

LETTERS

Systemic absorption of intranasal corticosteroids may occur and can potentially affect the hypothalamic–pituitary–adrenal axis

In their recent *CMAJ* Practice article on intranasal corticosteroids, Drs. Fowler and Sowerby¹ stated that this therapy is not associated with hypothalamic–pituitary–adrenal (HPA) axis suppression. However, scenarios exist in which suppression may occur; therefore, some additional details may be useful. In support of their statement, the authors cited only a review article that, in turn, cited another review article and other small, older studies. Most studies looking at the association between intranasal corticosteroid use and HPA axis suppression have had major design flaws, namely small numbers; use of presently outdated and less accurate cortisol assays; collection of adrenal tests as an exploratory secondary outcome; lack of differentiation between different types, doses and durations of glucocorticoids; and lack of clinically relevant data.

A 2015 systematic review and meta-analysis of primary data, using appropriate inclusion, exclusion and stratification criteria showed that 4.2% (95% confidence interval 0.5%–28.9%) of patients using intranasal steroids could have adrenal suppression when a biochemical definition was used.² The risk is likely increased with longer duration of use and with higher doses but is likely less than what is observed with inhaled steroids for asthma treatment.

However, in combination with medications that inhibit cytochrome P-450 3A4 (CYP3A4 inhibitors), which will slow systemic glucocorticoid metabolism, intranasal steroids may even cause Cushing syndrome,^{3,4} with rebound adrenal insufficiency after treatment is stopped, which emphasizes⁵ their potential for systemic absorption.

Although adverse clinical sequelae may be uncommon, modern laboratories' use of more specific cortisol immunoassays or mass spectrometry can show a low basal cortisol level when measured in a patient who is using intranasal or inhaled steroids, particularly in those receiving highly active antiretroviral therapy or azole antifungal agents. It is a common mistake to interpret this as "adrenal insufficiency" in need of replacement therapy instead of simply evidence that the synthetic glucocorticoid does indeed have systemic absorption and may be suppressing the HPA axis. A low level of serum cortisol in a patient using exogenous glucocorticoids is not an indicator of future HPA axis suppression, delayed recovery or clinical adrenal insufficiency after treatment is stopped. As intranasal steroids may be absorbed systemically and affect the HPA axis; decisions about when and how to stop such therapy should be carefully considered, in particular in patients undergoing treatment with CYP3A4 inhibitors.

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References

1. Fowler J, Sowerby LJ. Using intranasal corticosteroids. *CMAJ* 2021;193:E47-47.
2. Broersen LHA, Pereira AM, Jørgensen JOL, et al. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015;100:2171-80.
3. Hillebrand-Haverkort ME, Prummel MF, ten Veen JH. Ritonavir-induced Cushing's syndrome in a patient treated with nasal fluticasone. *AIDS* 1999;13:1803-1803.
4. Chen F, Kearney T, Robinson S, et al. Cushing's syndrome and severe adrenal suppression in patients treated with ritonavir and inhaled nasal fluticasone. *Sex Transm Infect* 1999;75:274-274.
5. Veilleux O, Lee TC, McDonald EG. Rebound adrenal insufficiency after withdrawal of ritonavir in a 65-year-old man using inhaled budesonide. *CMAJ* 2017;189:E1188-91.

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