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Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: a SOMA study

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ABSTRACT: Patients with mild intermittent asthma sometimes show signs of inflammation, and guidelines suggesting bronchodilator therapy alone as needed may be questioned.

The current study compared as-needed use of a rapid-acting β_2-agonist with as-needed use of a β_2-agonist and corticosteroid combination as the only medication in asthma patients with intermittent symptoms. A total of 92 nonsmoking asthma patients (of 187 screened) using only an inhaled β_2-agonist as needed (28 males, 64 females; mean age 37 yrs; mean forced expiratory volume in one second (FEV_1) 101% predicted, mean reversibility 6.5% pred and fractional exhaled nitric oxide (F_{ENO}) $\geqslant$20 parts per billion (ppb)) were randomised to treatment with formoterol (Oxis® Turbuhaler®) 4.5 μg as needed (n=47) or budesonide/formoterol (Symbicort® Turbuhaler®) 160/4.5 μg as needed (n=45) in a double-blind, parallel-group 24-week study.

The primary variable of efficacy was change in F_{ENO}. Baseline F_{ENO} was 60 ppb and 59 ppb in the budesonide/formoterol and formoterol groups, respectively. Mean reductions in F_{ENO} in the budesonide/formoterol and formoterol groups were 18.2 ppb and 2.8 ppb, respectively (95% confidence interval (CI) 7.5–23.5 ppb). The reduction in the budesonide/formoterol group occurred during the first 4 weeks of treatment and remained at this low level. Mean FEV_1 increased by 1.8% pred normal value in the budesonide/formoterol group and decreased by 0.9% pred normal value in the formoterol group (95% CI -4.7– -0.7). In the budesonide/formoterol group, use of $\geqslant$4 inhalations·day^{-1} of study medication was seen on 21 treatment days compared with 74 in the formoterol group.

In conclusion, as-needed use of an inhaled corticosteroid together with a rapid-acting bronchodilator may be more beneficial than a β_2-agonist alone in patients with intermittent asthma and signs of airway inflammation. The long-term benefits are unknown.

KEYWORDS: Asthma guidelines, budesonide, exhaled nitric oxide, formoterol, mild intermittent asthma, Turbuhaler®

Finnish and Swedish [1, 2], as well as international [3], asthma guidelines recommend that patients with mild persistent asthma (step 2 in the guidelines) should use an inhaled corticosteroid as first-line maintenance treatment. However, patients with mild intermittent asthma (step 1) are advised to use a rapid-acting β_2-agonist bronchodilator as needed, without the use of controller medication [3].

Patients with early, newly detected asthma already have elevated numbers of inflammatory cells, including eosinophils, in their airways [4]. In addition, eosinophilic bronchial inflammation can be found in subjects not fulfilling the functional diagnostic criteria for asthma [5, 6]. This condition has been called an asthma-like inflammation or pre-asthma [7]. In a 2-yr prospective Finnish study of children aged 7–12 yrs with asthmatic symptoms but with normal or nearly normal lung function (pre-asthma), one-third developed clinical asthma during the follow-up period, one-third became free of symptoms and one-third remained unchanged [8]. In patients with pre-asthma, regular maintenance treatment with an inhaled corticosteroid

SOMA: Symbicort or Oxis Monotherapy in Asthma.

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has been found to be highly beneficial compared with placebo [9].

About 60% of the asthmatic population in Finland has mild disease [1]. A proportion of these patients have mild persistent asthma and they clearly benefit more from maintenance therapy with an inhaled corticosteroid than from regular therapy with a β_2-agonist [10]. However, the majority of the patients with mild asthma have intermittent symptoms. It has never been tested whether anti-inflammatory medication would benefit these patients more than the recommended treatment of a rapid-acting β_2-agonist alone used as needed. In patients with persistent asthma (step 2–3), a temporary increase in the dose of inhaled corticosteroids in situations with increased symptoms is known to be beneficial and can prevent exacerbations [11]. Likewise, in patients with moderate-to-severe asthma (step 3), the use of a corticosteroid/β_2-agonist (budesonide/formoterol) combination as needed in addition to regular budesonide/formoterol maintenance treatment has been shown to improve airway function and to reduce the risk of severe exacerbations compared with higher maintenance doses of inhaled corticosteroids together with a short-acting β_2-agonist as rescue medication [12, 13].

