Salbutamol Easyhaler provides non-inferior relief of methacholine induced bronchoconstriction in comparison to Ventoline Evohaler with spacer: A randomized trial

Jussi Karjalainen, Ville Vartiainen, Antti Tikkakoski, L. Pekka Malmberg, Liisa Vuotari, Satu Lähelma, Ulla Sairanen, Mikko Vahteristo, Lauri Lehtimäki

ABCSTRACT

Background: Salbutamol is a cornerstone for relieving acute asthma symptoms, typically administered through a pressurized metered-dose inhaler (pMDI). Dry powder inhalers (DPIs) offer an alternative, but concerns exist whether DPIs provide an effective relief during an obstructive event.

Objective: We aimed to show non-inferiority of Salbutamol Easyhaler DPI compared to pMDI with spacer in treating methacholine-induced bronchoconstriction.

Methods: This was a randomized, parallel-group trial in subjects sent to methacholine challenge (MC) test for asthma diagnostics. Participants with at least 20 % decrease in forced expiratory volume in 1 s (FEV1) were randomized to receive Salbutamol Easyhaler (2 x 200 μg), Ventoline Evohaler with spacer (4 x 100 μg) or Budesonide-formoterol Easyhaler (2 x 160/4.5 μg) as a reliever. The treatment was repeated if FEV1 did not recover to at least –10 % of baseline.

Results: 180 participants (69 % females, mean age 46 yrs [range 18–80], FEV1/pred 89.5 [62-142] %) completed the trial. Salbutamol Easyhaler was non-inferior to pMDI with spacer in acute relief of bronchoconstriction showing a -0.083 (95 % LCL, -0.146) L FEV1 difference after the first dose and -0.032 (-0.071) L after the last dose. The differences in FEV1 between Budesonide-formoterol Easyhaler and Salbutamol pMDI with spacer were -0.163 (-0.225) L after the first and -0.092 (-0.131) L after the last dose.

Conclusion: The study confirms non-inferiority of Salbutamol Easyhaler to Ventoline Evohaler with spacer in relieving acute bronchoconstriction, making Easyhaler a sustainable and safe reliever for MC test and supports its use during asthma attacks.

1. Introduction

Inhalation is the preferred route of drug administration for patients with airway diseases such as asthma and chronic obstructive pulmonary disease. Short-acting β2-agonists, especially salbutamol, have long been a cornerstone in the treatment of acute asthma symptoms like shortness of breath. If the patient seeks medical attention due to exacerbation of asthma, the current standard practice is to administer salbutamol using either pMDI with a spacer or a nebulizer, to alleviate bronchoconstriction [1]. The challenge with pMDIs is the difficulty to coordinate inspiration with the release of the aerosol dose, and the speed and depth of the inhalation may not be optimal, which may reduce the effectiveness [2]. Spacers are used with pMDIs to avoid problems caused by poor coordination like high oropharyngeal drug deposition leading to throat irritation, dysphonia, and oral candidiasis [3]. Dry powder inhalers (DPIs) resolve the coordination problem since they are breath-actuated and they are easier to use than pMDIs [4]. They are small and easier to carry along than pMDIs with spacer. DPIs are also environmentally sustainable inhalers and e.g. Ventolin Evohaler pMDI has a carbon footprint approximately 40 times greater than Salbutamol Easyhaler DPI [5,6]. However, there is a persisting concern among clinicians that patients may not be able to use DPIs during an obstructive event, since a sufficient inspiratory flow is required [4,7]. Budesonide-formoterol combination is used as maintenance therapy in asthma. Moreover, its use as maintenance and reliever therapy (MART) has been shown to reduce the relative risk of severe
exacerbations of asthma [8–10]. There are studies showing that formoterol either alone or in combination with budesonide results in similar speed of relief as salbutamol [11–13].

