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Effects of HFA- and CFC-beclomethasone dipropionate on the bronchial response to methacholine (MCh) in mild asthma

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Summary Metered inhalers using chlorofluorocarbon (CFC) propellents have been gradually replaced by new devices that use hydrofluoroalkanes (HFAs) as their propellents, which are less harmful to the environment. This reformulation led to a substantial improvement of the previous technologies applied to inhalation devices and of the physical characteristics of drugs delivered. In particular, inhaled corticosteroids, such as beclomethasone dipropionate (BDP) which is of fundamental importance in the long-term management of bronchial asthma, took advantage of this reformulation.

Unlike the preparation beclomethasone dipropionate and chlorofluorocarbon (BDP-CFC) which was a suspension, that of beclomethasone dipropionate and a hydrofluoroalkane (BDP-HFA) is a solution and produces an aerosol with a mean aerodynamic particle size of 1.1 μm, which is much smaller than the particle size of 3.5–4.0 μm, obtained with the BDP-CFC. The particles of BDP-HFA can then deposit in the lungs in a larger amount, and particularly in the more peripheral airways where the inflammatory process starts in the case of bronchial asthma.

A 12-week use of BDP-HFA ensured a significant better control of the bronchial response to methacholine (MCh) than the corresponding use of BDP-CFC for the same duration. The therapeutic performance of BDP-HFA proved much higher and allowed the substantial reduction of the therapeuticdaily dose for the clinical asthma management, being the increased and more peripheral deposition of BDP-HFA is presumed to play a crucial role.

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Introduction

Inhaled corticosteroids are the cornerstones of asthma treatment, independently of the clinical severity of asthma.[1] It has been proved that their prolonged use leads to the control of clinical symptoms, of respiratory function, and of bronchial hyperreactivity, which is a peculiar feature of asthma and is closely related to the presence of airway inflammation.[2]

Beclomethasone dipropionate (BDP), a drug belonging to the class of corticosteroids, was the first synthetic corticosteroid delivered to asthmatics per inhalation and it still is one of the most widely used steroids for this purpose.

According to the regular formulation, BDP consists in a suspension with a chlorofluorocarbon (CFC) propellent which is delivered by a metered-dose inhaler (MDI). However, it is well known that the pulmonary deposition of such a metered preparation with the CFC propellent is poor and only a small part of the active drug actually can reach the airways.[3] Moreover, it has long been known that CFCs are harmful to the environment because they contribute to deplete the ozone layer.[4]

In order to replace CFCs, BDP has been reformulated with a new propellent, such as the hydrofluoroalkane (HFA) 134a, which is free of chlorine and is much less harmful to the environment.[5] This new development contributed to further improve the technologies for inhalation devices to a large extent, together with the knowhow on the physical properties of inhaled drugs, and their deposition pattern in the airways. It was also assumed that this new improvement could reduce the level of bronchial hyperreactivity to non-specific stimuli.

The aim of the present study was to compare the effects of BDP-CFC 1000 µg/day and of BDP-HFA 400 µg/day on the bronchial response to methacholine (MCh) in mild persistent asthmatics treated for 12 weeks.

Materials and method

The study was carried out according to a randomized, double-blind, cross-over design. Both treatments had a 12-week duration, with a 4-week wash-out period in- between (see Fig. 1). The wash-out period was considered long enough to re-establish the original bronchial response to MCh.[6] Only the use of short-acting β_2 adrenergic agents was allowed, whenever needed, during the wash-out period.

During the study, the patients' compliance to both treatments was calculated in terms of % of the prescribed daily dose, and diaries were supplied to all patients. Compliance was accepted as "sufficient" when $\geq$75% of treatment was assumed.[7]

Inclusion criteria were:

- age $\geq$18 years, of both sex;
- non-smoker;
- naïve to steroids;
- baseline $FEV_1 \geq 80\%$ predicted;
- baseline PD_{20} FEV_1 MCh $\leq$800 µg;
- use of short-acting β_2 adrenergics prn;
- no treatment with antihistamines, ketotifen, chromones, theophylline and leucotriene receptor antagonists in the previous 4 weeks;
- no exacerbation in the previous 4 weeks.

Further exclusion criteria were:

- pregnancy or breast feeding;
- serious systemic disorders;
- regular users of β-blockers, nitrates or anticoagulants;
- antibiotic treatment in the previous 4 weeks;

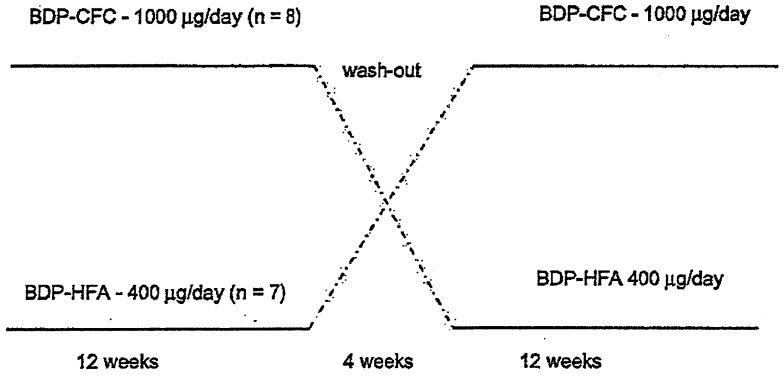

Figure 1 Experimental design of the study.

