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Anti-inflammatory effects of high-dose inhaled fluticasone *versus* oral prednisone in asthma exacerbations

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ABSTRACT: The objective of the present study was to investigate the kinetics of high doses of inhaled steroid fluticasone in comparison with oral steroid prednisone on plasma protein leakage and bronchial eosinophilia in adults with moderate asthma exacerbations.

The study design was a randomised, double-blind, placebo-controlled prospective trial. In total, 45 patients treated at the emergency department for moderate asthma exacerbations were recruited and 39 were assigned to receive fluticasone and placebo of prednisone (19 patients), or prednisone and placebo of fluticasone (20 patients). Medication was administered to all patients *via* a metered-dose inhaler and spacer (16 puffs; 4,000 μg·day^{-1} or placebo) plus one pill (prednisone 30 mg·day^{-1} or placebo). Spirometry and induced sputum for differential cell counts, albumin and α_2-macroglobulin levels and blood eosinophils, interleukin-5 and granulocyte-macrophage colony-stimulating factor levels were obtained before treatment and at 2, 6 and 24 h after treatment.

Symptoms clearly improved after 24 h in both groups. No differences were seen between groups in peak expiratory flow or forced expiratory flow in one second, which improved progressively but then decayed slightly after 24 h. Eosinophil counts in sputum also improved over time in both groups. The effect was faster with fluticasone than with prednisone, but was partially lost at 24 h. However, plasma proteins in sputum and eosinophil count in blood both decreased until 24 h, with no significant differences between groups. There was no correlation between eosinophil counts and plasmatic protein levels.

In conclusion, both treatments improved symptoms, airway obstruction and inflammation, and plasma protein leakage at 24 h. Prednisone reduced blood eosinophil counts, while fluticasone reduced airway eosinophil counts, suggesting that the anti-inflammatory performance of fluticasone is exerted locally.

KEYWORDS: Albumin, eosinophil, fluticasone, α_2-macroglobulin, plasma exudation, prednisone, sputum induction

Systemic corticosteroids are currently recommended in acute asthma because they prevent the progression of exacerbations, decrease the hospitalisation rate and reduce morbidity [1]. Despite general agreement that systemic corticosteroids play an important role in acute asthma, there are significant doubts about short-term efficacy. RODRIGO and RODRIGO [2] and STEIN and COLE [3] have reported that *i.v.* parenteral corticosteroids have no bronchodilator effect within the first few hours of an acute asthma exacerbation. However, a systemic corticosteroid effect does occur within the first 6–8 h after administration; this treatment probably requires a number of hours to effectively improve airflow obstruction, and some authors have questioned the efficacy of this treatment to control exacerbation during the first hours. The corticosteroid effect may be slow because these drugs require ligand-dependent activation of the corticosteroid receptor transcriptional factor [4].

Conversely, inhaled corticosteroids are recommended to control chronic asthma and reduce the need for oral prednisone [1, 5–7]. In acute asthma, they are only recommended for asthma treatment after emergency room discharge because they

For editorial comments see page 1035.

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reduce the chance of worsening after such attacks [8]. Other authors have suggested that high-dose inhaled corticosteroids in emergency rooms would act faster than oral or parenteral corticosteroids [9–14]. Confirmation of these data would necessitate important modifications in today's guidelines for acute asthma [15]. Additionally, some safety concerns have arisen because no data are available about the mechanism by which inhaled steroids could have a faster effect than systemic corticosteroids. In the previously mentioned editorial, McFADDEN [15] suggested that inhaled steroids would reduce oedema and plasma exudation quicker than oral steroids. However, a more complex mechanism cannot be discarded because early changes (within 2–3 h) in cellular and biochemical markers of bronchial inflammation have been described after systemic [16] and inhaled corticosteroid treatment [17, 18] in uncontrolled asthmatics.

