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Anti-inflammatory effects of high-dose inhaled fluticasone versush oral prednisone in moderate asthma exacerbations. A randomized clinical trial.

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ABSTRACT

STUDY OBJECTIVE: To study the kinetics of high doses of inhaled steroid fluticasone (F) in comparison with oral steroid prednisone (P) on plasma protein leakage and bronchial eosinophilia in adults with moderate asthma exacerbations.

DESIGN: A randomized, double-blind, placebo-controlled prospective trial.

SETTING, PATIENTS, INTERVENTIONS: Forty-five patients treated at the emergency department for moderate asthma exacerbations were recruited and 39 were assigned to receive either F and placebo of P (19 patients), or P and placebo of F (20 patients). Medication was delivered to all patients through a metered-dose inhaler and spacer (16 puffs; 4,000 micrograms/day or placebo) plus one pill (prednisone 30mg/day or placebo). Spirometry and induced sputum (IS) for differential cell counts (DCC), albumin and alpha2-macroglobulin levels and blood eosinophils, IL-5 and GM-CSF levels were obtained before treatment (t0) and at 2, 6 and 24 hours. .

RESULTS: Symptoms clearly improved after 24 hours in both groups. No differences were seen between groups in PEF or FEV1 which improved progressively but decayed slightly after 24 hours. Eosinophil counts in sputum also improved over time in both groups. The effect was faster with F than with P ($p=0.036$ adjusting by baseline) but was partially lost at 24 hours. However, plasma proteins in sputum and eosinophil count in blood both decreased until 24 hours with no significant differences between groups. There was no correlation between eosinophil counts and plasmatic protein levels.

CONCLUSIONS: Both treatments improved symptoms, airway obstruction and inflammation, and plasma protein leakage at 24 hours. P reduced blood eosinophil counts while F reduced airway eosinophil counts, suggesting F's anti-inflammatory performance is exerted locally.

Keywords: fluticasone, prednisone, eosinophil, plasma exudation, sputum induction, albumin, alpha2 macroglobulin

Introduction

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 et al[2] and other authors[3] have reported that parenteral corticosteroids (IV) have no bronchodilator effect within the first few hours of an acute asthma exacerbation. Despite a systemic corticosteroid effect does occur within the first 6-8 hours after administration, this treatment probably require some hours to effectively improve airflow obstruction, and these 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].

Inhaled corticosteroids, on the other hand, are recommended to control chronic asthma and reduce the need for oral prednisone[1,5,6,7]. In acute asthma, they are only recommended for asthma treatment after emergency room discharge because they 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 suppose 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 would have a faster effect than systemic corticosteroids. McFadden[15], in the previously mentioned editorial, suggested that inhaled steroids would reduce edema and plasma exudation quicker than oral steroids. However, a more complex mechanism cannot be discarded because early changes (within 2-3 hours) 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 randomized clinical trial was performed to study the mechanism through which inhaled steroids could act faster than oral steroids in acute asthma. We aimed to compare the effect of high doses of inhaled fluticasone with oral prednisone on airway plasma protein exudation. Relative indices of albumin and alpha2-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 IL-5 and GM-CSF in peripheral blood.

Material and methods.

Subjects.

All participants were recruited consecutively from among patients with acute asthma at the Emergency Department. The study was conformed to the Helsinki Declaration and was approved by the Hospital's ethic and clinical assays committee (CEIC). All participants gave written informed consent to participate in the study. Inclusion criteria were: patients with acute asthma patients aged between 16-65 years with no oral or IV steroid treatment in the last 4 weeks. All had been diagnosed of asthma from current or previous history of chest tightness, wheezing, dyspnea or cough in association with variable airflow limitation. Variable airflow limitation was documented from either methacholine airway hyperresponsiveness (PC_{20} < 8 mg/ml) if FEV_1 was ≥ 70% of predicted value, or 12% increases in FEV_1 after inhaled salbutamol 200 μg if FEV_1 was < 70%. 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: smokers or ex-smokers within the last year; treatment with oral or IV corticosteroids, cromoglycate, nedocromil, theophylline, allergen-desensitization injections, and leukotriene antagonists at any time in the 4 weeks prior to the study. Long-acting beta-agonists were