The current authors studied the treatment of patients with intermittent asthma and an increased level of nitric oxide (NO) in exhaled air by comparing as-needed use of the rapid-acting β_2-agonist formoterol with that of a budesonide/formoterol combination. A marker of airway inflammation, NO in exhaled air, was chosen as the primary variable of efficacy. Fractional exhaled NO ($F_{E}NO$) has been shown to be elevated in patients with asthma although it is not specific for asthma [14–16]. $F_{E}NO$ is a sensitive marker of the efficacy of anti-inflammatory treatment [17] and the measurements have been well standardised [18] and are reproducible [19].

Study design

The study was double-blind and randomised and had a parallel-group design. Separate randomisation at each study centre was performed in balanced blocks using a computer programme.

Patients selected for the study fulfilled the Global Initiative for Asthma (GINA) guidelines on functional criteria for mild intermittent asthma [3] and had a documented need of short-acting inhaled β_2-agonists for relief of asthma symptoms. The need for reliever medication during the preceding months was a maximum of 2 doses·week^{-1}, which was within the limits stated in GINA guidelines at the time of planning the study. The actual need was specified as use of terbutaline (Bricanyl® Turbuhaler®; AstraZeneca Pharmaceuticals, Södertälje, Sweden) 0.5 mg prophylactically or for relief of asthma symptoms on 1– (maximally) 5 days during the last 10 days of the run-in period to ensure that patients, when randomised, had some symptoms to be treated. Patients who used regular maintenance treatment for asthma were not randomised, and nor were patients who had used corticosteroids of any type periodically or regularly during the 3-month period prior to randomisation.

To qualify for the study, patients had to have an increase in forced expiratory volume in one second (FEV_1) $\geqslant$12%, or in peak expiratory flow (PEF) $\geqslant$15% (at any time of the day), after inhalation of salbutamol 0.4–0.8 mg; or terbutaline 0.5–1.0 mg; or a variability in PEF $\geqslant$15% on at least 2 days during a 2-week period; or a documented fall in FEV_1 $\geqslant$12% after an exercise test. Patients could fulfil more than one criterion and were included as soon as the first criterion was fulfilled. Furthermore, qualifying patients had to have a pre-bronchodilator FEV_1 of $\geqslant$80% pred and an $F_{E}NO$ $\geqslant$20 parts per billion (ppb), as most healthy subjects show concentrations below that level [20]. $F_{E}NO$ $\geqslant$20 ppb could be achieved either at enrolment (visit 1) or at randomisation (visit 2).

Patients were randomised to as-needed treatment with either budesonide/formoterol 160/4.5 μg (delivered doses) delivered *via* the inspiratory flow-driven dry-powder inhaler Turbuhaler® (Symbicort® Turbuhaler®; AstraZeneca Pharmaceuticals), or with formoterol 4.5 μg *via* Turbuhaler® (Oxis® Turbuhaler®; AstraZeneca Pharmaceuticals).

Patients were encouraged not to withhold as-needed medication but to use study medication as soon as they felt a need. Prophylactic use before exercise, for instance, was also allowed in the same way that patients had used their short-acting β_2-agonist before the study. Patients were not allowed to use more than 12 inhalations of study drug during a single day. Patients who required the maximal number of inhalations were treated with a course of oral prednisolone. If more asthma medication was needed, the patient was removed from the study.

There were five clinic visits: enrolment (visit 1), randomisation (visit 2) and after 4, 12 and 24 weeks of randomised treatment. The run-in period was 14 ± 2 days.

Written informed consent was obtained from each patient and the study protocol was approved by the health authorities in Finland and Sweden and the ethics committee at each study centre.

METHODS

At enrolment, pulse and blood pressure were recorded. Thereafter, $F_{E}NO$ measurement and spirometry were performed.

During the run-in and study periods, patients kept a diary card and recorded morning and evening PEF values (best of three measurements), asthma symptoms and use of study medication. At clinic visits, asthma-related and nonasthma-related serious adverse events (SAE) were recorded. Discontinuations of study treatment due to adverse events were noted.