- persons who could not understand the procedures of the protocol.

Lung function tests (FEV_1, PEF and $MMEF_{25-75}$) were carried out with a SyncMaster 510s spirometer made (Jäger, Germany), being results espressed in % of the predicted values (CECA).[8] All tests were performed after the wash-out period and at least 6 h after the administration of any short-acting β_2 adrenergic.

The bronchial response to MCh was determined three times in the case of all the patients, namely at the beginning of the study; after the first treatment period, and after the second treatment period. During the 4-week wash-out period in between, only short-acting β_2 adrenergics prn were allowed. The hyperresponsiveness to MCh was tested according to the ERS guidelines,[9] and the provocation dose was expressed in mcg of MCh required to induce a 20% FEV_1 drop from baseline (PD_{20} FEV_1). The bronchial challenge (methacholine Lofarma, Milan, Italy) was delivered by means of a Mefar MB3 dosimeter (Brescia, Italy). MCh was administered in doubling doses after a dose of phosphate buffer, being 50 µg the first MCh dose inhaled, up to the maximal cumulative dose of 3150 µg.

Statistics

A Wilcoxon matched-pairs signed-ranks test was used to compare mean values ± SD obtained for all variables (FEV_1, PEF, MMEF, and $PD_{20}FEV_1$ to MCh) at the end of each treatment period to the corresponding baseline values. The level of compliance to treatment was also compared in the two groups, and $P<0.05$ was the accepted level for statistical significance.

Results

After their informed written consent, 15 non-smoker, mild persistent asthmatics (8 males, mean age 30.1 y ± 10.8 SD, 11 atopics) were studied. Their lung function in baseline was: FEV_1 (forced expiratory volume in 1-s) = 102.1% pred. ± 5.9 SD; PEF (peak expiratory flow) = 105.5% pred. ± 8.4 SD; MMEF (maximum mid-expiratory flow 25–75% pulmonary volume) = 66.2% pred. ± 21.3 SD.

None of the patients had ever been treated with inhaled corticosteroids and only assumed short-acting β_2 adrenergic drugs when needed. All patients showed a marked bronchial response to MCh in baseline, being the PD_{20} FEV_1 = 178.1 µg ± 185.0 SD (PD_{20} corresponds to the cumulative dose of MCh that produces a FEV_1 decrease of 20% from baseline).

All patients completed the study. No exacerbation or infection of the upper or lower airways occurred during both the two treatment periods and the wash-out period. The overall compliance to the treatments (such as based on the patients' own reports) was 90.3% ± 5.2%, being therefore always confirmed above the declared threshold of 75%.

Table 1 reports mean values ± SD obtained for each spirometric variable in baseline and following both treatments, together with the corresponding level of compliance reached during each treatment period. No significant difference was observed between the two treatments (P = n.s.). Also the level of patients' compliance was comparable during the two treatments (P = ns).

Table 2 reports all the individual values of PD_{20} FEV_1 to MCh assessed for each patient in baseline and following both treatments (such as after BDP-CFC and after BDP-HFA) together with the corresponding mean values ± SD at the same experimental times. The results of the statistical comparison between post-treatment vs. baseline values are also reported in Table 2.

PD_{20} FEV_1 to MCh slightly changed following a 12-week treatment with BDP-CFC, being mean baseline value 178.1 µg ± 185.0 SD and the corresponding post-treatment mean value 319.3 µg ± 332.6 SD (P = 0.0437).

Unlike in the BDP-CFC treated patients, in those who assumed BDP-HFA for 12 weeks PD_{20} FEV_1 to MCh changed substantially from 178.1 µg ± 185.0 SD

Table 1 — Spirometric values before and after a 12-week treatment with BDP-CFC and BDP-HFA (mean values and standard deviations). The mean value of patient compliance in the two treatment periods is also reported. There is no significant difference between the two treatments.

	FEV_1	PEF	MMEF	Compliance
Base-line	102.1 ± 15.9	105.5 ± 8.4	66.2 ± 21.3	
After BDP-CFC	100.6 ± 14.7	109.6 ± 9.9	72.2 ± 26.5	89.8 ± 6.1
After BDP-HFA	104.6 ± 14.5	112.2 ± 15.4	72.5 ± 32.0	90.7 ± 4.4

Table 2 Values of PD_{20} FEV_1 recorded at different experimental times together with the statistical significance of the comparison vs baseline values (mean and standard deviation).

