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Stepping down from combination asthma therapy: The predictors of outcome

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ABSTRACT

Background: Stepping down from combination asthma therapy (inhaled corticosteroids (ICS) + long-acting β_2 agonists (LABA)) is often avoided due to fear of exacerbations, which may lead to over-medication in well-controlled asthma. A better knowledge about the predictors of outcome might encourage clinicians to start stepping down more often than previously.
Methods: In 55 subjects with well controlled asthma and combination therapy, LABAs were discontinued first, followed by ICS dose halving, and then cessation, in six weeks' intervals. The ability of Juniper's asthma control questionnaire (ACQ), ambulatory peak flow monitoring, spirometry, and hypertonic saline challenge to predict the outcomes of medication reductions were assessed.
Results: The proportions of subjects experiencing an exacerbation at each step were: 4 out of 55 subjects (7%) after LABA cessation, 4 out of 25 subjects (16%) after ICS dose halving, and 21 out of 46 subjects (46%) after ICS cessation. All exacerbations could be managed on an outpatient basis. There were 126 step-downs altogether. ACQ score < 0.29 (likelihood ratio 2.30 (1.05–5.05)), ACQ without spirometry < 0.15 (2.17 (0.96–4.90)) and FEV_1 > 96% of predicted (2.18 (1.03–4.61)) predicted a successful outcome after step-down. Cough responsiveness to saline, bronchoconstrictive responsiveness to saline, and peak flow variation were not associated with the outcome.
Conclusion: Combination therapy can often be reduced in controlled asthma but total cessation of ICSs must be carefully considered. Simple investigations, namely asthma control assessment by validated questionnaire and spirometry, help to predict the outcome of stepping down.
Trial registry: The study was registered in ClinicalTrials.gov database (https://clinicaltrials.gov, KUH5801124).

1. Introduction

According to current guidelines, subjects with controlled asthma should be considered for reduction (stepping down) of asthma medication to minimise side-effects and the costs of treatment [1]. In Finland, asthmatic subjects nowadays use more combined preparations (inhaled corticosteroid (ICS) plus long-acting β_2-agonist (LABA)) than preparations containing pure inhaled corticosteroids (ICS) [2]. As combination therapy is recommended only if ICSs offer insufficient asthma control [1], this finding indicates over-treatment of asthma. This has also been reported elsewhere [3]. Present literature suggests that the safest method for stepping down from combination therapy is reduction of ICS dose first, with subsequent LABA cessation [1,4–6]. However, prompted by reports about possible elevated mortality and an excess risk of asthma exacerbations with LABAs, the U.S. Food and Drug Administration (FDA) recommends cessation of LABAs first with subsequent ICS dose reduction [7]. Cessation of LABAs from combination therapy is reported to increase asthma symptoms and lead to a loss of asthma control [5,8]. Such fears may have hindered stepping down from combination therapy, possibly leading to over-treatment of asthma with LABAs [2,3]. A better knowledge about how to identify subjects who would tolerate medication reduction might encourage physicians to start reductions more often than previously. It has been widely acknowledged that more studies are needed to determine the predictors of outcome especially when LABAs are discontinued first from combination therapy [6,8,9].

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The main hypothesis of the present study was that cough responsiveness to hypertonic saline can predict the outcome during stepping-down from combination asthma therapy. The primary outcome variable was the occurrence of exacerbation after a medication reduction. Cough responsiveness to hypertonic aerosols is a novel asthma severity biomarker [10]. It is closely associated with asthma control and quality of life [11] and decreases during treatment with ICSs [12,13]. In the present study, cough responsiveness to saline was compared with more conventional asthma biomarkers in this setting.

2. Materials and methods

2.1. Subjects

The study was carried out in Kuopio University Hospital, Kuopio, Finland. The subjects were recruited between November 2013 and March 2015 utilising newspaper advertisements. The inclusion criteria included a doctor's diagnosis of asthma and right to special reimbursement for asthma medication expenses. This right, granted by the Finnish Social Insurance Institute, is obtained if at least one of the following conditions is fulfilled during the diagnostic process in a subject with asthmatic symptoms [14]: 1. At least 15% fall in forced expiratory volume in 1 s (FEV_1) after exercise challenge, 2. At least 12% improvement in FEV_1 or forced vital capacity (FVC) after inhaled bronchodilating drug in spirometry, 3. At least moderate degree of bronchial hyperresponsiveness to methacholine or histamine ($PD_{15} < 0.6$ or < 0.4 mg, respectively, Sovijärvi method [15]), 4. At least 20% spontaneous diurnal peak expiratory flow (PEF) variation in ambulatory peak flow monitoring on at least three days, 5. At least 15% improvement in PEF after inhaled bronchodilating drug in ambulatory PEF monitoring on at least three days.