The present randomised clinical trial was performed to study the mechanism through which inhaled steroids could act faster than oral steroids in acute asthma. The aim was to compare the effect of high doses of inhaled fluticasone with oral prednisone on airway plasma protein exudation. Relative indices of albumin and α_2-macroglobulin were calculated through the ratio between sputum and blood. Furthermore, the anti-inflammatory effects were assessed by the sputum eosinophil counts and the concentration of interleukin (IL)-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) in peripheral blood.

MATERIAL AND METHODS

Subjects

All participants were recruited consecutively from patients with acute asthma at the Emergency Department, Hospital de la Santa Creu i de Sant Pau, Barcelona, Spain. The present study conforms to the Helsinki Declaration and was approved by the hospital's Ethics and Clinical Assays Committee. All participants gave written informed consent to participate in the study. Inclusion criteria were as follows. 1) Patients had acute asthma and were aged between 16–65 yrs with no oral or *i.v.* steroid treatment in the last 4 weeks. 2) All had been diagnosed with asthma from current or previous history of chest tightness, wheezing, dyspnoea or cough in association with variable airflow limitation. 3) Variable airflow limitation was documented from either methacholine airway hyperresponsiveness (provocative concentration causing a 20% fall in forced expiratory volume in one second (FEV_1) <8 mg·mL^{-1}) if FEV_1 was $\geqslant$70% of predicted value, or 12% increases in FEV_1 after inhaled salbutamol 200 μg if FEV_1 was $<$70%. 4) The exacerbation was considered moderate to severe, but not life threatening at baseline, strictly in accordance with the Global Initiative for Asthma criteria [1].

Exclusion criteria included the following: 1) smokers or ex-smokers within the last year; and 2) treatment with oral or *i.v.* corticosteroids, cromoglycate, nedocromil, theophylline, allergen-desensitisation injections, and leukotriene antagonists at any time in the 4 weeks prior to the study. Long-acting β-agonists were permitted, but participants on this treatment were balanced between the two groups (block randomisation). Subjects with life-threatening exacerbations of asthma at baseline or any other serious medical conditions were excluded, *e.g.* heart disease, gastro-intestinal, liver or renal disease, or other chest disease which could interfere with the study outcome, as judged by the investigators.

Design and methods

A sequential, placebo-controlled, double-blind, clinical trial was designed comparing oral prednisone and inhaled fluticasone. Baseline measurements were recorded at admission. Severity of exacerbation was assessed from clinical history, physical examination, peak expiratory flow (PEF) measurement and oxyhaemoglobin saturation. Additionally, peripheral blood and sputum were collected. After initial treatment with nebulised salbutamol (1 mL in 3 mL of isotonic saline for 15 min with a Hudson jet nebuliser) and oxygen, patients were re-evaluated as either suitable or unsuitable for the study. They were then randomly treated with either a 30 mg·day^{-1} prednisone tablet plus 16 inhalations of fluticasone-like placebo, or a prednisone-like placebo tablet plus 16 inhalations (4,000 μg·day^{-1}) of fluticasone 250 μg.

Patients' allocation to treatment one or two was concealed by following computerised randomisation, codified by the hospital's Pharmacy Dept, who also packed and blinded all medications. Fluticasone and its placebo were kindly donated by GlaxoSmithKline (Madrid, Spain). Prednisone and its placebo were obtained from common sources. The appearance, taste and texture of the prednisone and placebo and fluticasone and placebo were similar, so the two were indistinguishable.

Each treatment was given in a single dose under supervision at baseline and at 24 h, as of which time patients were instructed to continue taking one tablet each morning and eight inhalations twice a day for 4 days. Measurements were made at baseline and at 2, 6 and 24 h. At each proposed time, asthma symptoms (cough, wheeze, chest tightness and breathlessness) were recorded. Measurements were performed in the following order: 1) symptoms score; 2) PEF; 3) peripheral blood withdrawal; and 4) sputum collection. The laboratory was blinded to clinical details during sputum and blood measurements. Inhaled medication was administered through a spacer camera according to the manufacturer's instructions and was always supervised by investigators. The following safety protocol was applied: participants were followed in the respiratory day-care setting for 6 h and then discharged if symptoms improved and PEF increased by $\geqslant$30% above baseline value. If the patients did not improve, they were kept in observation for 24 h. During observation, it had been previously established that patients would be shifted to the other arm in case of worsening (decrease of PEF $>$20% of baseline or clinical deterioration judged by the responsible physician). No other treatments were allowed other than nebulised salbutamol every 4 h and oxygen on demand. For safety reasons, patients were visited at 1 and 3 weeks after exacerbation. They were asked about treatment compliance and their home diary, in which their recorded PEF and symptoms were reviewed.