permitted, but participants on this treatment were balanced between the two groups (block randomization). Subjects with life-threatening exacerbations of asthma at baseline or any other serious medical conditions were excluded; e.g. heart disease, gastrointestinal, 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, oxyhemoglobin saturation. Additionally, peripheral blood and sputum were collected. After initial treatment with nebulized salbutamol (1 cc in 3 cc of isotonic saline for 15 min with a Hudson jet nebulizer) and oxygen, patients were re-evaluated as suitable or not for the study. They were then randomly treated with: A) a 30 mg/day prednisone tablet + 16 inhalations of fluticasone-like placebo, or B) a prednisone-like placebo tablet + 16 inhalations (4000 μg/day) of fluticasone 250 μg.

Patients' allocation to treatment A or B was concealed by following computerised randomisation, codified by the Hospital Pharmacy Department who also packed and blinded all medications. Fluticasone and its placebo were kindly donated by GlaxoSmithKline. 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 hours, as of which time patients were instructed to continue taking 1 tablet each morning and 8 inhalations twice a day for four days. Measurements were made at baseline and at 2, 6 and 24 hours. At each proposed time, asthma symptoms (cough, wheeze, chest tightness and breathlessness) were

recorded. Measurements were performed in the following order: symptoms score, PEF, peripheral blood withdrawal and 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 always supervised by investigators. The following safety protocol was applied: participants were followed in the respiratory day-care setting for 6 hours and then discharged if symptoms improved and PEF increased 30% or more above baseline value. If the patients did not improve, they were kept in observation for 24 hours. During observation, it had been previously established that patients would be shifted to the other arm in case of worsening (decrease of PEF over 20% of baseline or clinical deterioration judged by the responsible physician). No other treatments were allowed other than nebulized salbutamol every 4 hours and oxygen on demand. For safety reasons, patients were visited at one and three weeks after exacerbation. They were asked about treatment compliance and their home diary in which they recorded PEF and symptoms was reviewed.

Procedures.

Patient characteristics, physical examination. Sex, age, and 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 oxyhemoglobin saturation. Symptom severity was recorded on a 4 point scale (0 not at all; 1 mild, but I can continue work; 2 moderate intensity, I need to stop at least for a while; 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 ten minutes after salbutamol nebulization. Subjects were asked to blow their nose, rinse their mouth and swallow the water to minimize 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 (4ºC) and processed as soon as possible as described by Pizzichini et al[20]. Total cell count was obtained in a modified Neubauer hemocytometer. The cell viability was determined by the trypan blue exclusion method. The total and absolute number of cells per milligram of processed sputum were calculated. Four hundred non-squamous cells were counted in Wright-stained slides and the results expressed as a percentage and absolute number of the total non-squamous count.

Serum and sputum protein measurements. Albumin in sputum (mg/L) was measured by an immunoturbidimetric assay (Albumina Tina-quant© Ref 11875400, Roche/Hitachi, Roche Diagnostics GmbH, Mannheim, Germany) and in serum (g/L) by a colorimetric assay (ALB plus Ref 1929640, Roche Diagnostics GmbH, Mannheim, Germany). Alpha2-macroglobulin in sputum (mg/L) and serum (g/L) was measured by a nephelometric method (alpha-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 interleukin 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.

Sample size calculations: We aimed to recruit 18 to 20 patients with moderate to severe asthma exacerbations for each arm. These numbers would be sufficient respect to the primary outcome if there were an alpha specification of 0.05, a ß 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 alpha2-globulin.

Results were expressed as arithmetic mean (standard deviation) or median (interquartile range) depending on their distribution. Repeated measures analysis of variance (ANOVA) was used to analyze the effect of time as within-subject factor and the effect of treatment as between-subject factor in the model. Dependent variables were PEF, percentage of eosinophils and the relative indices of albumin and alpha2-globulin. Previous inhaled treatment was used as covariant. The factors were: within-subjects factor, "effect of time" (baseline, 2 hours, 6 hours and 24 hours) and between-subjects factor, "effect of treatment" (prednisone, fluticasone). Although there was no statistical significance between groups at baseline, there were some differences, so analyses were repeated adjusting by baseline data as covariant. Significance level was 95%.