Methacholine challenge (MC) test is commonly used in diagnosing asthma [14]. In this study, our objective was to show non-inferiority of Salbutamol Easyhaler DPI to Ventoline Evohaler pMDI with Volumatic spacer in treatment of methacholine induced bronchoconstriction among patients being investigated for asthma. We also wanted to provide further evidence on the applicability of Budesonide-formoterol Easyhaler as a reliever of bronchial obstruction.

2. Methods

2.1. Participants

Eligible participants comprised adults (18 years or older) indicated for MC test. In addition, participants had to demonstrate a FEV1 drop at least 20 % during the MC test compared to baseline spirometry. Participants were excluded if they fulfilled any of the exclusion criteria of the MC test; e.g. respiratory infection within 2 weeks, forced expiratory volume in 1 s (FEV1) < 60 % of predicted or < 1.0 L (in spirometry before the MC test), were pregnant or lactating, had used forbidden treatments before the study visit (short-acting β2-agonists within 12 h, long-acting β2-agonists within 36 h, ultra-long-acting β2-agonists within 48 h, long-acting anti-muscarinic agents within 168 h, short-acting anticholinergics within 12 h, oral theophylline within 24 h, and inhaled corticosteroids, leukotriene receptor antagonists, and chromones within 4 weeks), or had known hypersensitivity to the active substances or excipients of the study treatments. All participants provided written informed consent to take part in the study.

2.2. Study design

The study was an open, randomized, phase 4, parallel-group trial in two university hospital clinics in Finland (Tampere and Helsinki). After FEV1 drop at least 20 % in the MC test, eligible participants were randomly allocated (1:1:1) to receive one of the study treatments, Salbutamol Easyhaler, Ventoline Evohaler (the trade name in Finland) with Volumatic spacer or Budesonide-formoterol Easyhaler. The participants were randomized using a permuted block method. Randomization was performed by centre, i.e., randomized within each centre.

MC test was conducted according to the current technical standard [14]. Methacholine acts directly on specific airway muscle receptors and is taken via inhalation during a MC test under controlled medical setting. If inhalation of methacholine induces sufficient bronchoconstriction (FEV1 reduced at least 20 %) the test is considered positive and supports diagnosis of asthma [14]. Spirometry was performed and FEV1 value was recorded before the MC test, after inhalation of saline solution (retained as the baseline value), approximately 2 min after each methacholine dose and 10 min after the study treatment administration (Fig. 1). Cumulative doses of 18 μg, 72 μg, 270 μg, 810 μg and 2600 μg of methacholine were given with approximately 5 min intervals until the largest dose or a drop of at least 20 % in FEV1 was achieved. Spirometry was carried out according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines to assess lung function and provide standardized measurement of FEV1 [15].

Before the MC test participants were trained for the use of the treatment they would receive if randomization took place at the end of MC test. Participants in one group received two inhalations from Salbutamol Easyhaler 200 μg/dose device-metered DPI (total nominal dose of 400 μg and delivered dose of 360 μg). In the second group, two inhalations from Budesonide-formoterol Easihaler 160/4.5 μg inhalation were given (total delivered dose of 320/9 μg). The third group was given four doses of Ventoline Easihaler pMDI 100 μg/dose via Volumatic spacer (total nominal dose of 400 μg).

The study treatment was given 1—2 min after the FEV1 drop of at least 20 %. According to the standard test procedure, the participants not reaching FEV1 at least −10 % of baseline value after the first study treatment dose were given a second dose and spirometry was measured again after 10 min [14]. Safety of the study treatments was assessed by adverse events. Shortness of breath after FEV1 drop was not considered as an adverse event unless FEV1 remained below −10 % compared to baseline or there were still symptoms after second dose of the study treatment.

The participants were prompted to subjectively rate their shortness of breath after inhalation of saline solution (baseline), after at least a 20 % FEV1 drop, after the first dose of the study treatment and after the possible second dose of the study treatment before the spirometry. The measure used was the experience of shortness of breath on a scale ranging from 0 to 10, where a score of 0 indicates the absence of shortness of breath, and a score of 10 signifies shortness of breath at its maximum intensity [16].

