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Corticosteroid pharmacokinetic abnormalities in overweight and obese corticosteroid resistant asthmatics

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To the Editor:

According to the National Asthma Education and Prevention Program Expert Panel Report asthma guidelines corticosteroids are recommended for management of persistent asthma and treatment of airway inflammation¹. However, multiple NIH clinical trials have reported that asthmatics vary greatly in their response to corticosteroid therapy^{2, 3}. Patients that are insensitive to corticosteroid therapy or corticosteroid resistant (CR) present a significant management problem, as conventional treatment strategies are not effective. CR asthma is associated with persistent airway inflammation. These patients account for much of the morbidity and cost of the disease due to increased health care utilization, including frequent hospitalizations⁴.

Abnormal corticosteroid pharmacokinetics (PK) may contribute to suboptimal response to treatment in CR asthmatics. The effect of obesity on the disposition of drugs remains an important issue for clinicians as the incidence of obesity continues to increase world wide⁵. Selective changes in the drug volume of distribution related to drug physiochemical properties, the degree of plasma protein binding and tissue blood flow in obesity have been noted⁵. As well, alterations in drug clearance controlled by hepatic and renal physiology in obesity have been documented⁵. In obese individuals circulating serum cortisol

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concentrations were found to be in the normal or lower than normal range⁶. However, dysregulated 11 β -hydrosteroid dehydrogenase type 1 (11 β -HSD1) activity has been implicated in obesity⁷. 11 β -HSD1 acts as an oxoreductase converting inactive cortisone to active cortisol. Studies report decreased hepatic 11 β -HSD1 expression and activity in obese individuals. At the same time, increased 11 β -HSD1 in adipose tissue has been shown. Following weight loss after bariatric surgery hepatic 11 β -HSD1 activity increases, and adipose tissue 11 β -HSD1 activity decreases⁷. Urinary cortisol metabolites are increased in obese subjects, supporting fast clearance. Following weight loss, urinary glucocorticoid metabolites have been reported to be reduced^{8, 9}. Excessive adipose tissue production of cortisol in obesity supports development of metabolic syndrome¹⁰. How obesity influences PK of corticosteroids used for asthma treatment is unclear. The goal of this study was to assess oral prednisone absorption and clearance in CR asthma patients. We also aimed to assess prevalence of PK abnormalities in obese versus lean CR asthma patients and how they relate to airway inflammation in the lung.

Fifty CR asthmatics with a baseline FEV₁ $\geq$ 85% predicted, a β_2 -adrenergic response of $\geq$ 12% of baseline FEV₁, and a methacholine PC₂₀ value of less than 10mg/ml were recruited. The lower limit for methacholine challenge was a baseline FEV₁ $\geq$ 55% predicted. Corticosteroid response of asthmatics was classified based on changes in their prebronchodilator morning FEV₁ % predicted after a one week course of 40mg/day oral prednisone. Asthmatics were defined as CR if they had less than 10% improvement in FEV₁. Informed consent was obtained from all patients before enrollment in this study. The study was approved by the Institutional Review Board at National Jewish Health, Denver, Colorado. Body mass index (BMI) was calculated as kg/m² with subjects categorized as lean (BMI <25 kg/m²), overweight (BMI 25-30 kg/m²) and obese (BMI $\geq$ 30 kg/m²). Body surface area (BSA), m², was calculated by DuBois & DuBois formula [$0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$]. The Juniper Asthma Control Questionnaire (ACQ-7) (<http://www.qoltech.co.uk/acq.html>) was used to assess asthma control.

Prior to oral prednisone burst, all patients underwent fiberoptic bronchoscopies with the collection of bronchoalveolar lavage (BAL) performed according to the guidelines of the American Thoracic Society. Previous gene microarray study by our research group reported classical macrophage activation in BAL samples of CR asthmatics, with tumor necrosis factor alpha (TNF α) being one of the most elevated biomarkers¹¹. We therefore chose to evaluate TNF α mRNA expression in BAL samples of corticosteroid resistant asthmatics that were examined for steroid pharmacokinetics as a marker of airway inflammation. BAL cell RNA was extracted (Qiagen), and analyzed by real-time PCR for TNF α expression as previously described¹¹. Quantities of TNF α in BAL samples were normalized to the corresponding levels of the housekeeping gene (18s RNA).