Procedures

Patient characteristics and physical examination

Sex, age, history of smoking habits, allergen injection treatment, possible relevant allergen exposure or trigger of asthma exacerbation, symptoms of asthma and medications were recorded in a closed questionnaire. Physical examination was

performed, including measurement of oxyhaemoglobin saturation. Symptom severity was recorded on a four-point scale (0: not at all; 1: mild, but I can continue my work; 2: moderate intensity, I need to stop at least for a while; and 3: severe intensity, I cannot continue my work).

PEF technique

Patients were instructed and checked for adequate PEF technique following Global Initiative of Asthma recommendations [1].

Spirometry

Spirometry was performed with a Datospir 500 (Sibelmed S.A., Barcelona, Spain) according to the procedure and predicting values described by the European Respiratory Society [19].

Sputum induction and processing

Sputum was obtained 10 min after salbutamol nebulisation. Subjects were asked to blow their nose, rinse their mouth and swallow the water to minimise contamination with post-nasal drip and saliva. They were then asked to cough sputum into a sterile container. The specimen was put in the refrigerator (4°C) and processed as soon as possible, as described by PIZZICHINI *et al.* [20]. Total cell count was obtained in a modified Neubauer haemocytometer. The cell viability was determined by the trypan blue exclusion method. The total and absolute number of cells per milligram of processed sputum was calculated. In total, 400 nonsquamous cells were counted in Wright-stained slides and the results expressed as a percentage and absolute number of the total nonsquamous count.

Serum and sputum protein measurements

Albumin in sputum ($mg \cdot L^{-1}$) was measured by an immunoturbidimetric assay (Albumina Tina-quant© Ref 11875400; Roche/Hitachi, Roche Diagnostics GmbH, Mannheim, Germany) and in serum ($g \cdot L^{-1}$) by a colourimetric assay (ALB plus Ref 1929640; Roche Diagnostics GmbH, Mannheim, Germany). α_2-Macroglobulin in sputum ($mg \cdot L^{-1}$) and serum ($g \cdot L^{-1}$) was measured by a nephelometric method (α_2-macroglobulin antiserum, Ref SAM/15; Dade Behring, Marburg, Germany). The results were adjusted for the dilution applied (four times) and expressed as relative coefficient, calculated as sputum level divided by serum level.

White cell and IL blood measurements

Peripheral venous blood (20 mL) was drawn into adequate tubes from each subject. A white differential cell count on whole blood using automated counter was performed. IL-5 and GM-CSF were measured by doubled-sandwich ELISA.

Statistical analysis

In terms of sample size calculations, the present authors aimed to recruit 18–20 patients with moderate-to-severe asthma exacerbations for each arm of the study. These numbers would be sufficient with respect to the primary outcome if there were an α specification of 0.05, a β specification of 0.2 and at least a 50% difference between the two treatment groups, as described in a previous study [21]. The primary outcome was the relative indices of albumin and α_2-globulin.

Results were expressed as arithmetic mean$\pm$SD or median (interquartile range), depending on their distribution. Repeated-measures ANOVA was used to analyse the effect of time as a within-subject factor and the effect of treatment as the between-subject factor in the model. Dependent variables were PEF, percentage of eosinophils and the relative indices of albumin and α_2-globulin. Previous inhaled treatment was used as covariant. The factors were as follows: 1) within-subjects factor ''effect of time'' (baseline and 2, 6 and 24 h); and 2) between-subjects factors ''effect of treatment'' (prednisone, fluticasone). As there were some differences between groups at baseline (although the differences were nonsignificant), the analyses were repeated, adjusting by the baseline data as covariant. The level of significance was 95%.