Results

Four processable induced sputum samples were obtained in 39 of the 45 participants. Twenty were randomized to the prednisone group and 19 to the fluticasone group. Four cases were excluded as sputum samples were not suitable for processing (2 from each group). Two further cases were excluded because of chest X-ray infiltrates compatible with pneumonia. Table I describes anthropometric, spirometry and cytological characteristics of both groups. Twenty-four were on previous regular treatment with inhaled steroids, 15 on budesonide (5 in the prednisone and 10 in the fluticasone group) and 9 on fluticasone (5 in the prednisone and 4 in the fluticasone group). The

other 15 cases did not receive regular inhaled steroids (10 in the prednisone and 5 in the fluticasone group). The trigger was identified as upper airways infection in around 50% of the cases (10 in the prednisone group and 9 in the fluticasone group). The others seemed to be due to allergen exposure or unidentified. The acute exacerbation started on the same day only in three cases. The majority had symptoms for two or more days before admission. There was no significant difference at baseline between groups, particularly regarding the eosinophil counts (prednisone group 18 (24)% and fluticasone group 13 (20)%), the relative index of albumin (273 (214)/43(3) and 480(494)/ 43(3), respectively) or alpha2-macroglobulin (6(6)/2(1) and 17(23)/2(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 dyspnea and improved 24 hours later (see table II). However, there were no significant differences between groups (F=0.59, p=0.44; Figure 1).

Airway obstruction was similar between groups at baseline in PEF and FEV1 (table II), improving progressively during the first six hours and slightly decaying after 24 hours. There were no significant differences between treatment groups (F=0.03, p=0.89 and figure 2 for FEM or F=0.1.02, p=0.32 and figure 3 for FEV1).

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 faster and stronger in the fluticasone group (F=4.27, p=0.036 after adjusting by baseline values)

than in the prednisone group. This effect however was partially lost at 24 hours from baseline (figure 4).

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

Effect of treatment on plasmatic protein relative indices

Relative indices of plasmatic proteins decreased progressively during the first 24 hours with a slight recovery at 24 hours. There were no significant differences between treatment groups (F=0.27, p=0.60 and figure 6 for albumin or F=0.16, p=0.70 for alpha2macroglobulin, respectively).

Effect of treatment on blood interleukin levels.

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

Relationship between protein levels and sputum cells.

There was no significant correlation between eosinophil counts and albumin or alpha2 macroglobulin (r=0.11 p=0.54 and r=0.25 p=0.17) but there was a significant correlation between albumin or alpha2-macroglubulin levels and neutrophil counts (r=0.62 p=0.001 and r=0.58 p=0.001).

Discussion.

In the present study, high doses of the inhaled fluticasone were at least as effective as oral prednisone to treat moderate asthma attacks. At 24 hours, 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 that was significant as soon as two hours after inhalation, reaching a maximum at 6 hours. Prednisone also reduced sputum eosinophilia but starting at a mean of 6 hours after administration, and the decrease was weaker that fluticasone. On the other hand, prednisone showed a stronger and statistically significant reduction in blood eosinophilia as compared to fluticasone.

The usefulness of inhaled steroids in the emergency room is unclear. The recent Cochrane review of this topic[22] stated that inhaled steroids reduce re-admission rates in patients with acute asthma. Nevertheless, it is unclear whether inhaled corticosteroids used in addition to systemic corticosteroids provide any benefit. This review 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[24-25]. In the present study, both prednisone and high doses of fluticasone reduced airway obstruction and improved symptoms. Notwithstanding, this study was not designed to answer this question and we did not find sufficient statistical power to confirm this point. Our 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 others have investigated protein plasma leakage during asthma exacerbation[26-28] and shown that albumin leakage is highly increased as compared to that in stable

asthmatics. To our knowledge, this is the first paper to demonstrate the efficacy of oral and inhaled steroid treatments in improving plasma protein leakage within the first 24 hours of asthma exacerbation. Pizzichini et al[29] showed that oral steroids in severe exacerbations of asthma decreased fibrinogen levels at day seven. In our study, oral but also inhaled steroids began to decrease albumin and alpha2-macroglobulin as early as two hours 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 on the asthma exacerbation remains unknown. In a previous study we found that plasma leakage induced by inhaled adenosine 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 we found a significant relationship between FEV1 and the relative index of albumin in the acute phase.

