CLINICAL VIGNETTE

Too Much of a Good Thing, Iatrogenic Cushing's Syndrome

Karen Cheng, M.D.

Case Report

A 48-year-old female with moderately severe reactive airways disease, allergic rhinitis, supraventricular tachycardia, and low back pain was seen periodically for a second opinion in our office as she had an outside primary care doctor through her husband's insurance. On this visit, she noted increased bruising for the previous 3 months. She denied any nose bleeding, gum bleeding, or heavy menses. She denied any increased bleeding with her previous two breast biopsies, nor with the vaginal delivery of her only child. Further questioning revealed a stable weight but increased fatigue, flushing, and facial hair growth.

Outside labs revealed a normal comprehensive metabolic panel except for an elevated alkaline phosphatase of 127 and normal PT/PTT and platelet count. Her liver ultrasound confirmed hepatosteatosis but was otherwise unremarkable.

The patient's medications included inhaled fluticasone proprionate 110 ug - 2 puffs twice a day, intranasal fluticasone – 2 sprays in each nostril once a day, and inhaled salmeterol – 1 puff twice a day.

On physical examination, the patient had a normal blood pressure of 110/60. She had a full facies and evidence of increased skin fragility with upper extremity ecchymoses. Increased facial hair growth was noted on her upper lip, lateral cheeks, and chin. Finally, she also had an increased dorsocervical fat pad.

A late night serum cortisol was ordered and came back as less than 0.2 mg (reference range < 6 mcg/dl) with a normal free testosterone and DHEA-sulfate. An early morning cortisol was also low at 4 mcg/dl (reference range 8-25 mcg/dl) with an ACTH level of 11 pg/ml (reference range 5-27 pg/ml). A 24-hour urine free cortisol was 5.9 ug/d (reference range less than or equal to 45 ug/d).

Discussion

The patient's presentation was highly suggestive of Cushing's syndrome including the facial fullness, increased facial hair, dorsocervical fat pad, and bruising. However, her suppressed late night and early morning cortisol with an ACTH level in normal range suggested an iatrogenic or exogenous source of steroids. While she was on therapeutic doses of both the inhaled and intranasal fluticasone, it was postulated that the combination of the two caused an excess of circulating steroid and a suppression of her hypothalamic-pituitary-adrenal (HPA) axis. In fact, the presentation of her physical symptoms occurred only after the change to inhaled fluticasone from her previous inhaled beclomethasone. After a change back to beclomethasone, discontinuation of both inhaled and intranasal doses of fluticasone, and the addition of montelukast, her facial fullness and bruising greatly improved. A cosyntropin stimulation test done 6 months after the patient had discontinued both the inhaled and intranasal fluticasone was normal confirming normal function of her HPA axis.

Iatrogenic Cushing's syndrome is the most common cause of ACTH independent Cushing's syndrome. It is commonly caused by oral steroids prescribed for other diseases. However, the administration of synthetic glucocorticoid in any form including oral, injected, topical, or inhaled can induce symptoms. While there are several choices of inhaled corticosteroids, they are all chemically similar. However, fluticasone propionate (FP) has been shown to have a higher potency when compared to beclomethasone dipropionate (BDP) and budesonide (BUD). It is possible that the higher potency of FP, along with its longer half-life[1] and higher lipophilicity[2] could result in increased exogenous steroid side effects and increased suppression of the HPA axis.

Two extensive reviews of the literature comparing the relative efficacy/side effect ratios of FP versus BDP/BUD have been done. The first by Barnes et al. in 1998[3] has been criticized

for its lack of clear inclusion criteria for trials including an assessment of methodological quality. A more recent review by Adams et al.[4] was done for the Cochrane Collaboration In this review, FP when given at half the doses of either BDP or BUD was as efficacious in improving measures of airway caliber. However, there was not enough data to draw any conclusions about differences in symptoms. Increased hoarseness was noted with FP but not other side effects such as thrush or sore throat.

A meta-analysis of FP and adrenal effects in adult asthma[5] included 5 studies whose primary outcome was the measurement of adrenal function below the normal limit as assessed by a cosyntropin stimulation test. Fortunately, the conclusion was that FP had minimal effects on adrenal function when prescribed within the therapeutic dose range of 50 -500 ug a day. Our patient was receiving 440 ug a day with her inhaled FP but was also using intranasal FP with an additional dose of 200 ug. While a review of intranasal corticosteroids and adrenal suppression[6] did not reveal significant suppression of the HPA axis at recommended dosages, the combination of the intranasal and inhaled FP and perhaps an individual susceptibility led to the presentation of iatrogenic Cushing's syndrome in our patient.