RESULTS

Four induced sputum samples suitable for processing were obtained in 39 out of the 45 participants. In total, 20 patients were randomised to the prednisone group and 19 to the fluticasone group. Four cases were excluded because the sputum samples were not suitable for processing (two from each group). Two further cases were excluded because of chest radiograph infiltrates compatible with pneumonia. Table 1 describes anthropometric, spirometry and cytological characteristics of both groups. In total, 24 subjects were receiving previous regular treatment with inhaled steroids, 15 on budesonide (five in the prednisone and 10 in the fluticasone group) and nine on fluticasone (five in the prednisone and four in the fluticasone group). The other 15 cases did not receive regular inhaled steroids (10 in the prednisone and five in the fluticasone group). The trigger was identified as upper airways infection in ~50% of the cases (10 in the prednisone group and nine in the fluticasone group). Other triggers seemed to be due either to allergen exposure or reasons were unidentified. The acute exacerbation started on the same day in only three cases. The majority had had symptoms for $\geqslant$2 days before admission. There was no significant difference at baseline between groups, particularly regarding the eosinophil counts (prednisone group mean$\pm$SD 18$\pm$24% and fluticasone group 13$\pm$20%), the relative index of albumin (mean$\pm$SD 273$\pm$214/43$\pm$3 and 480$\pm$494/43$\pm$3, respectively) or α_2-macroglobulin (mean$\pm$SD 6$\pm$6/2$\pm$1 and 17$\pm$23/2$\pm$1, respectively). However, additional analysis adjusting by baseline values was performed because data between groups differed.

Effect of treatment on symptoms and airflow limitation

The symptom score, mainly in relation to physical activity, showed that both groups started with moderate-to-severe dyspnoea and improved 24 h later (table 2). However, there were no significant differences between groups ($F=0.59$, $p=0.44$; fig. 1).

Airway obstruction was similar between groups at baseline in PEF and FEV_1 (table 2), improving progressively during the first 6 h and decaying slightly after 24 h. There were no significant differences between treatment groups ($F=0.03$, $p=0.89$ for PEF (fig. 2); or $F=0.1.02$, $p=0.32$ for FEV_1 (fig. 3)).

Effect of treatment on sputum and blood eosinophil counts

In sputum, the prednisone group started with higher eosinophil counts, although the difference was not statistically significant. Both groups then improved eosinophil counts over time, but decreased more rapidly and more strongly in the fluticasone group ($F=4.27$, $p=0.036$ after adjusting by baseline

TABLE 1 Anthropometric, spirometry and cytological characteristics of patients in both groups

	Prednisone	Fluticasone	p-value
Subjects n	20	19	
Males n	7	4	
Age yrs	34 (19–68)	39 (20–69)	0.46
IC μg·day^{-1}	10 (502±740)	5 (568±553)	0.28
Symptom score	2.6±0.7	2.5±0.8	0.57
PEF L·min^{-1}	289±99	315±98	0.44 and 0.07
PEF %	54±15	63±16	
FEV$_1$ L	2.09±0.98	2.11±0.74	0.45 and 0.11
FEV$_1$ %	62±20	69±19	
Eosinophils %	18±24	13±20	0.83
Neutrophils %	49±29	56±36	0.67
Macrophages %	28±19	28±27	0.59
Lymphocytes %	2±2	2±2	0.51
Albumin sp/blood	273±214/43±3	480±494/43±3	0.45
α_2-Macro sp/blood	6±6/2±1	17±23/2±1	0.67

Data are presented as n (range), n (mean±SD) or mean±SD, unless otherwise stated. IC: previous treatment with inhaled corticosteroids and mean dose·day^{-1} received; PEF: peak expiratory flow; FEV$_1$: forced expiratory volume in one second; albumin sp/blood: albumin level in sputum (mg·L^{-1})/blood (g·L^{-1}); α_2-macro sp/blood: α_2-macroglobulin in sputum (mg·L^{-1})/blood (g·L^{-1}).

values) than in the prednisone group. This effect, however, was partially lost at 24 h from baseline (fig. 4).