PEF measurements were performed using a Mini Wright peak flow meter (Clement Clark, Harlow, UK).

Asthma symptoms were assessed every evening for the previous 24-h period using a scale from 0 to 10, where 0 was no symptoms and 10 denoted severe symptoms with inability to sleep or work.

The number of as-needed inhalations of the study drug was recorded in the diary every evening covering the previous 24-h period.

$F_{E}NO$ measurement and spirometry were again performed at visit 2 (randomisation visit) and at visits 3 to 5.

Measurement of exhaled nitric oxide

$F_{E}NO$ was measured using a chemiluminescence analyser connected to a computerised system (Niox; Aerocrine AB,

Stockholm, Sweden). The analyser was calibrated with a two-point calibration procedure using purified NO-free air and certified NO calibration mixture, according to the manufacturer's instructions. The online single exhalation technique, recommended by the American Thoracic Society (ATS) [18], was applied. Patients were seated, without a nose-clip, and asked to fill their lungs completely and to exhale slowly with a mean and instantaneous flow of 45–55 $mL \cdot s^{-1}$, for at least 10 s. The equipment includes a dynamic resistor, enabling stable flow and, in order to close the velum, a positive mouth pressure of 10–20 cmH_2O during exhalation. F_{eNO} was measured from the plateau phase of the F_{eNO} curve, where the plateau was considered acceptable if it lasted for $\geqslant 3$ s and if the regression analysis did not show deviation >10%. Exhalations that did not meet the ATS requirements were rejected, and the patient was asked to perform another exhalation. Measurements were repeated until three exhalations with specified mean, instantaneous flows, acceptable plateaus and F_{eNO} values within a 10% range were obtained. The mean value of these measurements was recorded. The equipment and procedures for the measurement of F_{eNO} in all participating centres were identical.

Spirometry

FEV_1 was recorded using a flow–volume spirometer, according to the recommendations of the European Respiratory Society [21]. Measurements were made with the subjects seated in an upright position, wearing a nose-clip. The highest FEV_1 of at least three reproducible forced vital capacity measurements was recorded. The spirometer was calibrated according to the manufacturer's specifications, and for each subject the same spirometer was used throughout the study. At each visit, spirometry was scheduled at the same time of the day (± 1 h) and after the measurement of F_{eNO}. Spirometric data were given at body temperature, pressure and saturated, and European reference values for spirometric tests in adults, adjusted by height, age and sex, were applied [22]. For bronchodilation tests, subjects inhaled a β_2-agonist (terbutaline sulphate 1.0 mg) and a new measurement was performed after 15 min.

Before the lung function tests, patients were not allowed to use rapid-acting β_2-agonist or the study drug for $\geqslant 8$ h.

Statistical analyses

The study was designed to show differences between the budesonide/formoterol and formoterol treatment arms. The statistical null hypothesis was that the treatments were similar. A 5% significance level, a two-sided alternative hypothesis, and a power of 90% were used in calculating the sample size.

The primary variable of efficacy, the mean change in F_{eNO} from the start of the study (mean F_{eNO} at visits 1 and 2) to treatment (mean F_{eNO} at visits 3–5), was used for calculating the sample size. A change in F_{eNO} of 1.5 ppb was set as the minimum treatment difference of interest in the study. Based on results of previous studies, the number of patients to be evaluated was to be 79 patients completing the intervention.

F_{eNO} measurements were analysed using an analysis of covariance. The change from visits 1 and 2 (mean of the two) to visits 3–5 was analysed using an analysis of variance including a method of multiple comparison of mean values of main effects. The secondary variables (asthma symptom scores, asthma-free days, morning and evening PEF measurements, number of inhalations of study drug and FEV_1) were analysed using an analysis of covariance including a method of multiple-comparison of mean values of the main effects.

All tests were two-sided and $p \leqslant 0.05$ was considered statistically significant. Whenever possible, 95% confidence intervals (CI) were calculated.

