11 Bellamy COC, McDonald C, Salter DM, Chetty U, Anderson TJ. Non-invasive ductal carcinoma of the breast. The relevance of histologic categorization. *Hum Pathol* 1993;24:16-23.
12 Silverstein MJ. Predicting local recurrence in patient with ductal carcinoma in situ. In: Silverstein MJ, ed. *Ductal carcinoma in situ of the breast*. Baltimore: Williams and Wilkins, 1997:271-84.
13 Fisher ER, Constantino J, Fisher B, Palekar AS, Paik SM, Suarez CM, et al. Pathologic finding from the national surgical adjuvant breast project (NSABP) protocol B-17: intraductal carcinoma (ductal carcinoma in situ). *Cancer* 1995;75:1310-9.
14 Douglas-Jones AG, Gupta SK, Attanoos RL, Morgan JM, Mansel RE. A critical appraisal of six modern classifications of ductal carcinoma in situ of the breast (DCIS): correlation with grade of associated invasive disease. *Histopathology* 1996;29:397-409.
15 Fisher B, Costantino J, Redmond C, Fisher ER, Margolese R, Dimitrov N, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993;328:1581-6.
16 Fisher B, Dignam J, Wolmark N, Mamounas E, Constantino J, Poller W, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from national surgical adjuvant breast and bowel project B-17. *J Clin Oncol* 1998;16:441-52.
17 Lagios MD, Page DL. Radiation therapy for in situ or localized breast cancer. *N Engl J Med* 1993:21:1577-8.
18 Page DL, Lagios MD. Pathologic analysis of the NSABP-B17 trial. Unanswered questions remaining unanswered considering current concepts of ductal carcinoma in situ. *Cancer* 1995;75:1219-22.
19 Recht A. Side effects of radiation therapy. In: Silverstein MJ, ed. *Ductal carcinoma in situ of the breast*. Baltimore: Williams and Wilkins, 1997:347-50.
20 Page DL, Dupont WD, Rogers LW, Jensen RA, Schuyler PA. Continued local recurrence of carcinoma 15-25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. *Cancer* 1995;76:1197-200.
21 Hansen N, Giuiliano A. Axillary dissection for ductal carcinoma in situ. In: Silverstein MJ, ed. *Ductal carcinoma in situ of the breast*. Baltimore: Williams and Wilkins, 1997:577-84.
22 Silverstein MJ, Rosser RJ, Gierson ED, Waisman JR, Gamagami P, Hoffman R, et al. Axillary dissection for intraductal breast carcinoma—is it indicated? *Cancer* 1987;59:1819-24.
23 Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg* 1995;222:394-401.
24 Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996;276:1818-22.
25 Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 1993;2:335-40.
26 Holland R, Faverly DRG. Whole organ studies. In: Silverstein MJ, ed. *Ductal carcinoma in situ of the breast*. Baltimore: Williams and Wilkins, 1997:233-40.
27 Silverstein MJ, Lagios MD, Lewinsky BS, Colburn WJ, Beron P, Craig PH, et al. Breast irradiation is unnecessary for widely excised ductal carcinoma in situ (DCIS) [abstract]. *Breast Cancer Res Treat* 1997;46:23.
28 Silverstein MJ, Lagios MD, Waisman JR, Martino S, Beron P, Lewinsky BS, et al. Margin width: a critical determinant of local control in patients with ductal carcinoma in situ (DCIS) of the breast [abstract]. *Proc Am Soc Clin Oncol* 1998;17:120A.
29 Sibbering MD, Blamer RW. Nottingham experience. In: Silverstein MJ, ed. *Ductal carcinoma in situ of the breast*. Baltimore: Williams and Wilkins, 1997:367-72.
30 Silverstein MJ, Lagios MD, Martino S, Lewinsky BS, Craig PH, Beron P, et al. Outcome after invasive local recurrence in patients with ductal carcinoma in situ of the breast. *J Clin Oncol* 1998;16:1367-73.
31 Solin LJ, Kurtz J, Fourquet A, Amalric R, Recht A, Bornstein BA, et al. Fifteen year results of breast conserving surgery and definitive breast irradiation for treatment of ductal carcinoma in situ of the breast. *J Clin Oncol* 1996;14:754-63.
32 Solin LJ, Fourquet A, McCormick B, Haffty B, Recht A, Schultz DJ, et al. Salvage treatment for local recurrence following breast conserving surgery and definitive irradiation for ductal carcinoma in situ (intraductal carcinoma) of the breast. *Int J Radiat Oncol Biol Phys* 1994;30:3-9.
33 Lakhani SR, Collins N, Stratton MR, Sloane JP. Atypical ductal hyperplasia: clonal proliferation with loss of heterozygosity on chromosomes 16q and 17p. *J Clin Pathol* 1995;48:611-5.
34 Stratton MR, Collins N, Lakhani SR, Sloane JP. Loss of heterozygosity in ductal carcinoma in situ of the breast. *J Pathol* 1995;175:195-201.
35 Radford DM, Phillips NJ, Fair KL, Ritter JH, Holt M, Donis-Keller H. Allelic loss and the progression of breast cancer. *Cancer Res* 1995;55:5180-3.
36 Fujii H, Marsh C, Cairns P, Sidranksy D, Gabrielson E. Genetic divergence in the clonal evolution of breast cancer. *Cancer Res* 1996;56:1493-7.