In contrast, prednisone reduced blood eosinophil counts more strongly than fluticasone, although no more rapidly ($F=11.862$, $p=0.0001$ after adjusting by baseline values; fig. 5).

Effect of treatment on plasmatic protein relative indices

Relative indices of plasmatic proteins decreased progressively during the first 24 h with a slight recovery at 24 h. There were no significant differences between treatment groups ($F=0.27$, $p=0.60$ for albumin (fig. 6) and $F=0.16$, $p=0.70$ for α_2-macroglobulin, respectively).

Effect of treatment on blood IL levels

The effect of treatment on blood IL-5 and GM-CSF levels was measured, but many determinations (>50%) could not be analysed because they were below the detection levels of the technique.

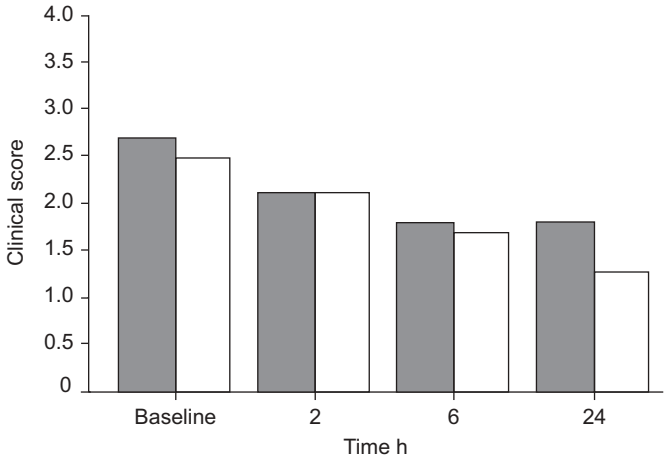

FIGURE 1. Symptom score at baseline and at 2, 6 and 24 h for the prednisone group (■) and fluticasone group (□).

Relationship between protein levels and sputum cells

There was no significant correlation between eosinophil counts and albumin or α_2-macroglobulin ($r=0.11$, $p=0.54$ and $r=0.25$, $p=0.17$, respectively), but there was a significant correlation between albumin or α_2-macroglubulin levels and neutrophil counts ($r=0.62$, $p=0.001$ and $r=0.58$, $p=0.001$, respectively).

DISCUSSION

In the present study, high doses of the inhaled fluticasone were at least as effective as oral prednisone in the treatment of moderate asthma attacks. At 24 h, both treatments improved symptoms, bronchoconstriction, eosinophilic bronchitis and plasma protein leakage. However, fluticasone showed a tendency to act faster than prednisone on bronchoconstriction and plasma protein leakage, although its main effect was the reduction of sputum eosinophilia, which was significant as early as 2 h after inhalation, reaching a maximum at 6 h. Prednisone also reduced sputum eosinophilia, but with effects being noticeable at a mean of 6 h after administration, and the decrease was weaker than that of fluticasone. Conversely, prednisone showed a stronger and statistically significant reduction in blood eosinophilia as compared with fluticasone.

TABLE 2 Absolute values obtained by times and treatment groups

	Prednisone				Fluticasone			
	Baseline	2 h	6 h	24 h	Baseline	2 h	6 h	24 h
Symptom score	2.68±0.75	2.11±1.15	1.79±1.08	1.79±1.03	2.47±0.84	2.11±0.81	1.68±1.00	1.26±1.10
PEF L·min^{-1}	289±99	351±91	371±108	319±121	315±98	361±108	347±112	332±114
FEV$_1$ % r.v.	61.6±19.8	71.9±18.9	74.0±18.7	64.7±21.5	69.1±18.8	78.9±20.1	76.8±20.6	71.6±20.1
Eosinophils %	18.2±23.8	16.6±20.7	12.2±15.7	13.0±17.2	13.3±19.8	7.3±8.4	4.8±7.6	6.4±14.0
Albumin$^{\#}$ mg·L^{-1}	273±214	298±238	229±249	263±302	480±494	302±258	268±255	294±324
α_2-Macroglobulin$^{\#}$ mg·L^{-1}	5.8±6.1	9.0±10.1	7.3±8.1	7.3±12.2	17.5±23.4	11.5±9.5	11.3±12.9	16.4±24.0

