Regular (up to 10 puffs 4-hourly) inhaled salbutamol should be prescribed at discharge after an asthma attack: myth or maxim?

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Shareable abstract (@ERSpublications)
The use of weaning plans is based on opinion that is not evidence based and in view of the weight of evidence countering this practice, we conclude that the benefit of prescribing regular salbutamol at discharge is a myth https://bit.ly/3Yx0TmM

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Abstract

Over the past 20 years, the concept of asthma weaning plans on discharge after an attack has crept into common practice, although the precise origin of these plans is unclear. High use of short-acting β_2-agonists (SABAs) may result in tolerance to their bronchodilator effects, thus diminishing their efficacy, particularly when they are most needed at the time of an acute attack. Furthermore, key warning signs of a deterioration in asthma control may be masked and the weaning plan may encourage the over-use and over-reliance on SABAs. Side-effects from over-use may also occur, including lactic acidosis, downregulation of the β_2-adrenoreceptor, increased allergen response and pro-inflammatory effects. The need for asthma education at discharge, a personal asthma action plan and vigilance about prescribing and ensuring adherence to maintenance therapy are definitely important. However, the current authors conclude that the benefit of prescribing regular salbutamol (up to 10 puffs every 4 h) at discharge after an acute asthma attack is a myth, and a very dangerous one.

Introduction

Asthma is the most prevalent chronic disease of childhood [1]. It affects one in 11 children within the UK alone [2], and globally the prevalence of asthma ever in adolescents is estimated at 10.5% [3]. Asthma confers a substantial financial burden, alongside high morbidity and consumption of healthcare services [4]. More pressingly, the National Review of Asthma Deaths (NRAD) delivered a sobering reminder that paediatric mortality still remains unacceptably high [5], with the UK having among the highest asthma-related mortality compared to other European countries [6, 7]. Asthma attacks are an all-too-common occurrence: it is estimated that almost 50% of children who have asthma will have an attack each year [8], resulting in high numbers of hospital admissions [9, 10]. The best predictor of risk of future asthma attacks is a previous attack [11]. Furthermore, poor asthma control and frequent symptoms are widely reported in population-based studies [12].

School-age asthma is usually a chronic inflammatory disorder characterised by variable airflow obstruction. The earliest medications for asthma were bronchodilators, dating from a time when asthma was primarily believed to be a disease of bronchoconstriction [13]. β_2-agonist bronchodilators act on the β_2-adrenergic receptor in the airways, leading to smooth muscle relaxation and bronchodilation. Importantly, these short-acting reliever inhalers have no effect on the underlying inflammation caused by and driving the asthma process. Furthermore, there is evidence that repeated use of relievers without inhaled corticosteroids (ICS) is dangerous, due to bronchoconstriction, reduced efficacy due to tolerance, and also that an inflammatory reaction may be induced [14–17]. This is discussed in more detail later in this article. The increasing understanding of the importance of inflammation in asthma ushered in the anti-inflammatory era

and the concept of ICS to prevent symptoms and attacks, with subsequent improvement in outcomes [18–20]. As-needed short-acting β_2-agonists (SABAs) have remained the mainstay of treatment to relieve symptoms and until recently SABAs have been recommended as the reliever of choice in all major guidelines. Although some guidelines, such as those from the National Institute for Health and Care Excellence (NICE) [21], recommend using SABA alone as required for patients with minimal symptoms, none recommend the use of regular SABA alone as maintenance treatment. In 2019, the Global Initiative for Asthma (GINA) not only abolished the SABA-only step in all patients, but also recommended a combination of ICS and formoterol (a fast-acting long-acting β_2-agonist) as the reliever of choice to be used "as needed" for adults and adolescents with mild asthma [22, 23]. There is high-quality evidence for this approach in young people aged $\geqslant$12 years [24], and evidence from two studies in younger children of the benefits of an anti-inflammatory reliever approach (using ICS whenever SABA is needed) compared to SABA only [18, 20]. Sadly, there is an evidence gap for the use of ICS–formoterol as-needed in younger children, which is currently being researched [25]. With this background evidence that regular use of SABAs is unsafe, and that these drugs do not treat the underlying inflammation driving an asthma attack, we propose that the use of these drugs regularly and in very high doses during the post-attack period is counterintuitive. SABAs remain an important and ubiquitous treatment for urgent management of asthma attacks. However, there is no evidence of benefit from the use of regular doses of SABA for children and young people in the immediate post-attack period: the so called "weaning plans".

The contention of this article is that the use of salbutamol weaning plans, which advise regular high-dose SABA in the aftermath of an asthma attack, when the acute presenting symptoms have been controlled, is both unnecessary and actually dangerous.

