Adrenal suppression with inhaled corticosteroids

Lipworth, Brian; Kuo, Chris; Jabbal, Sunny

Published in:
The Lancet Respiratory Medicine

DOI:
10.1016/S2213-2600(18)30148-6

Publication date:
2018

Document Version
Peer reviewed version

Elsevier Editorial System(tm) for The Lancet Respiratory Medicine

Manuscript Draft

Manuscript Number: THELANCETRM-D-18-00209

Title: Adrenal suppression with inhaled corticosteroids : the seed and the soil

Article Type: Correspondence

Corresponding Author: Professor Brian Lipworth, MD

Corresponding Author's Institution: University of Dundee

First Author: Brian Lipworth, MD

Order of Authors: Brian Lipworth, MD; Chris Kuo, MB ChB; Sunny Jabbal, MB ChB

Manuscript Region of Origin: UNITED KINGDOM

Adrenal suppression with inhaled corticosteroids : the seed and the soil

To the editor ,
Hawcutt et al report an increased susceptibility for blunting of the ACTH stimulated cortisol response with inhaled corticosteroids (ICS) in relation to the rs511198 polymorphism of the PDGFD gene locus , albeit in association with wide 95% confidence intervals [1] . Pointedly the low dose ACTH stimulation test has been shown to be less sensitive at detecting more subtle degrees of cortisol suppression compared to overnight or early morning urinary cortisol [2]. Their data does not appear to take into account other important factors which regulate cortisol suppression with ICS .
Genetic variation can only explain in part the propensity for adrenal suppression with ICS . Cortisol suppression with ICS can be thought of in terms of the seed and the soil . The seed is the particular drug and fine particle dose delivered to the lung , while the soil is the genetic susceptibility and systemic absorption from the lung .
Reduced airway calibre as FEV1 % predicted will result in lower drug absorption from the lung [3]. Hence patients with more severe airflow obstruction will serendipitously exhibit attenuated lung absorption when exposed to higher doses of ICS [4,5]. In terms of the drug the major pharmacologic factor is the degree of lipophilicity which in turn determines the degree of systemic tissue retention at steady-state , effectively resulting in prolonged drug release from a slow release reservoir . This explains why higher lipophilicity ICS such as fluticasone furoate and fluticasone propionate produce greater dose related adrenal suppression than beclometasone diproprionate or budesonide [6,7]. Lung deposition and fine particle dose will also alter the amount of drug available for absorption .For example inhaled fluticasone propionate via a spacer produces 5.5 fold greater cortisol suppression than a dry powder inhaler [8]. Thus a patient who possess the susceptible homozygous rs511198 genotype with a preserved FEV1 in the presence of prolonged exposure to fluticasone propionate via a spacer will be at high risk for developing adrenal suppression . When considering the risk of adrenal suppression in an individual patient the safest dose of ICS will be achieved by always trying to step down to lowest effective long term maintenance dose .

Dr Brian Lipworth , Dr Chris Kuo ,Dr Sunny Jabbal
Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee
DD19SY
Correspondence : b.j.lipworth@dundee.ac.uk

(Word count =359)

References

1. Hawcutt DB, Francis B ,Carr DF et al .Susceptibility to corticosteroid induced adrenal suppression: a genome wide association study .*Lancet Respir Med .doi 10.1016/S2213-2600(18)30058-4*

2. Wilson AM, McFarlane LC, Lipworth BJ. Effects of low and high doses of inhaled flunisolide and triamcinolone acetonide on basal and dynamic measures of adrenocortical activity in healthy volunteers. *Journal of Clinical Endocrinology and Metabolism* 1998; **83**(3): 922-5.
3. Brutsche MH, Brutsche IC, Munawar M, et al. Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study. *Lancet* 2000; **356**: 556-61.
4. Weiner P, Berar-Yanay N, Davidovich A, Magadle R. Nocturnal Cortisol Secretion in Asthmatic Patients After Inhalation of Fluticasone Propionate. *Chest* 1999; **116**(4): 931-4.
5. Lee DKC, Bates CE, Currie GP, Cowan LM, McFarlane LC, Lipworth BJ. Effects of high-dose inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal axis in asthmatic patients with severely impaired lung function. *Annals of Allergy, Asthma and Immunology* 2004; **93**(3): 253-8.
6. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Archives of Internal Medicine* 1999; **159**(9): 941-55.
7. Martin RJ, Szefler SJ, Chinchilli VM, et al. Systemic Effect Comparisons of Six Inhaled Corticosteroid Preparations. *American Journal of Respiratory & Critical Care Medicine* 2002; **165**(10): 1377-83.
8. Wilson AM, Dempsey OJ, Coutie WJR, Sims EJ, Lipworth BJ. Importance of drug-device interaction in determining systemic effects of inhaled corticosteroids. *Lancet* 1999; **353**(9170): 2128.