Many papers have shown a fast, strong effect of inhaled steroids on bronchial eosinophilic inflammation but such studies were generally performed on stable asthma or induced exacerbations. Very few data are available on natural 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 we can assume that corticosteroids should reduce blood and sputum eosinophilia in acute asthma. At least three studies[29-31] have reported that sputum eosinophilia improved after treatment with oral steroids. Pizzichini et al described an improvement in sputum eosinopilia and ECP levels at 24 hours, and this was supported by our findings.

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

The main limitation of our study is probably related to the high dose of fluticasone used, possibly not comparable with the doses used by others. In a very recent paper, Dr. Rodrigo[14] used 3000 microg/hour during 3 hours with excellent results. However, our 4000 microg/day is twice the fluticasone dose accepted for self-treatment of asthma attacks according to some guidelines. Differences in the dose used may be important because published papers which obtained better results tended to use higher doses of inhaled steroids and lower oral steroid doses[8,10,12-14] than those studies that found no benefits[11,23,25]. We could therefore speculate that the dose of inhaled steroids needed to provide a benefit in acute asthma should be considerably higher that used in stable asthma. The timing of the steroid administration may also be relevant. We observed the effect of both treatments was partially lost at 24 hours, suggesting that they 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 are

as effective as 4000 mcg/day of inhaled fluticasone as well as the comparison of this association versus oral prednisone alone.

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Table I Legend

Table I. Anthropometric, spirometry and cytological characteristics of patients in both groups. Data are in means (interval or standard deviation). N: number of cases, IC: previous treatment with inhaled corticosteroids and mean dose/day received, PEF: peak expiratory flow, Albumin sp/blood: albumin level in sputum (mg/L) / blood (g/L), A2macro sp/blood: alpha2 macroglobulin in sputum (mg/L) / blood (g/L).