Asthma SABA weaning plans

Over the past 20 years, the concept of asthma weaning plans has crept into common practice [26] and has been included as part of educational modules, particularly in the UK [27]. In these plans, salbutamol is prescribed routinely at discharge, to be administered at set intervals and doses, usually starting with 10 puffs every 4 h on the first day after discharge, eight puffs every 4 h on the second day, six puffs every 6 h on the third day, and so on, with a return to the previous step if symptoms remain troublesome. Although standard plans last for 3 or 4 days, some stretch over 7 or 8 days, by which time over 200 puffs of salbutamol are advised to have been given.

Rationale for use

The precise origin of these plans is unclear. However, they appear to have arisen from the laudable aims of giving clear written advice to parents on discharge and reducing length of stay. Those who promote them state that these plans provide "pragmatic, 'real world' advice that help paediatric units cope safely with the high volume of wheezing children they have to deal with" [28]. Complete resolution of an asthma attack may require a number of days or weeks and, thus, the majority of post-exacerbation care is likely to occur at home. An argument for the use of a salbutamol weaning plan is possibly an assumption by clinicians that abrupt cessation of bronchodilators, which likely will have been given with timed consistency prior to discharge, may appear counterintuitive. It may also cause anxiety for families. Another assumption by clinicians in favour of weaning plans may be that continued use of high-dose reliever treatment may reduce re-attendance by children following discharge, but there is no evidence that this is the case. Those who advocate for their use argue that putting the responsibility onto parents to ascertain when to give potential life-saving treatment is an unfair ask and therefore continued use of SABA provides a safety net [28]. However, there is no evidence, either from randomised controlled trials or real-world observational studies, to draw upon to support this practice, and as discussed in this article, the whole concept is intellectually fundamentally flawed.

Concerns about weaning plans

There are three main arguments to counter the use of weaning plans: 1) key warning signs of a deterioration in asthma control may be masked; 2) the plan encourages the over-use and over-reliance on SABAs; and 3) the potential harms of SABA-only use and SABA over-use, leading to increased vulnerability at the time of an attack.

Key warning signs of a deterioration in asthma control may be masked

One of the key warning signs of deteriorating asthma is the perceived need for an increase in reliever (usually SABA) medication. Most personal asthma action plans include recommendations relating to increased SABA use in the build-up to an attack and thresholds for seeking help. Why should those same parameters not be used post-attack? Why is it reasonable to expect children and young people or parents to gauge their or their child's symptoms pre-attack with advice as to when to seek help (which is the basis of

all asthma plans), but in the post-attack phase, simply advise regular treatment? Since bronchodilators should be effective for at least 4 h, children and young people and parents should be clearly advised to seek urgent medical assistance if relief does not last at least that long. The advice to use the SABA regularly in the weaning regimen removes that warning signal.

Not only may regular SABA use falsely reassure and conceal the patients' awareness of symptoms, but also it may result in inappropriate over-use for a child without symptoms, disrupting sleep and return to school. Furthermore, whilst a salbutamol weaning plan is initiated post-attack, families may extrapolate this intervention to future exacerbations and delay presentation, choosing instead to give regular, large doses of SABA at home. Tragically, this practice has been implicated in UK coroners' reports as a contributing factor in asthma-related deaths [29].

Encouraging the over-use and over-reliance on SABAs

Most weaning plans start with 10 puffs of SABA every 4 h, *i.e.* 60 puffs of SABA per day in the first day. Salbutamol inhalers usually contain 200 doses; therefore, at this rate, a single inhaler would last fewer than 4 days. The NRAD in the UK reported that high SABA prescribing (⩾12 inhalers per year) was a frequent finding in asthma-related deaths [5]. Almost 30 years ago, Suissa and co-workers [14, 15] demonstrated increased mortality associated with SABA over-use, (and reduction in mortality associated with increasing ICS use [30]). Epidemiological studies have associated SABA over-use at the time of an asthma attack with increased risk of hospitalisation or mortality [31]. More recently, the SABINA (SABA use IN Asthma) study reported an increase in asthma-related morbidity (asthma attacks) and mortality with SABA over-use, defined as the prescription of ⩾3 SABA inhalers per year [32]. The association was strongest for those on the highest treatment levels (GINA step 4–5) but held true even for those with supposedly "mild" asthma (GINA steps 1 and 2).

Such studies demonstrate associations and cannot imply causality. High SABA use may be a marker of poor disease control or indicative of discordance between SABA and ICS use; however, more worryingly, there is already evidence that excessive SABA use may in itself be harmful, as described in the next section, and excess use such as in weaning plans should be discouraged.