RESULTS

Patient demography

A total of 187 nonsmoking outpatients with a history of intermittent asthma were screened for F_{eNO} (fig. 1). Of these, 141 patients entered the run-in phase and 93, all Caucasian, were randomised for treatment. One patient never received randomised medication. Of the 92 patients in the study, 28 were males and 64 females. The mean (range) age of the included patients was 37 yrs (15–63) and they had experienced periodic asthma symptoms for a mean of 10 yrs. A standard bronchial challenge test using either histamine [22] or methacholine [23] was performed to characterise patients. Increased bronchial responsiveness (provocative dose (PD)15 of histamine causing a 15% fall in FEV_1 <1,600 μg; PD_{20} methacholine <2,600 μg) was present in 38 patients (87%) in the budesonide/formoterol group and in 38 patients (83%) in the formoterol group. Additional baseline demographic data are shown in table 1.

Fractional exhaled nitric oxide

Individual F_{eNO} values at baseline and during treatment in the two study groups are shown in figure 2. In the budesonide/formoterol group, the mean F_{eNO} at baseline was 59.8 ppb, which decreased to 39.4 ppb during treatment. The corresponding mean values in the formoterol group were 58.7 ppb and 54.4 ppb. The mean reductions in the two groups were 18.3 ppb and 2.8 ppb, respectively, with a significant difference of 15.5 ppb between the treatments ($p<0.001$; 95% CI 7.5–23.5).

Mean F_{eNO} levels during the study period are shown in figure 3. The reduction in $F_{e,NO}$ was rapid in the budesonide/formoterol group and occurred during the first 4 weeks of

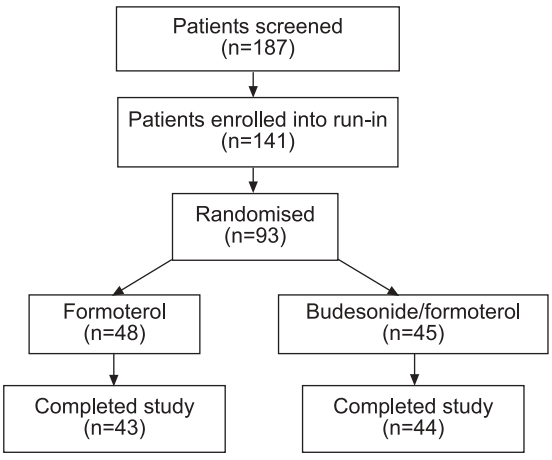

FIGURE 1. Patient disposition in the study.

TABLE 1 Baseline characteristics of patients randomised to as-needed treatment with budesonide/formoterol or formoterol

Variable	Budesonide/formoterol	Formoterol
Patients n	45	47
Female patients n	30	34
Age (range) yrs	34.8±10.9 (18–63)	36.5±12.1 (15–63)
Nonsmokers	35	42
Ex-smokers	10	5
Pack-yrs	1.2±2.6	0.6±2.0
FEV_1 % pred pre-bronchodilator	102.4±10.6	99.5±11.0
FEV_1 % pred post-bronchodilator	108.9±11.1	106.0±10.9
F_{ENO} ppb	59.8±40.0	58.7±41.5
Median (range) F_{ENO} ppb	48.4 (16–196)	39.0 (19–192)
Days without rescue medication during run-in %	65	70
Inhalations·day^{-1} of rescue medication during run-in	0.55±0.35	0.46±0.31
Patients with positive skin-prick test	33 (73)	30 (64)
Patients using anti-allergy drugs for rhinitis or other allergies	32 (71)	27 (57)
Patients with increased bronchial responsiveness to histamine or methacholine	38 (87)	38 (83)

Data are presented as mean±SD and n (%), unless otherwise stated. FEV_1: forced expiratory volume in one second; % pred: per cent predicted; F_{ENO}: fractional exhaled nitric oxide; ppb: parts per billion.

treatment. Thereafter a further modest reduction was observed. In the formoterol group, a small initial reduction was recorded followed by a modest increase over time. In the budesonide/formoterol group, an increase in F_{ENO} during the study occurred in only two patients (4%) and these patients each used <0.3 inhalations·day^{-1} of study medication. All patients using >0.3 inhalations·day^{-1} of budesonide/formoterol showed a decrease in F_{ENO}, and there was no difference between groups using 2.1–6.3, 7.0–11.2 or ⩾11.9 inhalations·week^{-1}. In the formoterol group, a total of 15 patients (34%) showed an increase in F_{ENO} over the study period.