Table I

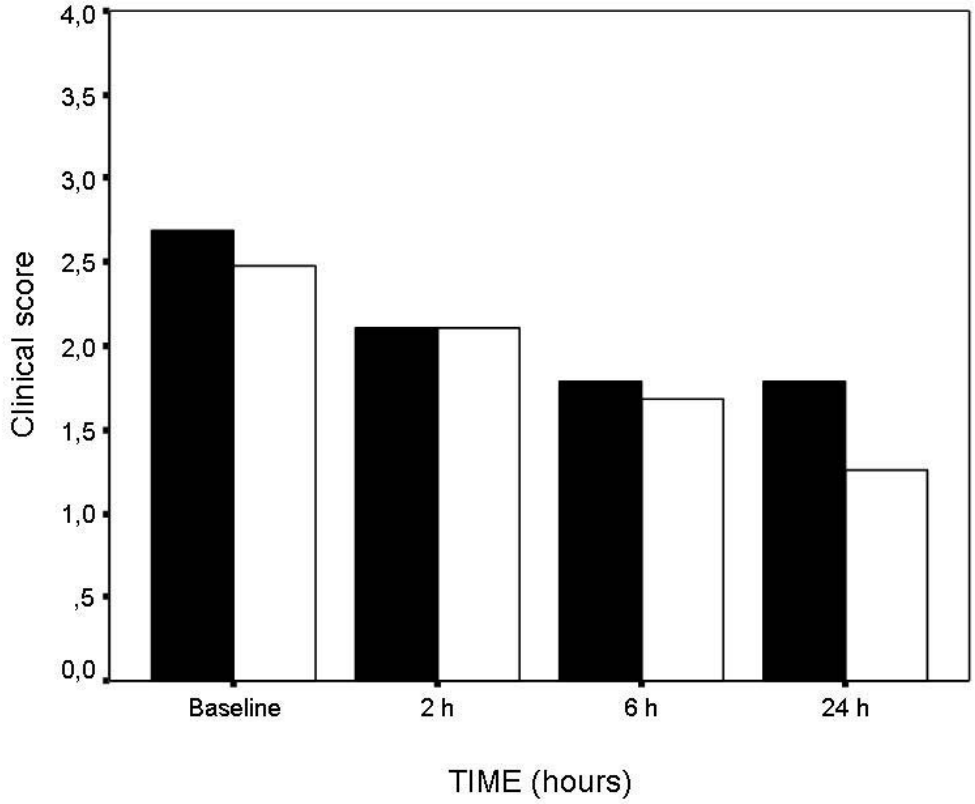
	Prednisone	Fluticasone	p value
N, males	20; 7	19, 4	
Age (years)	34 (19-68)	39 (20-69)	p=0.46
No. IC (mcg/day)	10, 502 (740)	5, 568 (553)	p=0.28
Symptom score	2.6 (0.7)	2.5 (0.8)	p=0.57
PEF Lpm and (%)	289 (99) Lpm 54 (15) %	315 (98) 63 (16) %	p=0.44 and p=0.07
FEV1 L and (%)	2.09 (0.98) 62 (20)%	2.11 (0.74) 69 (19)%	p=0.45 and p=0.11
Eosinophils (%)	18 (24)%	13 (20)%	p=0.83
Neutrophils (%)	49 (29)%	56 (36)%	p=0.67
Macrophages (%)	28 (19)%	28 (27)%	p=0.59
Lymphocytes (%)	2 (2)%	2 (2)	p=0.51
Albumin sp/blood	273 (214)/43(3)	480(494)/ 43(3)	p=0.45
A2macro sp/blood	6(6)/2(1)	17(23)/2(1)	p=0.67

Table II Legend