Other sources of exogeneous steroid exposure including topical clobetasol, a very high potency topical steroid used for treatment of psoriasis in adults, have been reported to cause Cushing's syndrome[7]. Indeed, there have even been cases caused by topical ocular steroids[8].

A final point to remember is that any drug that can inhibit hepatic cytochrome p (CYP) 450 3A4 isoenzymes can increase levels of fluticasone, a substrate of hepatic CYP3A4. One such drug is ritonavir, a commonly prescribed protease inhibitor prescribed in both pediatric and adult HIV- positive patients. A literature search produced 25 cases of significant adrenal suppression secondary to the administration of ritonavir with inhaled fluticasone and 3 cases with intranasal fluticasone[9]. The pharmacokinetics of fluticasone likely result in this notable interaction when compared to other inhaled corticosteroids. Other potent hepatic CYP3A4 inhibitors such as intraconazole, macrolides, and diltiazem should be used cautiously with fluticasone as well.

Key Points

1) Inhaled and intranasal corticosteroids have minimal if any effects on adrenal function when used at recommended therapeutic doses.
2) Of the inhaled corticosteroids, fluticasone proprionate with its higher potency secondary to its pharmacokinetics may increase the risk of developing adrenal suppression at doses above 500 ug/day. Other options include beclomethasone, budesonide, triamcinolone, and flunisolide and should be used at the lowest therapeutic dose.
3) Medications including ritonavir, itraconazole, macrolides, diltiazem and other inhibitors of the CYP3A4 hepatic isoenzymes can lead to increased systemic accumulation of fluticasone and other corticosteroids.

REFERENCES

1. **Szefler SJ**. Pharmacokinetics of intranasal corticosteroids. *J Allergy Clin Immunol*. 2001 Jul;108(1 Suppl):S26-31. Review. PubMed PMID: 11449203.
2. **Johnson M**. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. *J Allergy Clin Immunol*. 1996 Jan;97(1 Pt 2):169-76. Review. PubMed PMID: 8568148.
3. **Barnes NC, Marone G, Di Maria GU, Visser S, Utama I, Payne SL**. A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. International Study Group. *Eur Respir J*. 1993 Jun;6(6):877-85. PubMed PMID: 8339809.
4. **Adams NP, Lasserson TJ, Cates CJ, Jones P**. Fluticasone versus beclomethasone or udesonide for chronic asthma in adults and children (Review). *The Cochrane Collaboration, The Cochrane Library*. 2010; 1:1-361.
5. **Masoli M, Weatherall M, Holt S, Shirtcliffe P, Beasley R**. Inhaled fluticasone propionate and adrenal effects in adult asthma: systematic review and meta-analysis. *Eur Respir J*. 2006 Nov;28(5):960-7. Epub 2006 May 31. Review. PubMed PMID: 16737984.
6. **Bruni FM, De Luca G, Venturoli V, Boner AL**. Intranasal corticosteroids and adrenal suppression. *Neuroimmunomodulation*. 2009;16(5):353-62. doi: 10.1159/000216193. Epub 2009 Jun 29. Review. PubMed PMID: 19571596.
7. **Tempark T, Phatarakijnirund V, Chatproedprai S, Watcharasindhu S, Supornsilchai V, Wananukul**

S. Exogenous Cushing's syndrome due to topical corticosteroid application: case report and review literature. *Endocrine*. 2010 Dec;38(3):328-34. doi: 10.1007/s12020-010-9393-6. Epub 2010 Oct 23. Review. PubMed PMID: 20972726.

8. **Chiang MY, Sarkar M, Koppens JM, Milles J, Shah P**. Exogenous Cushing's syndrome and topical ocular steroids. *Eye* (Lond). 2006 Jun;20(6):725-7. Epub 2005 Nov 18. PubMed PMID: 16294208.
9. **Foisy MM, Yakiwchuk EM, Chiu I, Singh AE**. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. *HIV Med*. 2008 Jul;9(6):389-96. doi: 10.1111/j.1468-1293.2008.00579.x. Epub 2008 May 4. Review. PubMed PMID: 18459946.

Submitted on October 22, 2012