Data are presented as mean±SD. PEF: peak expiratory flow; FEV$_1$: forced expiratory volume in one second; % r.v.: % of reference value. $^{\#}$: level in sputum.

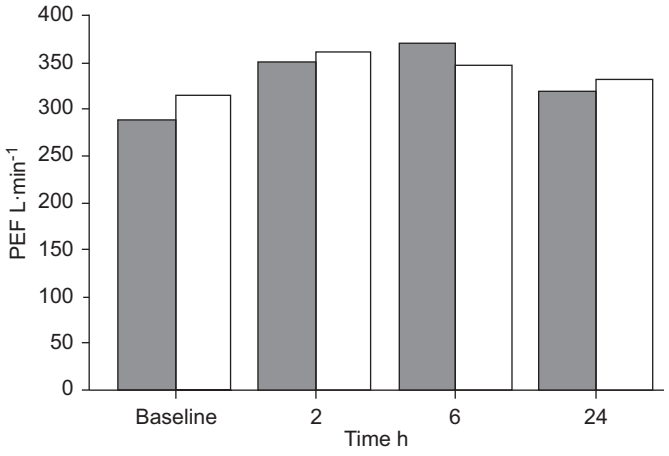

FIGURE 2. Peak expiratory flow (PEF) at baseline and at 2, 6 and 24 h for the prednisone group (■) and fluticasone group (□).

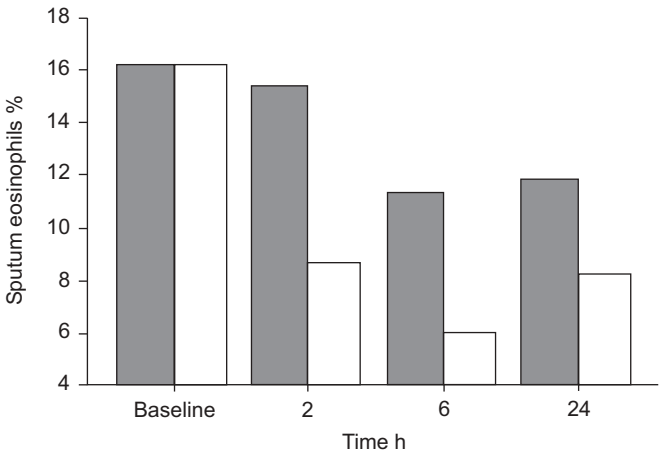

FIGURE 4. Estimated adjusted values of sputum eosinophil counts at baseline and at 2, 6 and 24 h for the prednisone group (■) and fluticasone group (□).

The usefulness of inhaled steroids in the emergency room is unclear. The recent Cochrane review of this topic [22] stated that inhaled steroids reduce readmission rates in patients with acute asthma. Nevertheless, it is unclear whether inhaled corticosteroids used in addition to systemic corticosteroids provide any benefit. The Cochrane review [22] did not find sufficient evidence that inhaled corticosteroids provide clinically relevant changes in pulmonary function or clinical scores in acute asthma. Moreover, there is insufficient evidence that inhaled corticosteroids alone are as effective as systemic steroids. Further research was thus recommended to clarify this point. Some authors have suggested that inhaled steroids seem to act faster than oral steroids on symptoms and airway obstruction [9–14], although there is considerable controversy on this point in children [23, 24]. In the present study, both prednisone and high doses of fluticasone reduced airway obstruction and improved symptoms. Notwithstanding, the present study was not designed to answer this question and sufficient statistical power was not found to confirm this point. The present results, however, clearly showed that both treatments reduced airway inflammation and plasma protein exudation, although in a different way.