Potential harms of SABA-only use and SABA over-use, leading to increased vulnerability at the time of an attack

High SABA use may result in tolerance to their bronchodilator effects, thus diminishing their efficacy, particularly when they are most needed at the time of an acute attack [33]. This is important to consider, given the deleterious nature of this cycle: the more SABA used, the less effective and, hence, the perception that even more needs to be used to relieve symptoms.

Various mechanisms that may lead to β_2-agonist receptor dysfunction have been described, but, currently, prevention of dysfunction and its consequences is not possible [34]. Unwanted adverse effects of inappropriate SABA use include lactic acidosis [35], downregulation of the β_2-adrenoreceptor, increased allergen response and pro-inflammatory effects [17, 36]. A randomised crossover trial in adults comparing regular to on-demand inhaled bronchodilators showed a clear deterioration in asthma control when bronchodilators were used regularly compared to on-demand, and there was evidence of increased adverse effects during regular use [37]. Furthermore, regular SABA use has been shown, in adults, to increase peak flow variability [38], and there is also evidence that regular SABA use increases airway eosinophilia [39]. This is particularly concerning in those not prescribed, or poorly adherent to, ICS.

There is also some evidence of the benefits of as-needed *versus* regular doses of SABAs during a hospital admission for an acute attack. Two randomised controlled trials have compared as-needed with regular SABA for adult inpatients hospitalised with an acute asthma attack [40, 41]. In the first study, participants were randomised to regular 4-hourly or as-needed nebulised salbutamol [40]. The as-needed group received less SABA and had reduced hospital stay and fewer side-effects. Those who had previously been admitted and received regular nebulised SABA reported that they preferred the as-needed regime. In the second study, patients were blinded to the treatment arm and received regular 4-hourly nebulisations of either salbutamol or normal saline, with additional salbutamol for breakthrough symptoms for both groups [41]. There were no differences in any of the clinical outcome measures between the groups; however, those in the as-needed group received significantly less salbutamol.

The global picture: climate change and the carbon footprint

There is a drive, both in the UK and European Union, to reduce the carbon footprint of asthma inhalers, primarily through the reduction of pressurised metered dose inhalers (pMDIs). Healthcare in England

alone is estimated to contribute up to 5% of the country's carbon footprint [42]. pMDIs are estimated to contribute 3.1% to that total [43] and a large majority of this is due to SABAs. The propellant employed in pMDIs contains hydrofluorocarbons (so called F-gases), which are influential greenhouse gases that persist within the environment for many years, acting as an air pollutant. Alternative propellants with very low global warming potential will be available within the next few years [44]. Alternatives, such as dry powder inhalers, are available; however, during the life cycle from manufacture to disposal, these contribute more to terrestrial and marine pollution than pMDIs [44]. Thus, reducing the use of large doses of SABA post-attack, and indeed preventing attacks in the first place, is arguably an effective way of reducing pMDI use and, hence, greenhouse emissions. Another possible solution would be to replace SABA reliever use after treating an acute attack with anti-inflammatory reliever therapy, with a two-in-one inhaler containing ICS together with either formoterol or SABA [25].

Furthermore, studies of as-needed anti-inflammatory reliever therapy [18, 20, 45, 46], consisting of ICS-containing reliever regimes, *versus* SABA for relief of symptoms show clearly that children and young people are able to take the responsibility to take the medication when their asthma flares up, and therefore provide supportive evidence for the use of this approach post-attack, which may reduce re-attendance. Further research may help to confirm this as an alternative method for post-attack management.

Conclusion

SABAs are an important component of the management of an acute attack; however, our concerns relate to the post-attack period when weaning plans are used. It is widely accepted that regular over-use of salbutamol is harmful, and the NRAD demonstrated that the period of greatest vulnerability to another asthma attack is in the 4 weeks immediately after an attack. Why then, at just this vulnerable time, would we want to over-use salbutamol, another known risk factor for asthma death? It is apparent that currently the evidence for optimal post-discharge asthma care for children is inadequate. The need for asthma education at discharge, a personal asthma action plan and vigilance about prescribing and ensuring adherence to maintenance therapy are definitely important [47]. Given that the use of weaning plans is based on a well-meaning but un-evidenced opinion, and in view of the weight of evidence countering this practice, we conclude that the benefit of prescribing regular salbutamol (up to 10 puffs every 4 h) at discharge after an acute asthma attack is a myth.

For those who still believe in weaning plans, we would offer these lines as written by Hilaire Belloc ("The Microbe"):

> But Scientists, who ought to know,
> Assure us that they must be so…
> Oh! let us never, never doubt
> What nobody is sure about!

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