Table II. Absolute values obtained by times and treatment groups. Data are in means (standard deviation). PEF: peak expiratory flow, Albumin: albumin level in sputum (mg/L), A2macro: alpha2 macroglobulin in sputum (mg/L).

Table II

Treatment	**Prednisone**				**Fluticasone**			
Time (hours)	**Baseline**	**2**	**6**	**24**	**Baseline**	**2**	**6**	**24**
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 (Lpm)	289 (99)	351 (91)	371 (108)	319 (121)	315 (98)	361 (108)	347 (112)	332 (114)
FEV1 (% 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)	273 (214)	298 (238)	229 (249)	263 (302)	480 (494)	302 (258)	268 (255)	294 (324)
A2macro (mg/L)	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)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Clinical score
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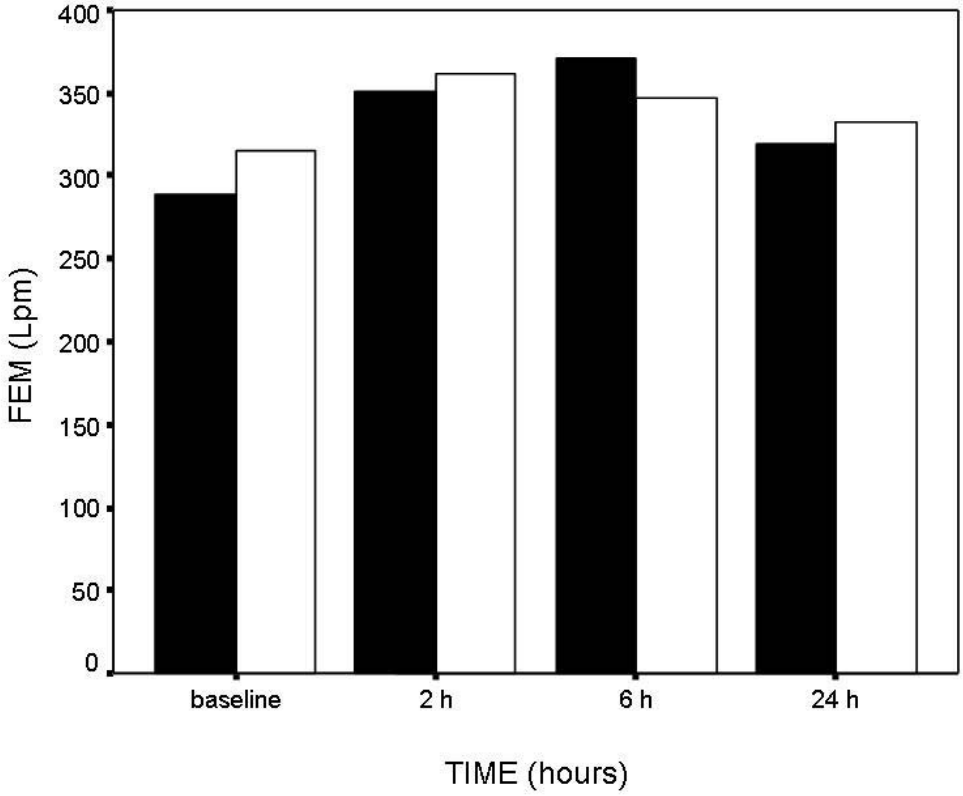
24 h
TIME (hours)

