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Inhaled budesonide in chronic bronchitis. Effects on respiratory impedance

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Inhaled budesonide in chronic bronchitis. Effects on respiratory impedance. G.J. Wesseling, M. Quaedvlieg, E.F.M. Wouters.
ABSTRACT: In a placebo controlled study the effects of 6 weeks' treatment with inhaled budesonide (1.6 mg daily) on the impedance of the respiratory system, spirometry and symptom scores were evaluated in 35 patients with chronic bronchitis with forced expiratory volume in one second (FEV_1)≥70% predicted. Thirty patients completed the study. No statistically significant differences in the changes in morning peak expiratory flow rate (PEFR), symptom scores, use of terbutaline rescue medication and FEV_1 were found between the placebo and the active treatment group. Budesonide treatment was found to result in a small decrease in resonant frequency and a less negative frequency dependence of resistance compared with the placebo group.
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The effects of anti-inflammatory drugs such as inhaled corticosteroids in asthma and chronic airflow obstruction have been extensively evaluated [1–4]. The effects of inhaled corticosteroids in patients with simple chronic bronchitis are less clear. Recently, ENGEL *et al.* [5] failed to demonstrate effects of inhaled budesonide on sputum expectoration, dyspnoea, sleep disturbances, ventilatory capacity and bronchial responsiveness in smokers with chronic bronchitis, and baseline forced expiratory volume in one second (FEV_1) ≥70% predicted).

The present study was performed to evaluate the effects of treatment with inhaled budesonide (1.6 $mg \cdot day^{-1}$) during 6 weeks on symptom scores, spirometric values and respiratory impedance in patients with chronic bronchitis without spirometric evidence of airflow obstruction. Impedance of the respiratory system was measured using the technique of forced oscillations, introduced by DUBOIS *et al.* [6] in 1956. This technique allows the determination of the resistance and reactance of the respiratory system during spontaneous, quiet breathing, and provides a method to study the mechanical characteristics of the respiratory system.

Material and methods

Study design

In a double-blind, randomized, placebo-controlled study, the effects of treatment with 2 inhalations four times a day of budesonide (1.6 $mg \cdot day^{-1}$) from a metered dose inhaler (MDI) during 6 weeks were studied in patients with chronic bronchitis without marked airflow obstruction (FEV_1≥70% predicted) [7].

On the entry visit a full history was obtained, and spirometric and impedance values were recorded. Patients were instructed how to use metered dose inhalers and the mini-Wright peak flow meter (Airmed, Clement Clarke International Ltd, London, UK). They were asked to register in a diary the morning peak expiratory flow rate (PEFR), the severity of cough, dyspnoea and sputum volume using a 0–3 point scale, to record fever and the use of the study medication and of concomitant medication and possible side effects.

The patients entered a single-blind placebo baseline wash-out period of one week, during which all medication was withheld except for inhaled terbutaline as rescue medication and 2 puffs four times daily from a placebo MDI using a Nebuhaler®. One week later, at visit 2, respiratory impedance measurements were repeated to obtain baseline values. On the third visit, after a treatment period of 6 weeks, during which the patients continued to record symptoms and morning peak expiratory flow rates in their diary, impedance and spirometric values were again obtained, in the same sequence as prior to the treatment.

Apart from the study medication and inhaled terbutaline as rescue medication, no other medication was allowed during the study period. Patients were asked to register the use of terbutaline in the diary.

The study was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Subjects

Thirty five subjects entered into the study. Anthropometric, spirometric and baseline impedance data at visit 2 are presented in table 1.

All patients suffered from chronic bronchitis, as defined by a history of chronic cough and expectoration of sputum during 3 months of at least 2 yrs. Selection criteria included a forced expiratory volume in one second (FEV_1) of at least 70% of predicted [7], and an increase in FEV_1 less than 15%, following inhalation of 0.5 mg terbutaline. Patients with documented heart, liver or renal disease were excluded from the study, as were patients unable to use metered dose inhalers or to keep diaries. Thirteen patients were female, mean age was 50.4 yrs (range 29–69) and 16 patients were current smokers, all others were ex-smokers.

Table 1. – Anthropometric, spirometric and impedance characteristics (n=35).

		Mean	SD
Age	yrs	52	
Sex	F/M	11/24	
Height	cm	166	
Weight	kg	77.1	
FEV_1	l	2.84	0.69
FEV_1	% pred	96	17.39
Rrs (8)	kPa·s·l^{-1}	0.347	0.095
Rrs (28)	kPa·s·l^{-1}	0.320	0.081
Xrs (8)	kPa·s·l^{-1}	-0.064	0.058
f_0	Hz	14.76	4.955

SD: standard deviation; FEV_1; forced expiratory volume in one second; Rrs (8), Rrs (28): resistance at 8 and 28Hz, respectively; Xrs (8): reactance at 8Hz; f_0: resonant frequency.