Changes in F_{ENO} were analysed for the influence of covariates, *i.e.* country (Finland, Sweden), presence of allergy, bronchial hyperresponsiveness and sex. None of the covariates influenced the results.

Forced expiratory volume in one second

The mean FEV_1 at baseline in the budesonide/formoterol group was 3.54 L. This increased to 3.59 L following treatment (mean increase 0.07 L). The corresponding mean values in the formoterol group were 3.29 L and 3.25 L (mean decrease 0.03 L). The difference between groups' change in FEV_1 was 0.098 L and reached statistical significance (p=0.0059; 95% CI -0.17– -0.03).

In the budesonide/formoterol group, the mean FEV_1 increased from 102.4% pred normal to 104.2% (difference 1.8%). The corresponding mean values in the formoterol group were 99.5% pred normal and 99.2% (decrease of 0.9%). The difference between treatments in the change in FEV_1 expressed as % pred normal was -2.7, and this again reached statistical significance (p=0.0087; 95% CI -4.7– -0.7).

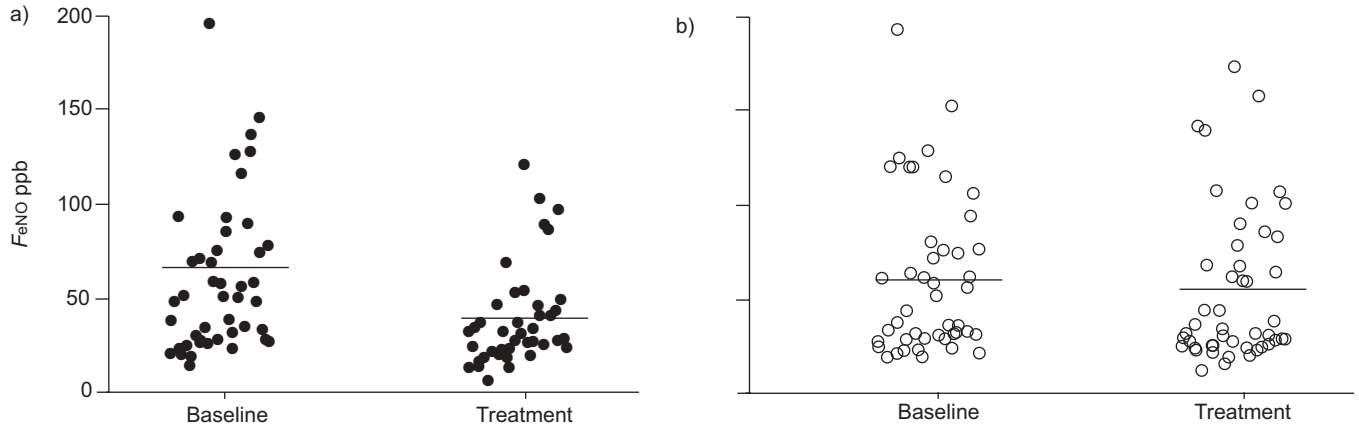

FIGURE 2. Individual fractional exhaled nitric oxide (F_{ENO}) values in a) the budesonide/formoterol (●) and b) the formoterol (○) groups at baseline (visits 1 and 2) and during treatment (visits 3–5).

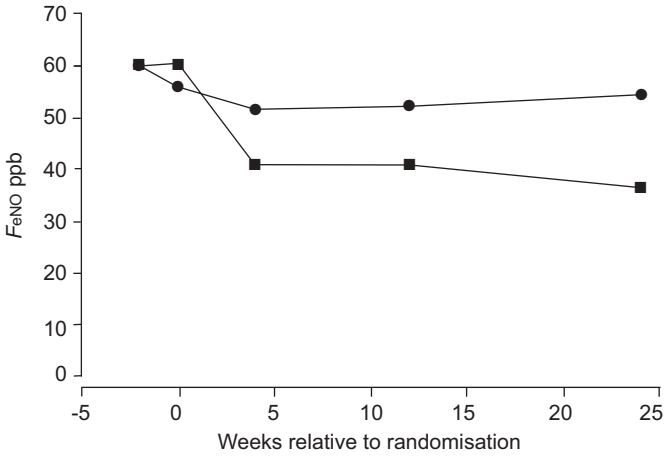

FIGURE 3. Mean fractional exhaled nitric oxide (F_{eNO}) over time in the budesonide/formoterol (■) and formoterol (●) groups.

