Reminder of important clinical lesson

Adrenal insufficiency secondary to inappropriate oral administration of topical exogenous steroids presenting with hypercalcaemia

Rahila Sarwar Bhatti,¹ Michael D Flynn²

¹Diabetes & Endocrinology Department, Guy's & St Thomas Hospital, London, United Kingdom;

²Diabetes & Endocrinology Department, Kent & Canterbury Hospital, Canterbury, United Kingdom

Correspondence to Dr Rahila Sarwar Bhatti, rsbhatti91@hotmail.com

Summary

A 59-year-old Caucasian gentleman presented with malaise, fatigue and proximal muscle weakness. He had history of long-standing roseate psoriasis treated with topical clobetasol propionate (dermovate). On admission, he had significant postural hypotension, and hypercalcaemia. Endocrinological investigation revealed hypercalcaemia, a serum cortisol of <30 nmol/l, a flat short synacthen test and undetectable adrenocorticotrophic hormone. He was treated with hydrocortisone. The abrupt withdrawal of the topical steroids by the patient precipitated the Addisonian crisis. Further enquiry documented inappropriate oral administration of clobetasol for more than 10 years in addition to prescribed topical usage.

BACKGROUND

Glucocorticoids are used in the treatment of allergic, dermatological and autoimmune diseases due to their anti-inflammatory effects. Systemic side effects have been reported in literature following their oral or intravenous administration.¹ Topical steroids are used to maximise the therapeutic effects at the site of inflammation and to minimise systemic effects.² Topical steroids do have systemic absorption and can cause secondary adrenal failure with the application of only 7.5 g per week of clobetasol propionate.³ Inappropriate use by the patient can result in unrecognised secondary adrenal suppression.

CASE PRESENTATION

A 59-year-old Caucasian man presented as an emergency twice, 2 weeks apart, with a short history of malaise, fatigue, postural dizziness and proximal leg weakness. He had background history of long-standing roseate psoriasis and had been prescribed (dermovate) clobetasol propionate 0.5 mg/g ointment. On his initial admission, he was found to have calcium of 3.5 mmol/l (NR 2.2–2.6 mmol/l) treated with fluids and intravenous pamidronate. On readmission with the same symptoms he was treated for a clinical diagnosis of Addisonian Crisis.

His blood pressure was 114/59 mm Hg lying, 94/59 mm Hg standing. He was not pigmented. He was empirically treated with intravenous hydrocortisone and fluid resuscitation.

He was self medicating with cod liver oil capsules containing vitamin D 10 mcg daily. On further questioning, he admitted to ingesting topical steroids for last 10 years. He had been putting dermovate scalp application six drops a day into squash and an inch of dermovate ointment in peanut butter sandwiches per day (estimated dose of 25 g/week of clobetasol propionate). He stopped taking it during his first admission 2 weeks ago.

INVESTIGATIONS

On first admission, investigations showed: sodium: 138 mmol/l, potassium: 4 mmol/l, creatinine: 56 µmol/l, albumin 26 g/l, corrected calcium: 3.5 mmol/l, phosphate: 1.56 mmol/l, erythrocyte sedimentation rate: 40 mm/h, parathyroid hormone: <5 ng/l, serum ACE: 63 IU/l, normal serum protein electrophoresis, urine Bence-Jones proteins not detected, vitamin D: 74 nmol/l (ref. range 50–75 nmol/l), negative antineutrophil antibody, negative antineutrophil cytoplasmic antibody, CT scan of chest, abdomen and pelvis showed no evidence of malignancy and there was no evidence of myeloma on skeletal survey. The cause of his hypercalcaemia was not identified. Adrenal suppression was not suspected.

On readmission, investigations revealed: sodium 142 mmol/l, potassium 3.2 mmol/l, creatinine 39 µmol/l, epidermal growth factor receptor >90 units, Hb 12.2 g/dl, white cell count $6.3 \times 10^9/l$, platelets $234 \times 10^9/l$, corrected calcium 2.2 mmol/l. Random cortisol <30 nmol/l, thyroid stimulating hormone 2.4 mIU/l, T4 14 pmol/l.

A short synacthen test demonstrated a baseline plasma cortisol <30 nmol/l and 30 min post-tetracosactrin 79 nmol/l. adrenocorticotrophic hormone <10 (N 5–46).

TREATMENT

On first admission, he was treated for hypercalcaemia. On second admission, he was treated with intravenous hydrocortisone on clinical suspicion of Addisonian crisis.

OUTCOME AND FOLLOW-UP

He was treated with replacement hydrocortisone. He is being followed up in outpatient clinic with aim to try to gradually decrease his oral hydrocortisone replacement and restore normal adrenal function.

DISCUSSION

The history and clinical findings in our patient led us to the conclusion that he was suffering from secondary adrenal failure caused by withdrawal of long-term potent topical steroids.