Patient's initials	Base-line MCh dose (μg)	MCh dose after BDP-CFC (μg)	MCh dose after BDP-HFA (μg)
N.R.	612	544	1786
S.E.	236	49	687
F.M.	181	229	173
N.A.	290	451	191
R.E.	450	950	2638
C.A.	50	66	52
P.A.	95.8	128	749
M.Y.	95	50	50
R.S.	0.05	0.05	165
Z.G.	0.05	5	87
G.I.	400	844	1850
G.S.	0.05	50	408
C.M.	100	436	2100
T.A.	50	173	750
DB.G	112	815	2450
Mean ± SD	178.1 μg ± 185.0	319.3 μg ± 332.6*	942.0 μg ± 946.1**,***

*$P = 0.0437$ vs. baseline; **$P = 0.0059$ vs. baseline; ***$P = 0.0045$ vs. BDP-CFC.

in baseline to 942.0 μg ± 946.1 SD at the end of the treatment period ($P = 0.0059$).

When the two treatments were compared in terms of bronchial response to MCh, BDP-HFA proved significantly more effective than BDP-CFC ($P = 0.0045$).

Discussion

Inhaled corticosteroids are fundamental to the management of bronchial asthma[1] since they can generally reduce inflammation and the bronchial response of the airways to non-specific stimuli.[2]

Inflammation-induced bronchial hyperresponsiveness is substantial even in mild bronchial asthma, since persistent inflammation affects peripheral airways particularly, being T cells and eosinophils much more represented than in proximal airways.[10]

In patho-physiological terms, conventional indicators of lung function cannot inform on the functional state of small airways (such as those with a diameter ⩽2 mm) specifically, because they only contribute 10% to the total airflow resistance. Nevertheless small airways show clear inflammatory changes since the early stages of asthma, and all the structural changes deriving may represent the biological basis for the airway "remodelling", another peculiar feature of persistent asthma.[11] Moreover, recent studies tend to support the hypothesis that the inflammation of small airways and the thickening of airway basal membrane may play a crucial role in determining and supporting bronchial hyperresponsiveness.[12–15]

Therefore, any effective antiasthma drug should be targeted to all the bronchial tree but particularly to peripheral airways because at this level occur those biological events which give rise to the disease, sustain its patho-physiological pattern, and reflect the progression of the disease.

This kind of therapeutic goal can be pursued and obtained by improving the engineering of the devices for the drug delivery, but also by improving the physical characteristics of the active drug and of the propellent used.[16]

Differently from the past, the introduction of HFAs enabled BDP to be now employed as a solution rather than as a suspension.

Furthermore, the active substance is now released by the device as an aerosol constituted of particles of a much smaller mean diameter (1.1 μm) than previously (3.5–4 μm), when CFC was the propellent. Consequently, the respirable fraction of the active drug is significantly larger, and the increased pulmonary deposition (both in the central and in the peripheral airways) corresponds to a substantially reduced proportion of the active drug which stops in the oropharynx.[17–18]

The BDP therapeutic performance was highly improved and side effects reduced, particularly in

terms of oropharyngeal mycosis. In the case of BDP-HFA, scintigraphic measurements confirmed that 60–70% of the active drug reaches the lungs and is uniformly distributed in the airways (central, intermediate and peripheral airways), and that only 18% deposits in the oropharynx.[17] This performance is quite different from that of previous BDP-CFC, when the pulmonary deposition was no more than 25% and the oropharyngeal deposition of 60–90%.[18]

The larger respirable fraction of aerosol particles and the higher pulmonary deposition obtained with HFA led to the reduction of the BDP daily dose, with consistent advantages in terms of safety and tolerability.[19] Several studies indicate that BDP-HFA can be used by halving the doses of BDP-CFC in adult asthmatics, with equivalent effects on respiratory symptoms.[20–22]

Also in children it has also been recently found that BDP-HFA 100–200 µg/day corresponds to BDP-CFC 200–400 µg/day, delivered by means of an expansion chamber.[23,24]

Unlike previous studies on BDP-HFA where FEV_1 and PEF were the unique parameters used to assess the therapeutic performance,[20,24] up to now only one group of authors studied the efficacy of BDP-HFA in asthmatics on the basis of the bronchial response to MCh, even though they measured the solely air trapping by high-resolution computed axial tomography.[25]

The present study is the first one at our knowledge that assessed the effects of ultrafine BDP on the bronchial hyperresponsiveness to MCh. Data seem to confirm that BDP-HFA is much more effective than BDP-CFC even after only a 12-week treatment: BDP-HFA produces in fact a systematic and a greater increase (such as double) in the threshold of MCh bronchial response. It is probably due to the particular pattern of pulmonary deposition of HFA. The BDP-HFA therapeutic performance has in fact been found to be *better* than twice as much BDP-CFC as regards protection from hyperreaction to MCh.

This medium-term therapeutic performance is clearly higher to that obtained with the conventional BDP+CFCs. Moreover, the physico-chemical properties of BDP-HFA, which is a solution, probably contribute to a much better long-term patient's tolerability and compliance.

Concluding, present data seem to confirm that the new aerosol propellants which facilitate the active drugs to reach all targets therapeutically important in the airways are steadily improving the therapeutic options beyond the standard use of inhalation corticosteroids.

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