Fig 1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TIME (hours)

Fig 2

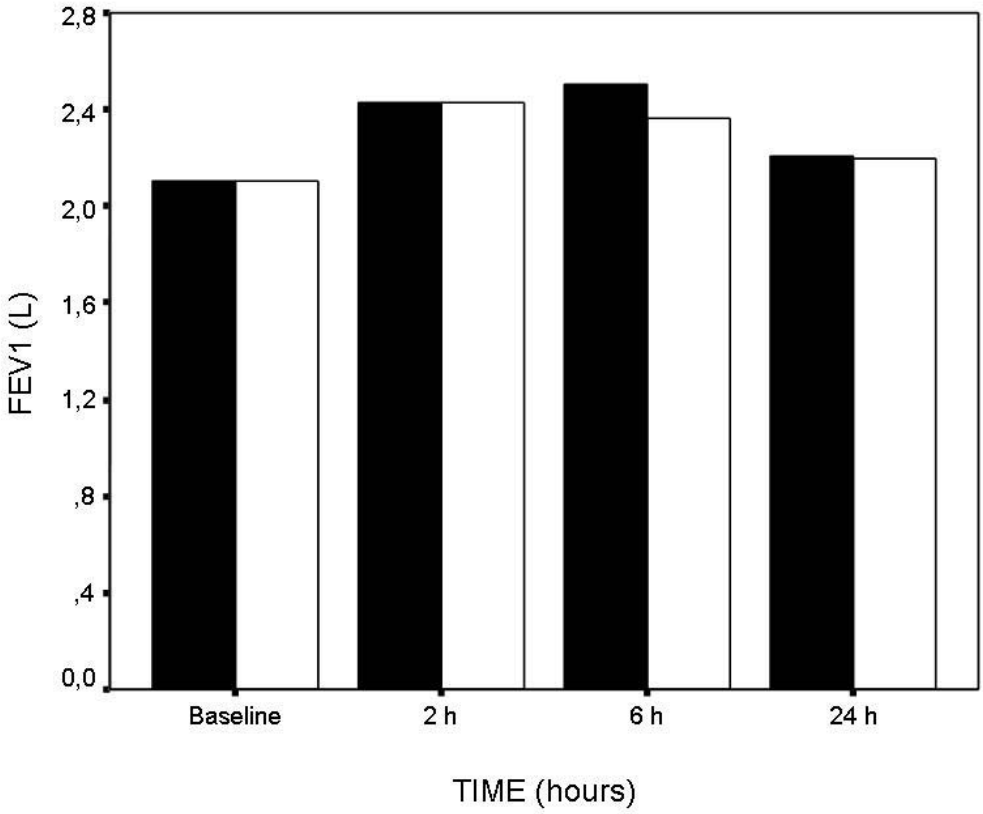

Fig 3

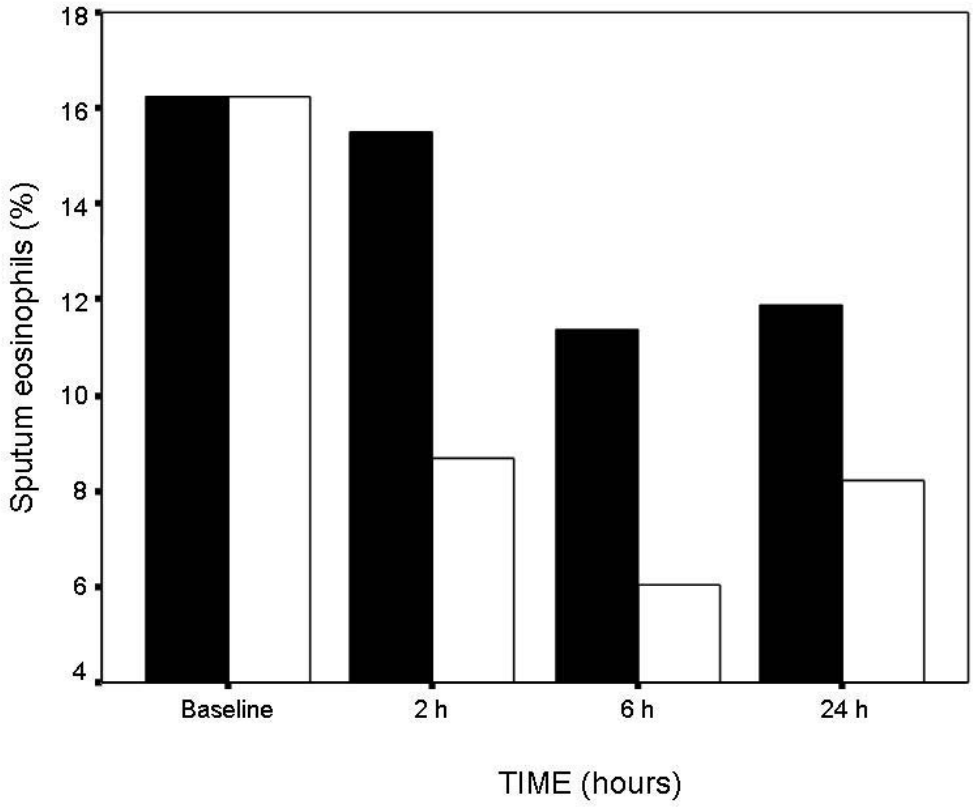
18
16
14
12
10
8
6
4
Sputum eosinophils (%)
Baseline
2 h
6 h
24 h
TIME (hours)