Inspiratory flow profiles for Easyhaler inhalers were assessed both before MC test and during the administration of the first dose of study treatment, i.e. in the presence of bronchoconstriction. The flow measurements were recorded through the inhaler according to the method described previously [17]. Two inspiratory flow curves were recorded, and peak inspiratory flow (PIF) was analyzed.

All study procedures were performed at a single visit. The study was approved by Tampere University Hospital Ethics Committee (Committee reference: R21100 M; EuDrAC number: 2021-001573-22; Clinicaltrials.gov: NCT05084222) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study is reported using the CONSORT reporting guidelines [18].
2.3. Endpoints

The primary endpoint of the study was mean change in FEV₁ from the baseline to FEV₁ after the first dose of study treatment.

Secondary endpoints were relative recovery (percentage change) of FEV₁ after the study treatment dosing when compared to baseline, proportion of participants who recover to FEV₁ at least −10 % from the baseline, and shortness of breath scores at different time points. All outcomes were considered also after the last dose of study treatment, i.e. after the first dose or second dose in case second dose was needed. In addition, the proportion of participants for whom the PIF through the inhaler was at least 30 L/min before MC test and during induced bronchoconstriction were reported in Easyhaler groups.

2.4. Statistics

The study was designed to demonstrate non-inferiority of Salbutamol Easyhaler to Ventoline Evohaler with Volumatic spacer in treatment of induced bronchoconstriction.

Sample size calculation was based on non-inferiority margin of 0.170 L, one-sided alpha 0.05, power of 90 %, estimated difference in FEV₁ was 0 L, common standard deviation of the change from baseline 0.29 L, and drop-out rate from the study population was estimated to be 15 %. The non-inferiority margin used (0.170 L) is approximately two thirds of the reported clinically meaningful difference in FEV₁ [19,20].

Standard descriptive statistics were used to evaluate participants’ baseline characteristics. The primary endpoint was analyzed by calculating the difference in proportions of participants recovering between treatments and the respective confidence interval. Shortness of breath scores between the treatments were compared using analysis of variance.

Results are presented for per-protocol (PP) population. Analyses were also completed for full analysis set (FAS). Similar comparisons were carried out between Budesonide-formoterol Easyhaler and Ventoline Evohaler with spacer as additional analyses.

3. Results

Between November 2021 and June 2023, 601 participants were assessed for eligibility. Most of the participants attended at the Tampere study centre (87 %). Of all screened participants, 180 met the eligibility criteria and were randomized to the study (Fig. 2); 147 participants at Tampere and 33 at Helsinki centre. All 180 participants completed the study and were included in the FAS. Four participants were excluded from the PP analysis (Fig. 2).

The participant characteristics are presented in Table 1. Women constituted the majority in all groups (69 % of all participants). The mean age across the groups ranged from 44 to 47 years, 97 % of participants were white. The FEV₁ before the MC test demonstrated comparable means between the groups. The mean FEV₁ % of predicted was 89.5 % with a fairly large range (62–142). The methacholine dose to induce at least 20 % drop in FEV₁ was similar between the groups. The average cumulative methacholine dose needed was 1775 μg. The average FEV₁ % of predicted was 65 % (range 42–109) at the end of the MC test.

Table 2 shows the absolute and estimated FEV₁ values from the adjusted statistical model at different study steps during MC test. After the first dose of study treatment the participants in the Salbutamol Easyhaler group recovered to 0.110 L below the baseline and in the Ventoline Evohaler with spacer group to 0.020 L below the baseline. When the last dose of the study treatment was considered, the recovery in the Salbutamol Easyhaler group was up to 0.060 L below the baseline, and the Ventoline Evohaler with spacer group stayed at 0.020 L below the baseline (Table 2). Respectively, in Budesonide-formoterol Easyhaler group the participants recovered to 0.190 L below the baseline after the first dose and 0.120 L below the baseline when the last dose was considered. Fig. 3 illustrates the change in the FEV₁ values in each group compared to the baseline.