Lung function measurements

Spirometric values were derived from the best of three maximal expiratory flow-volume curves (Jaeger® transferscreen) and values were recorded as absolute values and as a percentage of predicted. Reversibility was noted as the percentage increase in FEV_1 above baseline after inhalation of 0.5 mg terbutaline by Nebuhaler®.

Impedance of the respiratory system was measured by means of the technique of forced oscillations (FOT), as described by DUBOIS *et al.* [6]. A complex pseudo random-noise signal containing the fundamental frequency of 4 Hz, with its harmonics up to 52 Hz, appearing with random phase shift is used as was introduced by LANDSÉR *et al.* [8]. The method is extensively described elsewhere [8, 9]. Measurements were performed during 8 s, with the subject seated, supporting the cheeks and the floor of the mouth with both hands. For each of the investigated frequencies an impedance value was calculated, which was then partitioned into a real part or resistance (Rrs) and an imaginary part or reactance (Xrs). Rrs is the equivalent of a total resistance in a resistance-inductance-capacitance (R-L-C) circuit. Xrs is determined by the inertial and elastic properties of the respiratory system: at lower frequencies Xrs is negative, because at lower frequencies reactance is influenced mainly by the capacitance of the system. At higher frequencies Xrs becomes positive by the influence of the inertial properties of the respiratory system. The frequency at which Xrs equals zero is called the resonant frequency (f_0).

At each visit, three successive impedance measurements were performed and the results of each set of impedance measurements were averaged at each frequency. The following impedance measures were evaluated: the resistance at 8 and 28 Hz (Rrs (8) and Rrs (28)), the reactance at 8 Hz (Xrs (8)), resonant frequency (f_0), frequency dependence (FD) of resistance defined as Rrs (28) minus Rrs (8) divided by 20, reflecting the slope of the resistance *versus* frequency curve.

Data analysis

Diary card data averaged for days 1–7 and for days 29–42 and lung function values of visits 2 and 3 were compared using students' t-tests for unpaired observations for the comparisons of the findings between the two treatment groups. Paired t-tests were used for comparisons within each group.

P-values ≤ 0.05 were considered as statistically significant.

Results

Of the 35 patients entered into the study 5 patients failed to complete the study, due to withdrawal of consent (1 patient), lack of co-operation (1×), an intercurrent pertussis infection during the wash-out period (1×), persistent coughing after inhalation of the study drug (budesonide, 1×) and an intercurrent pneumonia after 4 weeks (placebo group, 1×). Thus, it is thought that one patient dropped out due to side effects resulting from budesonide treatment. Of the 30 patients who completed the study, 14 were randomized to treatment with budesonide, 16 received placebo. Both treatment groups were comparable with respect to all demographic and lung function values.

Comparing FEV_1, morning PEFR, scores for cough, dyspnoea, sputum volume and fever, and use of rescue medication between the two treatment groups before (days 1–7) and at the end (days 29–42) of the treatment period, it was found that the improvements were larger in the budesonide group, but the differences were not statistically significant between the 2 groups (table 2). In the budesonide group mean morning PEFR increased significantly from 362.2 $l \cdot min^{-1}$ to 404.3 $l \cdot min^{-1}$, and in the placebo group PEFR increased from 354.8 $l \cdot min^{-1}$ to 396.7 $l \cdot min^{-1}$ ($p<0.05$). In the budesonide group the score for sputum volume decreased significantly from 1.74 (days 1–7) to 1.31 (days 29–42, $p<0.05$). Apart from persistent coughing in 1 patient in the budesonide group, no serious side effects were reported.

Table 2 – Symptom scores, morning peak-expiratory flow rate and use of terbutaline rescue medication at the start (days 1–7) and the end (days 29–53) of the treatment period

		PEFR $l \cdot min^{-1}$	Cough 0–3	Dyspnoea 0–3	Sputum 0–3	Terbutaline puffs·day^{-1}
BUD	Days 1–7	362.2	1.62	1.40	1.74	1.88
	Days 29–53	404.3*	1.28	1.10	1.31*	1.15
PLAC	Days 1–7	354.8	1.40	0.86	1.91	0.56
	Days 29–53	396.7*	1.31	0.64	1.86	0.29

*: $p<0.05$; n=30; BUD: budesonide, n=14; PLAC: placebo, n=16; PEFR: peak expiratory flow rate.

Table 3 – Values for FEV_1 and for resistance at 8 and 28 Hz, reactance at 8 Hz, resonant frequency and frequency dependence of resistance of 30 patients with chronic bronchitis before (T1) and after the treatment period (T2)