One day after the last dose of oral prednisone patients underwent a modified prednisone PK study. Patients' blood samples were obtained at baseline, 2h and 6h post oral prednisone administration (40mg/1.73m² of body surface area, with a maximum of 50mg) and analyzed using high performance liquid chromatography for plasma prednisolone concentrations. Upon oral administration prednisone gets absorbed, followed by conversion into an active form, prednisolone, by 11 β -HSD1 in the liver. Plasma prednisolone concentration at 2h was

used as a surrogate of prednisone absorption. Prednisone absorption was considered impaired if the 2h plasma prednisolone level was <400 ng/ml. Prednisolone clearance was calculated based on the 6h post dose concentration using the following: $\log \text{clearance} = 2.66 + [6\text{h post dose concentration}] [-0.00167]$. Prednisolone clearance >255ml/min/1.73m² was considered rapid, while prednisone clearance <147ml/min/1.73m² was considered slow¹². Prednisone absorption and prednisolone clearance were compared using the reference values from patients with severe asthma collected in our institution.

Patients' clinical variables were analyzed using descriptive statistics. ANOVA was used to for multiple group comparison. The Graph Pad Prism, version 5.0 (San Diego, CA) was used for all statistical calculations. P values ≤ 0.05 were considered significant. Linear regression analysis was performed to examine relationship between plasma prednisolone concentrations, BAL TNFα levels and BMI.

After a one week course of oral prednisone there was no significant improvement in lung function of CR asthma patients recruited, however, all patients demonstrated bronchodilator reversibility (**Table 1**). Bronchodilator reversibility was a requirement for the study to confirm that patients had asthma. Based on oral prednisone PK data there were the following responses: 54% of patients had normal prednisone absorption and normal prednisolone clearance, 20% showed impaired prednisone absorption only, 12% had impaired prednisone absorption and rapid prednisolone clearance, and 14% had slow prednisolone clearance (**Table 1, Fig. E1**).

We noted a relationship between patients' BMI and prednisone PK (**Table E1**). The prevalence of patients with abnormal prednisone absorption/fast prednisolone clearance was significantly greater among patients with BMI>25 kg/m² (overweight/obese patients) than among lean patients (BMI<25 kg/m²) (21.43% compared to 0%, p=0.0284, Fisher's exact test). Patients with abnormal prednisone absorption/fast prednisolone clearance had a trend for the highest mean BMI and BSA among all PK groups (**Table 1**). Also, a trend for greater prevalence of patients both with abnormal prednisone absorption and abnormal prednisone absorption/fast prednisolone clearance was observed among obese/overweight patients (BMI>25 kg/m²) as compared to lean patients (BMI<25 kg/m²) (42.86% compared to 18.18%, p=0.0761, Fisher's exact test) (**Table E1**). Despite the adjustment of prednisone dose based on BSA (a standard practice for prednisone dosing), with an increase in BMI there was a significant reduction in prednisone absorption and an increase in prednisolone clearance (**Fig. 1A,B**). A trend for a higher proportion of patients with abnormal prednisone absorption and abnormal prednisone absorption/fast prednisolone clearance was observed among patients with poor asthma control (ACQ-7>1.5; bronchodilator reversibility greater than 20% FEV₁ % predicted (**Tables E2, E3**, p=0.0813 and p=0.0860)). Patients in the ACQ-7>1.5 group had the highest BMI (**Table E2**). No difference in BMI was observed among patients with different FEV₁ reversibility categories (**Table E3**). Together patients with abnormal prednisone absorption and abnormal prednisone absorption/fast prednisolone clearance had significantly lower FEV₁/FVC ratio as compared to patients with normal prednisone pharmacokinetics (Mean±SD, 76.1±10.7% vs. 83.6±10.2%, p<0.05) (**Table 1**).

A significant inverse relationship between plasma prednisolone 2h concentration and BAL cell TNF α mRNA levels was observed. This relationship was no longer significant, if adjusted for patients' BMI, suggesting that this relationship was influenced by BMI (**Fig. 1C**). A positive correlation between TNF α mRNA in BAL and prednisolone clearance was observed, with significant increase in BAL TNF α mRNA with increased prednisolone clearance, even if adjusted for BMI, suggesting that this relationship was influenced by something other than BMI, possibly hepatic and renal physiology in CR asthma (**Fig. 1D**).