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Lesson of the week

Childhood Cushing's syndrome induced by betamethasone nose drops, and repeat prescriptions

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Iatrogenic Cushing's syndrome secondary to oral corticosteroid treatment is well documented, as is systemic absorption of topical steroid preparations that are potent or used for a long time. However, frank Cushing's syndrome as a result of inhaled or intranasal corticosteroids is not well recognised. We present two cases of childhood Cushing's syndrome secondary to prolonged use of intranasal betamethasone.

Case reports

Case 1

A boy aged 7 years was referred to the endocrine clinic with a history of growth failure associated with obesity. Over the past two years his weight had increased from the 50th to the 97th centile with height falling from the 10th to the 3rd centile. He had no history of note apart from mild atopy and chronic catarrh, for which he had been prescribed 0.1% betamethasone nasal drops.

On examination he was cushingoid with normal prepubertal genitalia. His blood pressure was 165/75 mm Hg (>95th centile for age). Pituitary Cushing's syndrome was diagnosed clinically and he was admitted for endocrine assessment. We expected to find high serum cortisol concentrations, but cortisol was undetectable (<24 nmol/l) and he did not respond to stimulation by insulin hypoglycaemia. Adrenocorticotrophic hormone was also undetectable. A 24 hour urine sample showed extremely low adrenal steroid metabolite concentrations, indicating severely impaired adrenal function. Computed tomography of the brain and adrenal glands showed no abnormality.

The drug history was reviewed. Over the past 19 months he had been using 0.1% betamethasone sodium phosphate nose drops continuously, at a dose of two drops per nostril twice daily. Twenty seven repeat prescriptions had been issued during this time.

We diagnosed Cushing's syndrome secondary to systemic absorption of intranasal betamethasone. The steroid nose drops were discontinued and replaced by xylometazoline, a sympathomimetic nasal preparation. Because of the severity of the adrenal suppression maintenance hydrocortisone was started at 10 mg/m^2/day with instructions to double the dose during acute infections. The boy's adrenal function will be retested after one year and we expect to wean him off hydrocortisone. At review five weeks after stopping betamethasone he had lost 1 kg and his cushingoid appearance had lessened. His blood pressure was normal.

Children should have betamethasone nose drops prescribed for only short periods

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Case 2

A boy with Down's syndrome was referred to the endocrine clinic aged 3½ years with irritability, excessive weight gain, and change in appearance. He had been well since surgery for duodenal atresia shortly after birth and had no cardiac lesion, but over the past nine months he had been gaining weight, particularly around the face and abdomen. His thyroid function had been checked and was normal.

On examination he was severely cushingoid with weight just above the 95th centile and height below the 3rd centile for children with Down's syndrome. A year previously his weight had been on the 3rd centile and height on the 10th centile. Cushing's syndrome was diagnosed clinically and, because of his age and history, an adrenal tumour was suspected. However, imaging of both pituitary and adrenal glands showed no abnormality. His basal cortisol concentration was low (<24 nmol/l) and he had impaired response to stimulation with low dose synacthen (500 ng/1.73 m^2), with a peak cortisol concentration of only 144 nmol/l. This was consistent with adrenal suppression. Urinary steroid analysis showed extremely low adrenal steroid metabolite concentrations.

Further inquiry revealed that the boy had been prescribed 0.1% betamethasone sodium phosphate nasal drops (one drop to each nostril twice daily) constantly by repeat prescription over 27 months for chronic catarrh. Iatrogenic Cushing's syndrome was diagnosed and the betamethasone nose drops discontinued. Maintenance hydrocortisone was not started because of the adrenal response to synacthen stimulation, although hydrocortisone was recommended for cover during acute infections until complete recovery of adrenal function. Endocrine testing will be repeated after 6-12 months. At review four weeks after stopping betamethasone he had lost 0.8 kg and his cushingoid features were regressing.

