aged 4–11 years, have shown a reduced asthma attack frequency with a regular plus as-needed budesonide-formoterol regimen. What more evidence do we need?

There are two more reasons that the intermittent, as-needed budesonide-formoterol approach should be the way forward. The first is that the medical community has notably failed to convince patients to regularly take inhaled medication, and there is no sign that this issue will change; only the most unwavering optimist would think that e-alerts and other modern reminders will transform behaviour in the long term. The second is that the blue inhaler is a killer; numerous asthma deaths occur in those who are using SABA for relief in increasing quantities but not using ICS.[1] If SABA on their own were not available, and these patients were thus compelled to use budesonide-formoterol for relief therapy, it seems highly likely that lives would be saved. Given the abundance of evidence for the as-needed budesonide-formoterol approach, what is the justification for retaining SABA alone, with their highly dubious safety profile, when we have something at least equally effective but without the safety concerns? Similar thinking led to the then Minister of Health, Helen Clark, taking fenoterol off the market in New Zealand, thus saving numerous lives.[7]

Of course, no treatment is perfect. Intermittent regimens require the patient to perceive that they are symptomatic, and there are undoubtedly people with asthma who do not always notice worsening airflow obstruction. It is expected, but unproven, that because they feel well this subgroup of patients is unlikely to take regular medication. It could be that patients who do not respond to intermittent regimens should be assessed for poor symptom perception and switched to regular ICS, but use budesonide-formoterol for acute relief of symptoms.

What needs to happen now? The *Lancet* Commission on asthma[8] proposed that asthma should be deconstructed into treatable traits, including eosinophilic airway inflammation, and suggested that isolated SABA therapy was wrong. Considering Beasley and colleagues' study,[2] the treatment of adult patients with even mild eosinophilic asthma should be intermittent budesonide-formoterol, not SABA. Given the consistency of the results of using regular plus as-needed budesonide-formoterol in patients from age 6 years upwards, it is likely that these results would apply to children with eosinophilic asthma at all ages. It is urgent that the study by Beasley and colleagues[2] is repeated in children older than 6 years to test the as-needed budesonide-formoterol approach in this age group. This approach should also be tested in selected children younger than 6 years. The INFANT study[9] showed that aeroallergen sensitisation and elevated peripheral blood eosinophil count predicted a good response to ICS, and this is the group in which an intermittent combined ICS and LABA approach should be tested. This would require the use of a combination metered dose inhaler and spacer to ensure adequate drug delivery.

The two most important consequences of the study by Beasley and colleagues[2] are, first, that SABA should cease to be prescribed for eosinophilic airway disease, at least in adults, necessitating an immediate and radical revision of guidelines. It is unfortunately impractical to take SABA as a single agent off the market altogether, given that ICS might not be indicated in some airway diseases at the extremes of age, namely non-atopic wheeze in children younger than 5 years, and chronic obstructive pulmonary disease. However, it should be considered negligent to prescribe SABA to adults in any other context. The second important consequence is that the medical community should reflect on their mistakes. As a so-called therapeutic community, we have been guilty of uncritically repeating guidelines for far too long. In the words of Bertie Wooster, 'Jeeves, this nuisance must now cease!'

Andrew Bush
Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London SW3 6NP, UK
a.bush@imperial.ac.uk

I declare no competing interests.

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