Number of inhalations of study medication

In the budesonide/formoterol group, patients used a mean of 3.9 inhalations·week^{-1} of study medication (terbutaline Turbuhaler®) during the run-in period. This increased in use during the study to 5.7 inhalations·week^{-1}. The proportion of rescue-free days was 52%. In the formoterol group, patients used 3.2 inhalations·week^{-1} of terbutaline during run-in and 5.9 inhalations·week^{-1} of formoterol during the treatment phase. The proportion of rescue-free days was 56%. The number of inhalations of study medication·day^{-1} did not differ significantly between the groups (p=0.41; 95% CI -0.14–0.33).

The total number of days during the study when patients had used more than 4 inhalations·day^{-1} is shown in figure 4. A total of 21 such days were reported in the budesonide/formoterol group compared with 74 days in the formoterol group.

Patient-recorded outcomes

Asthma symptom scores, asthma-free days and morning and evening PEF values are listed in table 2. There were no significant differences between the treatment groups in any of these outcome variables.

Safety

A total of eight patients discontinued the study during the run-in period. After randomisation, six patients discontinued for various reasons, none owing to an adverse event. No treatment failures occurred.

Three SAEs were reported in the budesonide/formoterol group. One patient had a severe attack of migraine and one patient suffered a traffic accident (tibial fracture). A third patient became pregnant after 12 weeks in the study. Mola hydatidosa was diagnosed at abortion. No SAEs were reported in the formoterol group.

DISCUSSION

This is the first study to evaluate the efficacy of adding an inhaled corticosteroid to a rapid-acting (and in this case also long-acting) β_2-agonist for as-needed treatment of patients with intermittent asthma who do not use any regular medication. The addition of budesonide to as-needed treatment with formoterol resulted in a significantly reduced level of airway inflammation, measured by F_{eNO}, and also in a small improvement in lung function compared with formoterol alone.

The patients fulfilled clinical and lung functional criteria for mild intermittent disease. The majority reported a history of allergy and exhibited increased bronchial responsiveness to histamine or methacholine. The patients had a history of use of rapid-acting β_2-agonists not more than twice a week during the preceding month, which was consistent with the GINA guidelines at that time [3]. In the 2005 updated version, if medication is required more than once a week over a 3-month period, the patient should be considered to have mild persistant asthma [3]. However, for the current study, patients were advised to use as-needed medication as soon as they experienced the slightest symptom of asthma. Prophylactic use was accepted in the same situations as before the study. Consequently, as-needed use of terbutaline on a maximum of 5 out of 10 days during the run-in period was considered acceptable for the study without jeopardising the diagnosis