Expressed as a percentage change, the mean drop of FEV₁ after the last methacholine dose was similar in all groups varying from 26.8 % in the Salbutamol Easyhaler group to 26.1 % in the Budesonide-formoterol Easyhaler group. After the first dose participants in Salbutamol Easyhaler group recovered on average (SD) to −3.9 (6.6) % of the baseline whereas participants in Ventoline Evohaler with spacer recovered to −7.8 (6.6) % of the baseline. The respective relative recovery for
Budesonide-formoterol Easyhaler group was –8.2 (7.6) %. After the last dose, FEV₁, recovered to –4.2 (3.5) % in Salbutamol Easyhaler, –2.7 (5.6) % in Ventoline Evohaler with spacer, and to –5.2 (5.3) % in Budesonide-formoterol Easyhaler group.

Salbutamol Easyhaler was found to be non-inferior to Ventoline Evohaler with Volumatic spacer according to the pre-set criterion of –0.170 L (Fig. 4). The difference (lower 95 % confidence limit [CL]) between the treatments after first dose was –0.083 (–0.146) L. After the last dose, the difference between Salbutamol Easyhaler and Ventoline Evohaler with spacer was –0.032 (–0.071) L. The difference between Budesonide-formoterol Easyhaler and Ventoline Evohaler with spacer was –0.163 (–0.225) L after the first dose and –0.092 (–0.131) L after the last dose. The results of FAS population are in line with the presented results of PP population.

Following the first dose, 64.4 % of the participants in Salbutamol Easyhaler group and 86.2 % in Ventoline Evohaler with spacer group, had the FEV₁, reverted to at least –10 % of baseline (p-value 0.0048). When the last dose was considered, the proportion was 98.3 % in both groups (p-value 0.9903). The corresponding proportions were 62.7 % and 93.2 % in Budesonide-formoterol Easyhaler group, respectively.

There was a significant difference when Budesonide-formoterol Easyhaler was compared to Ventoline Evohaler after the first dose (p-value 0.0025) but not after the last dose (p-value 0.1731).

Evaluation of shortness of breath following at least 20 % drop in FEV₁ showed comparable scores between the groups (mean from 4.3 to 4.6) (Table 3). All post-dose assessments revealed a clear decrease in shortness of breath across all groups with the mean scores ranging from 1.8 to 2.0 after the first dose. Comparisons between Salbutamol Easyhaler or Budesonide-formoterol Easyhaler and Ventoline Evohaler with spacer demonstrated no statistically significant differences in shortness of breath after the first or the last dose.

All participants in both Easyhaler groups achieved PIF at least 30 L/min before methacholine test in at least one inhalation. During bronchoconstriction, 100 % (58/58) of participants in the Budesonide-
4. Discussion

We studied the efficacy of Salbutamol Easyhaler in comparison to the current standard practice, pMDI with spacer, in the treatment of methacholine induced bronchoconstriction. The results show that Salbutamol Easyhaler is non-inferior to Ventoline Evohaler with Volumatic spacer in the acute relief of bronchoconstriction.

These results are in line with existing literature on efficacy of Salbutamol Easyhaler. Hahtela et al. [21], Nieminen et al. [22], Vidgren et al. [23] and Randell et al. [24] concluded that the clinical effects of salbutamol via Easyhaler and pMDI are equivalent in adults. In children between 5 and 18 years of age who presented at an emergency or outpatient department due to acute asthma salbutamol administered via pMDI with Volumatic spacer or Easyhaler, as compared to administration by nebulization, provided effective relief of acute asthma exacerbation [25]. In another study in children aged 4-16 years bronchodilatory effects of 200 μg salbutamol through the Easyhaler and from a pMDI with spacer were equal [26].