Glucocorticoids are one of the most widely used drugs in clinical practice. Topical glucocorticoid therapy is used to deliver effective dose of the steroid to the target organs without systemic effects. Several factors influence the systemic absorption of topical steroids. The diseased skin results in loss of skin as a barrier resulting in some systemic absorption of the drug.⁴ Moreover, skin may act as a store resulting in delayed absorption even after single topical application.⁵ Therefore, small doses of potent topical steroids can have a prolonged systemic effect such as suppression of the hypothalamic-pituitary-adrenal axis. There have been reports of acute adrenal insufficiency following cessation of topical steroid treatment.⁶

Clobetasol propionate is considered as a very potent topical steroid, when given systemically has standard glucocorticoid activity and binds with high affinity to the glucocorticoid receptor. Allenby *et al* studied the effects of clobetasol propionate on hypothalamo-pituitary adrenal axis in 39 patients. He concluded that use of more than 50 g per week of topical application of clobetasol propionate can cause adrenal suppression.⁷ Ohman *et al* described three cases of secondary adrenal failure caused by less than 50 g per week (7.5, 25 and 30 g per week) of clobetasol propionate after 4 months of cessation of therapy.³ However, in our patient it is difficult to quantify the amount being absorbed in view of oral ingestion in addition to the topical administration. Our patient was using 100 g tube of clobetasol propionate in 4 weeks in addition to 100 ml dermovate scalp application (contains 0.05% w/w of clobetasol propionate). Each gram of the 0.05% ointment contains clobetasol propionate 0.5 mg in a base of propylene glycol, sorbitan sesquileoate and white petrolatum. He was using an estimated amount of 12.5 g topical steroid orally per week and 12.5 g per week topically.

Although hypercalcaemia is an infrequent presenting sign of adrenal insufficiency, it is a well-recognised complication. It has been reported to occur with primary adrenal insufficiency and with secondary adrenal failure.⁸ There are a number of mechanisms for hypercalcaemia in adrenal insufficiency. Adrenal insufficiency causes hypovolemia, and a consequent reduction in glomerular filtration rate resulting in reduction in the amount of calcium filtered at the glomerulus, as well as increase in proximal tubular reabsorption of calcium and sodium. On rehydration with normal saline, there is normalisation of the glomerular

filtration and the level of filtered calcium.⁹ In addition, there is calcium mobilisation from the bone. However, in one study histology suggested that bone remodelling in the trabecular bone surfaces was less than normal and it was postulated that there was either an increase in non-trabecular bone resorption or an increase in calcium transport from the interstitial bone fluid by lining cells. Glucocorticoid receptors in bone and steroid treatment reduce the influx of calcium into circulation.¹⁰

Learning points

- ▶ Consider the possibility of adrenal insufficiency when observing a case of hypercalcaemia.
- ▶ When topical clobetasol propionate is used chronically, it should be borne in mind that secondary adrenal failure is likely to occur even when small amounts (7.5 g per week) are used. Because of this, oral glucocorticoid supplementation should be used during episodes of stress, for example, intercurrent infections and surgery.
- ▶ It is very important to take good history to identify the underlying cause as in our case further questioning revealed additional steroid use.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Buttgereit F**, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an old spear. *Lancet* 2005;**365**:801–3.
2. **Hopkins RL**, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. *Endocrinol Metab Clin N Am* 2005;**34**:371–84.
3. **Ohman EM**, Rogers S, Meenan FO, *et al*. Adrenal suppression following low-dose topical clobetasol propionate. *J R Soc Med* 1987;**80**:422–4.
4. **Schaefer H**, Zesch I, Stuttgart G. Skin permeability. In: Stuttgart G, *et al*, eds. *Handbuch der Haut und Geschlechtskrankheit Ergänzungswork, B and 1*. Berlin: Springer Verlag 1981:632–9.
5. **Riegelman S**. Pharmacokinetics. Pharmacokinetic factors affecting epidermal penetration and percutaneous adsorption. *Clin Pharmacol Ther* 1974;**16**(5 Part 2):873–83.
6. **Scoggins RB**, Kliman B. Percutaneous absorption of corticosteroids: systemic effects. *N Engl J Med* 1965;**273**:831–40.
7. **Allenby CF**, Main RA, Marsden RA, *et al*. Effect on adrenal function of topically applied clobetasol propionate (Dermovate). *Br Med J* 1975;**4**:619–21.
8. **Vasikaran SD**, Tallis GA, Braund WJ. Secondary hypoadrenalism presenting with hypercalcaemia. *Clin Endocrinol (Oxf)* 1994;**41**:261–4.
9. **Muls E**, Bouillon R, Boelaert J, *et al*. Etiology of hypercalcaemia in a patient with Addison's disease. *Calcif Tissue Int* 1982;**34**:523–6.
10. **Montoli A**, Colussi G, Minetti L. Hypercalcaemia in Addison's disease: calcitropic hormone profile and bone histology. *J Intern Med* 1992;**232**:535–40.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Bhatti RS, Flynn MD. Adrenal insufficiency secondary to inappropriate oral administration of topical exogenous steroids presenting with hypercalcaemia. *BMJ Case Reports* 2012;10.1136/bcr.03.2012.5983, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow

Keep up to date with all published cases by signing up for an alert (all we need is your email address) <http://casereports.bmj.com/cgi/alerts/etoc>