	BUD		PLAC		p-value BUD *vs* PLAC
	mean	SD	mean	SD	
FEV_1 l					
T1	88.4	19.0	92.5	15.0	NS
T2	90.8	19.3	92.5	15.5	NS
$\underline{R}rs$ (8) kPa·s·l^{-1}					
T1	0.349	0.107	0.349	0.091	NS
T2	0.323	0.086	0.355	0.113	NS
$\underline{R}rs$ (28) kPa·s·l^{-1}					
T1	0.325	0.085	0.317	0.074	NS
T2	0.320	0.082	0.347	0.103	NS
$\underline{X}rs$ (8) kPa·s·l^{-1}					
T1	-0.064	0.053	-0.074	0.066	NS
T2	-0.052	0.052	-0.069	0.055	NS
f_0					
T1	14.80	5.72	15.44	4.35	NS
T2	13.31	5.51	17.34	7.54	$p<0.05$
FD kPa·s·l^{-1}					
T1	-0.0012	0.0008	-0.0010	0.0006	NS
T2	-0.00015	0.0006	-0.0004	0.0004	$p<0.05$

BUD: budesonide; PLAC: placebo; FEV_1: forced expiratory volume in one second; $\underline{R}rs$ (8), $\underline{R}rs$ (28): resistance at 8 and 28 Hz, respectively; f_0: resonant frequency; FD: frequency dependence of resistance; T1, T2: before and after treatment period, respectively; NS: not significant.

Table 3 lists the changes in respiratory impedance values of the two treatment groups before and after the treatment period. Inhalation of budesonide results in significant differences in the resonant frequency ($p<0.05$) and in frequency dependence of resistance ($p<0.05$) compared with the control group. No significant changes in impedance data within both groups could be demonstrated after the treatment period.

Discussion

A beneficial effect of inhaled corticosteroids on asthma and chronic airflow obstruction has been well established 1–4, and recently, WEIR *et al.* [10] reported that inhaled beclomethasone diproprionate (1.5 mg daily) was more effective than placebo in non-asthmatic chronic airflow obstruction. Furthermore, inhaled corticosteroids have been demonstrated to reduce bronchial hyperresponsiveness [11–13]. It is thought that corticosteroids act by reducing airway inflammation [14, 15], a consistent finding in chronic asthma [14] and in chronic bronchitis [15].

The effects of inhaled corticosteroids in chronic bronchitis without airflow obstruction are less clear. Recently, ENGEL *et al.* [5] reported a study on inhaled budesonide in smokers with chronic bronchitis with normal ventilatory capacity. These authors found that budesonide 0.80 mg daily did not improve symptom scores, ventilatory capacity or airway responsiveness as expressed by the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}). WATSON *et al.* [16]

found no effect of treatment with 1.2 mg inhaled budesonide on FEV_1, bronchodilator response and PC_{20} in middle aged smokers with bronchial hyperresponsiveness.

In the present study we have found no significant reduction in cough, sputum volume, fever and use of rescue medication, or increase in PEFR or FEV_1 as compared to placebo after 6 weeks treatment with inhaled budesonide 1.6 mg daily.

Apart from spirometry, we have used the technique of forced oscillations to assess possible effects of inhaled budesonide on the impedance of the respiratory system. This technique allows the evaluation of the mechanical characteristics of the respiratory system during spontaneous quiet breathing. The sensitivity of this technique has been demonstrated especially in the absence of gross abnormalities [17]. In analysing impedance values obtained with the technique of forced oscillations, CLÉMENT *et al.* [18] concluded that healthy subjects can be distinguished from patients with pulmonary complaints on the basis of increased resistance values especially at lower frequencies, negative frequency dependence of resistance (a decrease in resistance with increasing frequency), lower average reactance values resulting in higher values for resonant frequency, and a more linear course of reactance with frequency.

In spite of the absence of evidence of airflow limitation in the values obtained with spirometr, in our study population, frequency dependence of resistance was found to be slightly negative.

Significant differences in resonant frequency and in frequency dependence of resistance were found between the budesonide group and the placebo group after the treatment group. The differences in the changes in FEV_1 were not significant. To our knowledge, ours is the first study on changes in respiratory impedance after treatment with inhaled corticosteroids in patients with chronic bronchitis.

In summary, treatment with inhaled budesonide during 6 weeks in patients with chronic bronchitis without airflow obstruction induced no statistically significant effects on morning PEFR, FEV_1, symptom scores and use of rescue medication whilst statistically significant though limited effects on respiratory impedance could be demonstrated.

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Le budesonide en inhalation dans la bronchite chronique. Ses effets sur l'impédance respiratoire. G.J, Wesseling, M. Quaedvlieg, E.F.M. Wouters.

RÉSUMÉ: Au cours d'une étude contrôlée par placebo, les effets d'un traitement de 6 semaines par le budesonide en inhalation à raison de 1.6 mg par jour su l'impédance du système respiratoire, sur la spirométrie et les scores de symptômes, ont été évalués chez 35 patients atteints de bronchite chronique, dont le VEMS était ≥70% des valeurs prédites. Trente patients ont achevé l'étude. Aucune différence significative n'a été observée dans les modifications du débit expiratoire de pointe matinal, des scores de symptômes, de l'utilisation de terbutaline des secours, et du VEMS, entre le groupe traité par placebo ou par médicament. Le traitement par budesonide s'est avéré entraîner une diminution légère et une dépendance de la résistance à l'égard de la fréquence moins négative par comparaison avec le groupe placebo.
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