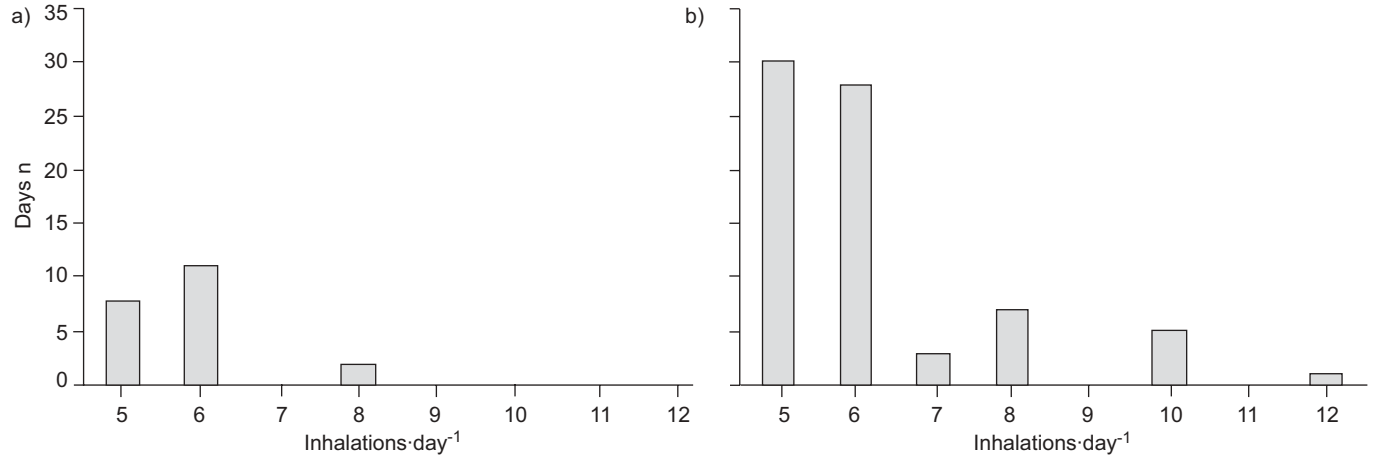

FIGURE 4. Distribution of number of days with >4 inhalations of study medication during the study. a) Budesonide/formoterol group; b) formoterol group.

TABLE 2 Patient-reported asthma symptom scores (scale 0–10), asthma-free days (asthma score 0 and no use of study medication), and morning and evening peak expiratory flow (PEF) values

	Budesonide/formoterol		Formoterol		Difference#	p-value
	Baseline	Treatment	Baseline	Treatment		
Asthma symptom score	1.53 (1.31)	1.29 (1.10)	1.67 (1.54)	1.36 (1.23)	-0.04	0.787
Asthma-free days %	45.2 (47.1)	42.9 (41.5)	44.3 (46.7)	43.6 (50.0)	-1.53	0.738
Morning PEF L·min^{-1}	470	482	454	462	4.7	0.38
Evening PEF L·min^{-1}	492	500	470	478	-0.4	0.94

Data are presented as mean (median), unless otherwise stated. #: least significant mean.

of mild intermittent asthma. However, the current authors cannot exclude the possibility that some patients had mild persistent asthma and should have been candidates for maintenance therapy with budesonide.

Patients with mild intermittent asthma are asymptomatic for various periods of time and should have a normal airway function (FEV1 and PEF $\geqslant$80% pred normal values). When symptomatic, they exhibit signs of airway inflammation but mostly only a mild degree of airway narrowing [4, 9]. It is known that regular treatment with corticosteroids lowers elevated *F*eNO towards normal levels quite rapidly [24, 25], and a dose-response relationship has been documented [26, 27]. Withdrawal of corticosteroid therapy results in a significant increase in *F*eNO [28]. It is also known that even regular treatment with β_2-agonists does not affect *F*eNO [29]. In the current study, a rapid decrease in *F*eNO occurred between beginning medication and the next visit (4 weeks) in the budesonide/formoterol group but not in the formoterol group. The difference between treatments in the change in *F*eNO (15.5 ppb) was quite large, and the decrease in *F*eNO in the >budesonide/formoterol group ran in parallel with an improvement in FEV1, which makes the results clinically more interesting. As the patients had intermittent asthma, as-needed therapy was not expected to result in changes in baseline airway function or in asthma symptom scores. The current authors recorded these variables but did not use questionnaires to measure health-related quality of life.

Absolute *F*eNO values do not necessarily define the actual severity of asthma. In adult patients with mild asthma not using inhaled corticosteroids, a mean *F*eNO of 49 ppb has been reported [19]. In a 4-week study in patients with mild persistent asthma, regular treatment with budesonide Turbuhaler® 100 μg·day^{-1} resulted in a decrease in exhaled NO from 29 to 21 ppb and with 400 μg·day^{-1} from 32 to 16 ppb, while placebo left levels unchanged [30]. Consequently, the reduction in *F*eNO with as-needed budesonide/formoterol in the present study (-18.2 ppb) appears to be in the range obtained with regular use of inhaled corticosteroids. However, *F*eNO after 24 weeks' treatment was still above the reference range.