After the first dose of study treatment, the FEV₁ recovered in all treatment groups on average clearly above the –10 % level compared to the baseline which is set as the safety limit for sufficient recovery in the chosen MC test. The proportion of participants with FEV₁ at least –10 % of baseline was higher in Ventoline Evohaler group compared to Easyhaler groups but there was no difference in the shortness of breath as rated by the study participants. This most likely indicates that remaining difference in FEV₁ compared to baseline was too small for the patients to perceive. In the literature, a clinically meaningful difference in FEV₁ has often been defined as 200 or 250 mL [19, 27-31], and e.g. Santanello and coworkers [32] determined that asthmatic patients can on average perceive a change in FEV₁ of 230 mL or larger. In real-life, patients do not measure FEV₁ and they treat the shortness of breath by titrating the reliever dose as per their need to alleviate symptoms. Based on shortness of breath scores, the subjective need for additional doses would have been the same with all study treatments. After the last dose FEV₁ reverted close to baseline in all groups.

Although the results show non-inferiority between the salbutamol treatments in clinical efficacy for relief of methacholine induced bronchoconstriction, Ventoline Evohaler with Volumatic spacer performed slightly better after the first dose. In the study by Randell et al. [24] salbutamol Easyhaler provided equivalent bronchodilation compared to Ventoline Evohaler without spacer in histamine induced bronchoconstriction. In the MC test setting Ventoline is administered with a spacer and each individual dose is separately sprayed into a spacer and then inhaled maximizing its efficacy. However, in real life when pMDI devices such as Ventoline are used to relieve acute bronchoconstriction, most patients use it without a spacer [33]. According to Mazhar et al. [34] and Silkstone et al. [35] the relative lung and systemic bioavailability of salbutamol from a pMDI is significantly greater when administered through a spacer than without one. Also, even after training and
coaching by specialized asthma nurse, approximately 30 % of the patients with asthma fail the inspiratory maneuver to correctly use a pMDI without a spacer [36]. In the study by Broeders et al. [37] the proportion of patients who could inhale via pMDI without a spacer correctly during asthma exacerbation was even lower (14 %) stressing the importance of using spacer with the pMDI. Thus, it is likely that the small difference between Salbutamol Easyhaler and Ventoline Evoorhaler with spacer observed in this controlled study vanishes in real-life settings. Previous studies comparing the effectiveness of different DPIs and pMDIs in alleviating bronchoconstriction have also indicated comparable results between inhalers [38].

The study population consisted of patients indicated for MC test as diagnostics for asthma. They had on average a moderate airflow obstruction after methacholine (FEV₁, 65 % of predicted) [39]. Patients hospitalized due to an acute asthma exacerbation may demonstrate more severe bronchoconstriction. For example, Arnold et al. [40] report a median FEV₁, 52 % of predicted. However, a DPI in comparison to pMDI with spacer has been shown to be equally effective in emergency treatment of severe dyspnoea (FEV₁ 39 % of predicted) indicating that inspiratory flow is not as much reduced as expiratory flow and remains adequate for the use of a DPI even with more severe obstruction [41]. It is also worth noting that this study aimed to answer the question if patients are able to use a salbutamol DPI instead of pMDI during an obstructive event rather than to evaluate dose potency of the studied products. That would have required at least two dose levels on the steep part of the salbutamol dose response curve [42,43].

Budesonide-formoterol relieved bronchoconstriction induced by methacholine to a lesser extent after the first dose but not after the last dose compared to salbutamol pMDI. The result can be compared to another study in which half of the doses of ours were given. Kearns et al. [44] compared bronchodilator response of salbutamol pMDI and budesonide-formoterol Turbuhaler DPI at 2 min after dosing in adults with stable asthma. They concluded that the non-inferiority of budesonide-formoterol compared to salbutamol via pMDI was not supported. Budesonide-formoterol is used as maintenance or as MART therapy. In MART use regular maintenance doses are taken whereas in the study by Kearns and coworkers [44], similarly to ours, β-adrenoceptor antagonists were withdrawn for an appropriate washout period. Therefore, in clinical use patients using budesonide-formoterol as a reliever, would have maintenance dose taken no more than 12 h earlier. Ankerst et al. [45] found formoterol and salbutamol to have an equal effect on bronchodilation with doses 9 μg of formoterol and 200 μg salbutamol indicating that those doses might be closer to equipotency than the doses chosen for this study (9 μg and 400 μg). This is also supported by the results of Beach and coworkers [46] who found the effect of formoterol and salbutamol identical when formoterol dose was twice compared to the dose in our study (24 μg metered dose), but salbutamol dose was the same (400 μg).