The duration of asthma had to be at least two years and the duration of combination therapy with constant dosing at least six months. Asthma had to be stable: No courses of oral corticosteroids or hospital admissions due to asthma within one year and Juniper's Asthma Control Questionnaire score (first six questions, ACQ6) equal or less than 0.75 [16]. Exclusion criteria were presence of another chronic respiratory disease, presence of severe co-morbidity, history of smoking more than 10 pack-years, and pregnancy. Seventy subjects were screened. Of them, 14 subjects were not eligible for the following reasons: ACQ6 > 0.75 (six subjects), >10 pack-years smoking history (three subjects), irregular use of combination therapy (three subjects), and denied (two subjects). Fifty-six subjects were recruited and 55 had at least one medication step-down with full follow-up (Table 1). Altogether, there were 126 medication reductions with full follow-up.

The sample size calculations were aimed to investigate the ability of cough responsiveness to hypertonic saline to predict a successful medication reduction. We considered clinically relevant a two-fold probability for successful medication reduction among saline non-responders compared with saline responders. It was assumed that before reduction, 80% would be saline negative and 20% saline positive among controlled asthma patients, based on our previous study [10]. Furthermore, it was assumed that 30% of the saline negative patients would experience exacerbation. By this means it was calculated that 126 medication reductions would be required to provide 80% power at the 0.05 level.

This study was conducted in accordance with the amended Declaration of Helsinki. Research Ethic Committee, Hospital District of Northern Savo approved the protocol (118//2011), and written informed consent was obtained from all patients. The study was registered in ClinicalTrials.gov database (https://clinicaltrials.gov, KUH5801124).

Table 1
The baseline characteristics of the 55 subjects with at least one medication step-down with full follow-up.

Participants n	55
Age	58.8 ± 11.7
Female sex	37 (67%)
Body mass index	28.3 ± 4.95
Atopic subjects	34 (62%)
Chronic rhinitis	16 (29%)
Ex-smokers	17 (31%)
Current smokers	0 (0%)
Asthma duration, years	16.2 ± 9.2
Combination asthma therapy duration, years	8.49 ± 5.46
Inhaled corticosteroid daily dose, budesonide equivalent μg	604 ± 329
Subjects with leukotriene receptor antagonists	5 (9%)
Asthma control questionnaire score, 6 questions	0.25 ± 0.27
Asthma control questionnaire score, 7 questions	0.34 ± 0.33
Run-in period daily mean peak flow variation, percent	4.45 ± 2.35
FEV_1 percent of predicted[a]	97.4 ± 14.4
Coughs-to-dose ratio, coughs/Osm/kg	4.84 ± 7.34
Subjects with positive cough response to saline	13 (24%)
Response-to-dose ratio, % change in FEV_1/Osm/kg	1.24 ± 2.02
Subjects with positive bronchoconstrictive response to saline	1 (2%)

Data is expressed as means ± SDs or as percentages.
[a] The predicted values are from Ref. [20]. FEV_1 = forced expiratory volume in 1 s.

2.2. Protocol

The duration of the study was 20 weeks. During the run-in period the subjects used their previously prescribed combination therapy for two weeks (Fig. 1). During that time and the rest of the study the subjects filled in asthma diary and recorded their PEF three times every morning and evening. After that the LABA was discontinued (step one) and the subjects continued the use of their previously prescribed ICS with the same device and dose as previously for six weeks. There were various ICS preparations and the ICS doses are expressed as those clinically equipotent with budesonide [1]. After that the subjects with a daily ICS dose of more than 400 μg of budesonide were instructed to halve the ICS dose using the same device as before (step two) and it was continued for another six weeks. After that the ICS was discontinued (step three) and the subjects were followed up for another six weeks. The subjects with an initial ICS dose of 400 μg or less of budesonide proceeded directly from step one to step three. The study continued until the subject experienced asthma exacerbation or was successfully weaned off LABAs and ICSs for six weeks. After that the study ended. On the last visit the subjects were instructed to contact their general practitioners in case of later increase in asthma symptoms.

Before each visit, LABAs were discontinued for 12 h and short-acting β_2 agonists for 6 h. During each visit ACQ was filled in. Spirometry was performed according to international guidelines [17]. Bronchodilator test was not performed. Finally, hypertonic saline challenge was performed. The mean daily PEF variation was calculated for the 14 days preceding each visit. The physician responsible for the changes in medications was blinded from the PEF recordings, spirometry, and hypertonic saline test result. The medication adherence was monitored utilising the counters of the inhalation devices.

An exacerbation was defined by at least one of the following criteria:

1. Awakening at night due to asthma symptoms during two consecutive nights.
2. PEF less than 3 standard deviations from the mean value obtained during the run-in period on three consecutive days.
3. Bronchodilator use more than once a day on three consecutive days.