The study was powered based on change in *F*eNO and not on the occurrence of asthma symptoms. As patients with mild intermittent asthma have normal airway function and only temporary symptoms, it was not a surprise that both treatments, which contain the same dose of formoterol, decreased asthma symptoms. The frequency of asthma-free days was also similar in the two groups, but treatment differences were apparent with regard to the number of days with higher levels of as-needed use. Compared with the formoterol group, significantly fewer patients in the budesonide/formoterol group needed >4 inhalations of as-needed medication on any day. Likewise, the number of days on which any patient needed more than four inhalations was lower in the budesonide/formoterol group than in the formoterol group. The reduced frequency of as-needed use may indicate that patients using intermittent corticosteroids had fewer or shorter periods of uncontrolled asthma.

On >50% of the study days, patients did not take as-needed medication. There was a modest increase in the mean number of daily as-needed doses in both treatment groups: from 3.9 to 5.7 inhalations·week^{-1} in the budesonide/formoterol group and from 3.2 to 5.9 inhalations·week^{-1} in the formoterol group. These increases may reflect an overall study effect. Patients were advised to use as-needed medication as soon as they had some minimal symptoms, and this instruction may have modified behaviour.

A limitation of the study is that no reference group with regular budesonide treatment was included. Therefore, it is not known what would have happened in such a group compared with the as-needed use of budesonide. However, the first aim of the current study was to discover whether the addition of budesonide on an as-needed basis had any effect compared with the β_2-agonist alone in patients with intermittent asthma. As this has now been demonstrated, the comparison with maintenance budesonide therapy has to be investigated in future studies. However, it cannot be excluded that regular budesonide therapy had resulted in lower levels of *F*eNO but the effect on symptoms, airway function and use of reliever medication is more difficult to postulate. In this study, a limited use of budesonide/formoterol resulted in marked reduction in *F*eNO. Only two patients, using budesonide/formoterol intermittently (<2 doses·week^{-1}) did not achieve a reduction in *F*eNO. No difference in *F*eNO reduction was seen between patients using 2–>11.9 inhalations·week^{-1}.

Patients with intermittent asthma rarely accept medication prescribed for regular use. Even patients with mild persistent asthma seldom adhere to regular prophylactic medication. If prescribed an inhaled corticosteroid for maintenance

treatment, many patients tend to discontinue that treatment within weeks or months if they become symptom free [30].

Regular maintenance therapy may not always be required in adult patients with mild asthma [31]. A study in Finnish children with mild persistent asthma showed that periodic treatment with budesonide was almost as effective as regular maintenance treatment when the children with newly detected asthma had initially received regular treatment with budesonide for 6 months [32]. Further studies using intermittent treatment with inhaled corticosteroids in mild asthma need to be undertaken.

The results of this study cannot be extrapolated to all patients with intermittent asthma. The studied patients had been selected based on a high level of NO in exhaled air. Therefore, the results are only applicable to patients with intermittent asthma and signs of airway inflammation. Furthermore, the long-term implications of a treatment strategy that uses an inhaled corticosteroid on an as-needed basis in addition to an inhaled rapid-acting β_2-agonist are not known. This will have to be evaluated in future long-term follow-up real-life studies. Futhermore, clinical studies with as-needed budesonide/formoterol compared with regular anti-inflammatory therapy measuring other markers of airway inflammation than *F*eNO should now be considered.

The main target of asthma treatment is the airway inflammation. In a recent study, patients had their doses of inhaled corticosteroid adjusted, in a stepwise manner, on the basis of either *F*eNO measurements or an algorithm based on conventional guidelines [33]. The final mean daily dose of the inhaled corticosteroid and exacerbation rate were lower during the follow-up year in the *F*eNO group. Patients requiring temporary as-needed medication may, in fact, experience a ''mini-exacerbation'' of asthma with not only some bronchoconstriction but also an increase in airway inflammation.

Based on the results of this study, a new treatment concept may be considered and should be further investigated. The question should be asked whether as-needed medication in asthma should target not only the bronchoconstriction but also the underlying inflammation. This could, in practice, be achieved by giving the patient a combination of a rapid-acting bronchodilator and an inhaled corticosteroid.

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