Fig 4

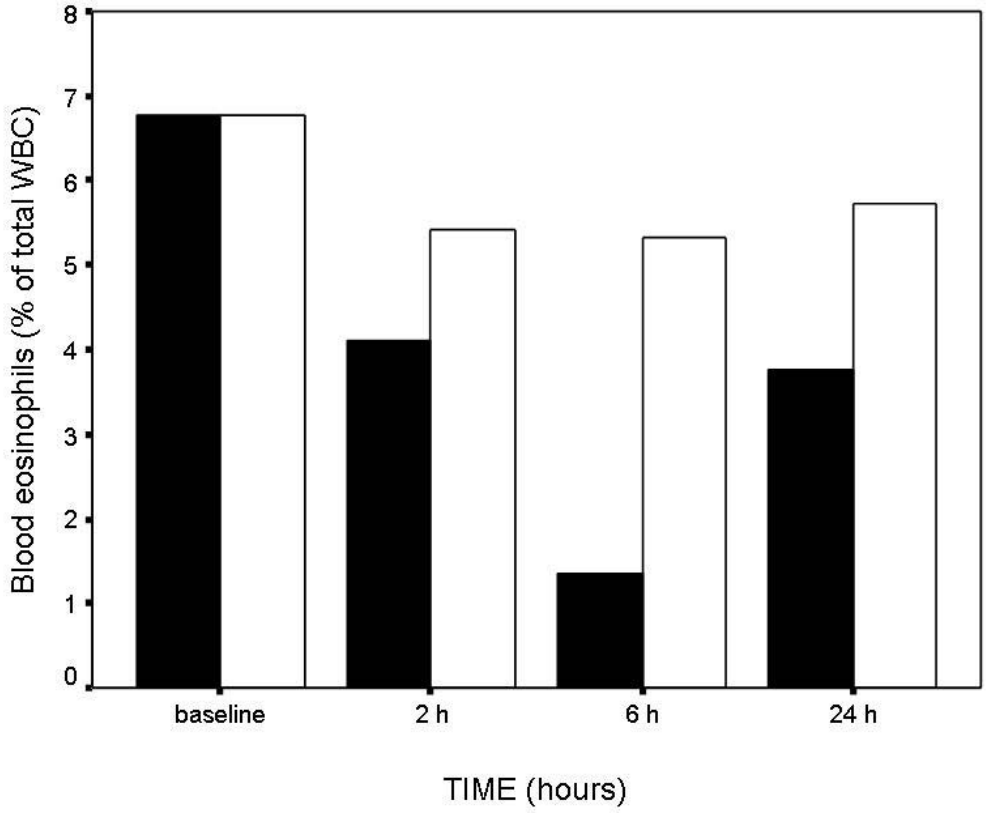
Blood eosinophils (% of total WBC)
8
7
6
5
4
3
2
1
0
baseline
2 h
6 h
24 h
TIME (hours)

Fig 5

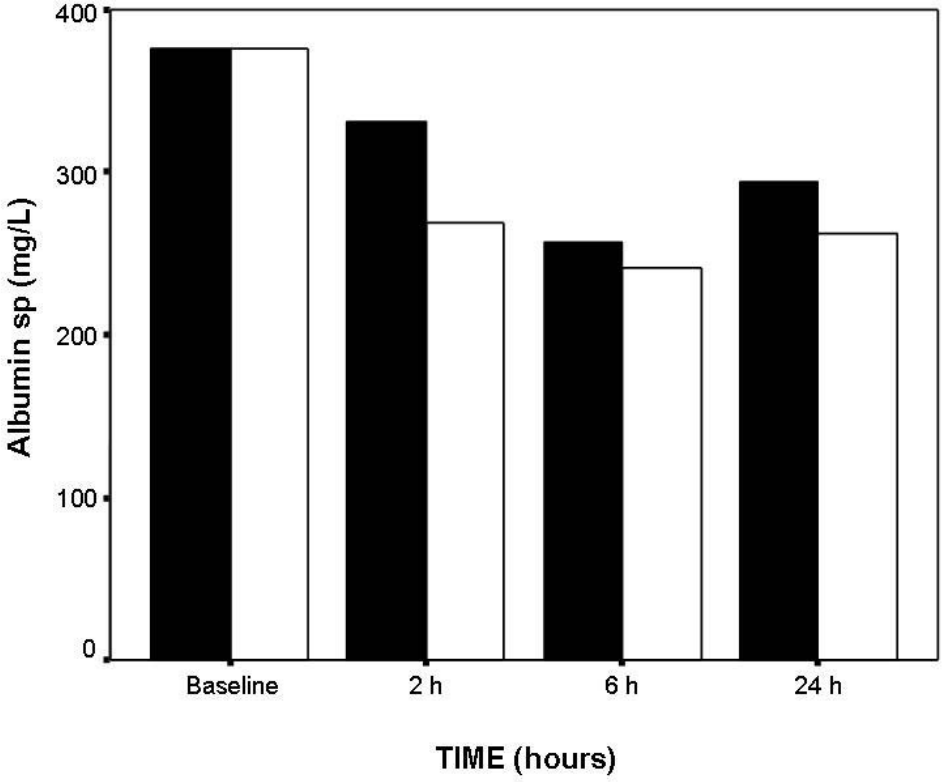

Fig 6