In patients with stable asthma, many authors have established that there is an increased plasma exudation in the airways. This correlates with bronchial hyperreactivity to histamine and decreases after corticosteroid therapy. A few other groups have investigated protein plasma leakage during asthma exacerbation [25–27] and have shown that albumin leakage is highly increased as compared with that in stable asthmatics. To the present authors' knowledge, the present study is the first to demonstrate the efficacy of oral and inhaled steroid treatments in improving plasma protein leakage within the first 24 h of asthma exacerbation. PIZZICHINI *et al.* [28] showed that oral steroids in severe exacerbations of asthma decreased fibrinogen levels at day 7. In the present study, oral, but also inhaled, steroids began to decrease albumin and α_2-macroglobulin as early as 2 h after treatment. The reason for this discrepancy could lie in the different plasma proteins tested in each study, but whatever the case, the clinical relevance of this plasma leakage in the asthma exacerbation remains unknown. In a

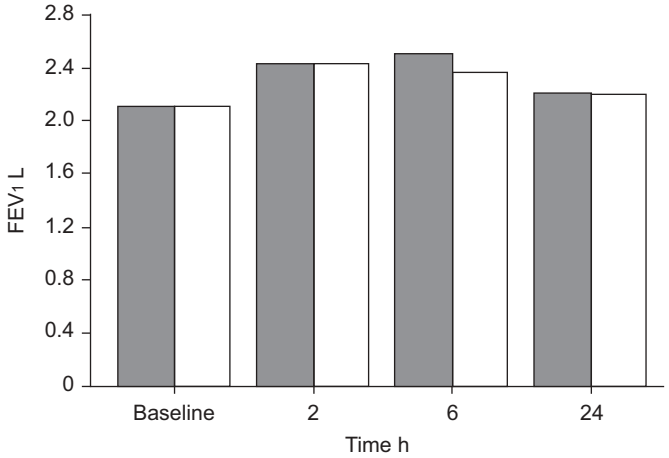

FIGURE 3. Estimated adjusted values of forced expiratory volume in one second (FEV_1) at baseline and at 2, 6 and 24 h for the prednisone group (■) and fluticasone group (□).

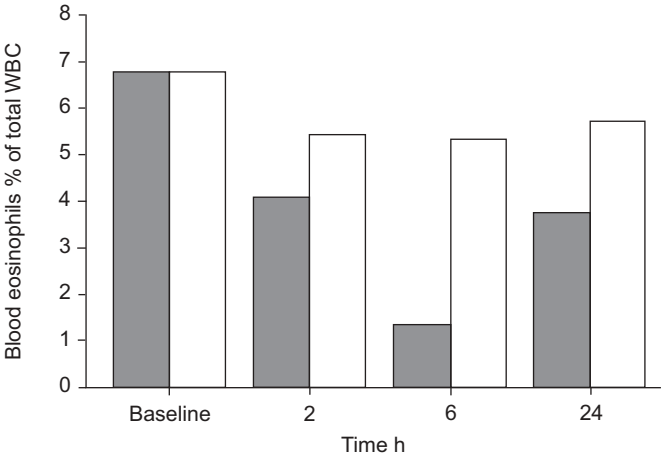

FIGURE 5. Blood eosinophil counts of white blood cells (WBC) at baseline and at 2, 6 and 24 h for the prednisone group (■) and fluticasone group (□).