The data in our current study suggest that overweight/obese asthmatics with poor responses to oral prednisone burst should be evaluated for abnormalities in prednisone PK. In this study, we used a modified PK evaluation that involves only three time points for the evaluation of plasma prednisolone concentration, i.e. baseline, 2h and 6h post oral prednisone administration. A complete PK evaluation with blood sampling every hour over the course of 24h and comparison to i.v. drug administration would provide more detailed information about prednisone interconversion, prednisone absorption abnormalities (fast, delayed, reduced), prednisolone clearance abnormalities (rapid, delayed, slow) and inform about drug blood and tissue distribution (volume of distribution). These data will help design the strategy for corticosteroid PK correction.

Our data suggests that poor absorption and/or rapid clearance of corticosteroids among obese patients may contribute to persistent airway inflammation and their suboptimal response to systemic steroid. Dosing strategies to overcome oral prednisone PK abnormalities (substitutions for corticosteroids with high retention in the lung (methylprednisolone), liquid corticosteroid preparations, or intravenous administration) can be considered for these patients. Data from Szeffler and collaborators have demonstrated liquid corticosteroid preparations can overcome absorption abnormalities¹³. The specifics of oral prednisone PK abnormalities (e.g. intestinal absorption, interconversion, metabolism, or clearance) in asthma and the relationship to obesity require further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BAL cells	bronchoalveolar lavage cells
CR asthma	corticosteroid resistant asthma
PK	pharmacokinetics
FEV₁	forced expiratory volume in one second

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Clinical Implications

Overweight/obese corticosteroid resistant asthmatics have a higher prevalence of prednisone pharmacokinetic abnormalities, which may contribute to suboptimal response to corticosteroids and persistent airway inflammation. If oral steroids are needed in this group, then strategies to overcome pharmacokinetic abnormalities should be considered.

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Figure 1.

Relationships between patients' BMI, BAL inflammatory response and oral prednisone pharmacokinetics in CR asthma patients.

(A) Significant inverse relationship between patients' BMI and prednisolone 2h concentration. (B) Significant correlation between patients' BMI and prednisolone clearance at 6h post oral prednisone administration. (C) Significant inverse relationship between prednisolone 2h concentration and BAL TNF α mRNA levels. (D) Significant correlation between the rate of plasma prednisolone clearance at 6h and BAL TNF α mRNA levels.

Table 1

Patient characteristics *

	Oral prednisone pharmacokinetics				P value (ANOVA) **
	Normal	Abnormal absorption	Abnormal absorption/fast clearance	Slow clearance	
Number of subjects	27	10	6	7	
Age, yrs	37±11	35±13	33±12	33±13	
Gender (Male/Female)	13/14	6/4	4/2	3/4	
Race (C/AA/Other)	17/5/5	6/1/3	1/2/3	5/1/1	
BMI, kg/m ²	28.7±8.0	26.5±5.5	34.0±7.4	24.0±5.2	0.09
BSA, m ²	1.90±0.27	1.95±0.19	2.15±0.10	1.79±0.16	0.07
Dose of prednisone for PK study, mg	45±7	47±5	48±4	41±10	
Plasma prednisolone at 2h post oral prednisone administration, ng/ml	504±97	357±29	293±38	662±125	*** <0.0001
Plasma prednisolone clearance obtained from 6h post oral prednisone administration, ml/min/1.73 m ²	180±21	220±27	277±20	116±18	*** <0.0001
IgE, U/ml	317±62.5	791±1505	274±161	205±149	
Number of positive skin tests	5±4	6±5	7±3	8±3	
PC ₂₀ , Methacholine, mg/ml	1.4±2.2	1.6±1.8	1.3±0.6	1.7±1.7	
ACQ-7 score	2.0±1.0	2.0±0.6	2.0±0.7	1.4±0.9	
eNO, ppm	35±31	44±31	44±38	35±32	
Baseline FEV ₁ % predicted	72.6±10.1	72.5±8.1	69.2±13.5	72.0±12.0	
FEV ₁ % predicted in response to bronchodilator	17.3±13.3	19.4±8.3	23.3±12.4	13.0±8.3	
FEV ₁ % predicted in response after 1 week prednisone burst	-1.6±6.8	0.8±6.1	-0.9±7.1	0.8±4.6	
FEV1/FVC, %	83.5±10.2	77.9±10.7	73.0±10.9	84.1 ±13.6	0.12
Corticosteroid medications					
ICS	10	3	3	2	
None	17	7	3	5	

* All values reported as Mean±SD.

** The blanks under p value column are not significant.

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Statistically significant differences were expected based on values of prednisone absorption and prednisolone clearance.