Comment

Although iatrogenic Cushing's syndrome from oral steroids is well recognised, it is not usually associated with intranasal corticosteroids. Indeed, the National Asthma Campaign advocates the safety of intranasal steroids in its hay fever fact sheet.[1] However, since 1980 there have been four case reports of adrenal suppression secondary to intranasal corticosteroids.[2–5]

Significant systemic absorption of intranasal steroids is not surprising given their pharmacokinetics. Corticosteroids are generally well absorbed from sites of local application. The degree of absorption from the intranasal route depends on several factors, including the number of drops instilled, the vascularity and surface area of the nasal mucosa, and the time the solution remains in contact with the mucosa. In addition, some of the solution will undoubtedly be swallowed and readily absorbed by the gastrointestinal tract.

Betamethasone, one of the mainstays of treatment for nasal congestion in children, is a potent corticosteroid which is very water soluble as the sodium phosphate ester and has a long duration of action (half life >36 hours compared with 8-12 hours for hydrocortisone).[6] It is mainly metabolised in the liver, but the rate is slower than for natural corticosteroids.[7] This, together with the lower protein binding affinity and enhanced glucocorticoid activity of betamethasone,[8] explains its increased potency and prolonged half life compared with natural corticosteroids.

It may also be difficult to administer the prescribed number of drops accurately to the nose of an uncooperative child. Indeed, in these two cases the number of repeat prescriptions exceeds that expected for the prescribed dose and duration of treatment. According to the manufacturers one bottle of betamethasone, which contains 10 ml, is equivalent to around 300 drops. At a dose of two drops per nostril twice daily (as in case 1) it would be expected to last 38 days. We believe that inadvertent overdose, together with prolonged use, was important in these cases. Although evidence is lacking, metered dose nasal sprays are less likely to produce accidental overdose since they are simpler to use and deliver an accurate dose. Fluticasone nasal spray, which has low bioavailability and may be more effective,[7] is a reasonable alternative to betamethasone nasal drops.

Nasal steroid drops are important in treating ear, nose, and throat complaints in children. However, our experience suggests that treatment with betamethasone nasal drops should not be prolonged and that the potential difficulties with administration and possible overdose should be considered. Betamethasone nasal drops should not be supplied on a repeat prescription basis. In particular, we would caution general practitioners against prescribing the treatment for more than six weeks.

The cases described may represent the tip of an iceberg. Many children with milder cases may escape detection, perhaps because they have stopped taking their treatment. Further work is required to establish a safe dose and duration of treatment and we are currently planning a prospective cross sectional study of children receiving betamethasone nose drops, paying attention to the method of administration.

1 National Asthma Campaign. *Hay fever factsheet*. London: NAC, 1996.
2 Stevens DJ. Cushing's syndrome due to the abuse of betamethasone nasal drops. *J Laryngol Otol* 1988;120:219-21.
3 Daman Willems CE, Dinwiddie R, Grant DB, Rivers RP, Zahir M. Temporary inhibition of growth and adrenal suppression associated with the use of steroid nose drops. *Eur J Pediatr* 1994;153:632-4.
4 Heroman WM, Bybee DE, Cardin MJ, Bass JW, Johnsonbaugh RE. Adrenal suppression and cushingoid changes secondary to dexamethasone nose drops. *J Pediatrics* 1980;96:500-1.
5 Nutting CM, Page SR. Iatrogenic Cushing's syndrome due to nasal betamethasone: a problem not to be sniffed at! *Postgrad Med J* 1995;71:231-2.
6 Helfer EL, Rose LI. Corticosteroids and adrenal suppression. Characterising and avoiding the problem. *Drugs* 1989;38:838-45.
7 Gilman AG, Goodman LS. *The pharmacological basis of therapeutics*. 9th ed. New York: McGraw-Hill, 1996.
8 Begg EJ, Atkinson HC, Gianarakis N. The pharmacokinetics of corticosteroid agents. *Med J Aust* 1987;146:37-41.

Endpiece

The golden mean

Almost every progress in our art is apt to become at first disproportionately exaggerated, later on equally disproportionately deprecated, and finally to emerge often enough, if at all, with considerable diminution of its original prestige.

Felix Semon, 1901

Submitted by Ann Dally, Wellcome Institute for the History of Medicine