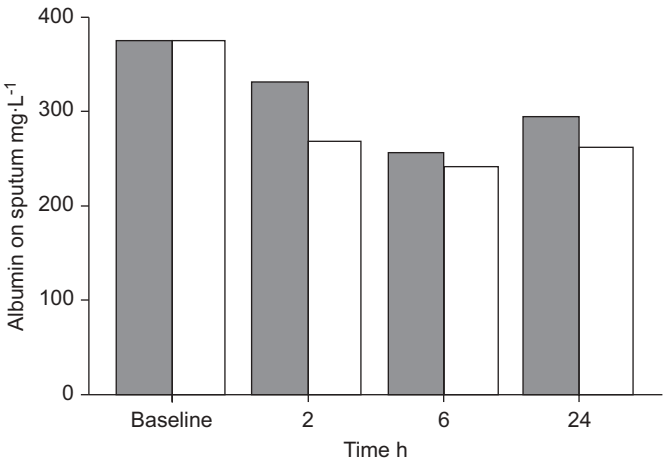

FIGURE 6. Estimated adjusted levels of albumin in sputum at baseline and at 2, 6 and 24 h for the prednisone group (■) and fluticasone group (□).

previous study [21], the present authors found that plasma leakage in acute asthma was weakly related to the degree of airway obstruction, suggesting that this effect may not account for the final severity of the exacerbation. Despite the fact that some relationship clearly exists, the importance of this finding should be further determined, since in the current study, a significant relationship between FEV1 and the relative index of albumin in the acute phase was found.

Many studies have shown a rapid, strong effect of inhaled steroids on bronchial eosinophilic inflammation, but such studies were generally performed on subjects with stable asthma or induced exacerbations. Very few data are available on naturally occurring exacerbations, probably because of the difficulty in obtaining bronchial secretions in the acute phase. The main outcome measure studied by many groups is, therefore, the improvement in airway obstruction [2], which is not a direct inflammatory marker. Data concerning the effect of inhaled steroids on sputum eosinophilia are not available in acute asthma. However, exacerbations induced by stepping down the inhaled corticosteroid therapy confirm this evidence and it can be assumed that corticosteroids should reduce blood and sputum eosinophilia in acute asthma. At least three studies [28–30] have reported that sputum eosinophilia improved after treatment with oral steroids. PIZZICHINI *et al.* [28] described an improvement in sputum eosinophilia and eosinophil cationic protein levels at 24 h. This was supported by the present authors' findings.

If inhaled steroids can act faster than systemic steroids, as suggested from the present results, the question is how this occurs. MCFADDEN [15] suggested that inhaled steroids may improve exacerbations faster by reducing bronchial oedema. The present data do not support this possibility because both treatments improved plasma leakage in a similar way. The explanation suggested from the present findings is a faster anti-inflammatory effect of inhaled steroids, probably due to a reduction in bronchial eosinophil survival.

The main limitation of the present study is probably related to the high dose of fluticasone used, which is possibly not comparable with the doses used by others. In a very recent paper, RODRIGO [14] used 3,000 $\mu g \cdot h^{-1}$ during 3 h with excellent results. However, the dose used in the present study (4,000 $\mu g \cdot day^{-1}$) is twice the fluticasone dose accepted for self-treatment of asthma attacks according to some guidelines [31]. Differences in the dose used may be important, because published studies that obtained better results [8, 10, 12–14] tended to use higher doses of inhaled steroids and lower oral steroid doses than those studies that found no benefits [11, 24, 32]. Therefore, it could be speculated that the dose of inhaled steroids needed to provide a benefit in acute asthma should be considerably higher than that used in stable asthma. The timing of the steroid administration may also be relevant. The present authors observed that the effect of both treatments was partially lost at 24 h, suggesting that treatment should perhaps be administered twice daily to maintain efficacy.

In conclusion, high-dose inhaled fluticasone appears to have a faster and stronger effect in reducing airway inflammation than oral prednisone and to be at least as effective as prednisone in reducing plasma exudation, bronchial obstruction and symptoms in moderate exacerbations of asthma. The early combination of inhaled steroid to oral prednisone could therefore be more effective than prednisone alone in acute asthma. Further studies are needed to investigate whether lower doses of inhaled fluticasone are as effective as the 4,000 $\mu g \cdot day^{-1}$ dose, as well as the comparison of this association *versus* oral prednisone alone.

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