The study provides also, for the first time, evidence of patients’ ability to achieve sufficient PIF via Easyhaler during bronchoconstriction. Patients who achieve PIF of 30 L/min or higher obtain consistent doses from Easyhaler [47–49]. Pooled data from earlier studies in patients with asthma and COPD have shown that close to all patients achieved PIF of 30 L/min through the inhaler [17,50]. In this study there were only a few participants with PIF below 30 L/min during study treatment inhalation, and therefore, ability to generate a sufficient inspiratory flow is not limiting use of Easyhaler DPI even during airway obstruction supporting the applicability of Easyhaler during an asthma attack or exacerbation.

5. Conclusions

The study confirms the non-inferiority of Salbutamol Easyhaler to Ventoline Evoorhaler with Volumatic spacer in relief of acute obstructive event. Thus, Easyhaler DPI is an environmentally sustainable choice for administration of a reliever medication in MC test and the result supports its use during an asthma attack or exacerbation.

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CRediT authorship contribution statement

Jussi Karjalainen: Writing – review & editing, Resources, Methodology, Conceptualization. Ville Vartiainen: Resources, Methodology, Conceptualization. Antti Tikkakoski: Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. L. Pekka Malmberg: Writing – review & editing, Resources, Investigation. Liisa Vuotari: Writing – review & editing, Resources, Investigation, Conceptualization. Satu Lähtelma: Writing – review & editing, Visualization, Supervision, Resources, Methodology, Conceptualization. Ulla Sairanen: Writing – review & editing, Visualization, Resources, Methodology, Conceptualization. Lauri Lehtimäki: Writing – review & editing, Visualization, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. JK reports payment or honoraria for lectures, presentations or educational events from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Novartis and Orion Pharma and participation on an Advisory Board from GlaxoSmithKline and MSD. VV reports being former employee of Orion Pharma and having received personal consultation and lecture fees from Orion Pharma and having been in sustainability advisory board of Orion Pharma. AT reports payments for lectures or presentations from Chiesi and GlaxoSmithKline and participation on an Advisory Board from Chiesi. LPM reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Chiesi and Orion Pharma. LV reports research grant from Tuberculosis foundation of Tampere. LL reports personal fees for lecturers and/or advisory board meetings from ALK, Astra Zeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, GSK, Menarini, Orion Pharma and Sanofi. SL, US and MV are employees of Orion Pharma.

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Appendix A. Supplementary data

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References

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Jussi Karjalainen\textsuperscript{a}, Ville Vartiainen\textsuperscript{b}, Antti Tikkakoski\textsuperscript{c}, L. Pekka Malmberg\textsuperscript{d}, Liisa Vuotari\textsuperscript{e}, Satu Lähelma\textsuperscript{f,}\*, Ulla Sairanen\textsuperscript{f}, Mikko Vahteristo\textsuperscript{f}, Lauri Lehtimaki\textsuperscript{a}

\textsuperscript{a} Allergy Centre, Tampere University Hospital, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
\textsuperscript{b} Heart and Lung Center, Helsinki University Hospital, Finland and Faculty of Medicine, University of Helsinki, Finland
\textsuperscript{c} Clinical Physiology and Nuclear Medicine, Tampere University Hospital, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
\textsuperscript{d} Skin and Allergy Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
\textsuperscript{e} Clinical Physiology and Nuclear Medicine, Tampere University Hospital, Faculty of Medicine and Life Sciences, University of Tampere, Finland
\textsuperscript{f} Orion Corporation, Espoo, Finland

The authors would like to add a graphical abstract to the publication, please find below.

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* Corresponding author. Allergy Centre, Tampere University Hospital, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.
E-mail address: satu.lahelma@orionpharma.com (S. Lähelma).

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