BMJ 2014;349:g4843 doi: 10.1136/bmj.g4843 (Published 30 July 2014)

EDITORIALS

Glucocorticoid replacement

Pending further studies of new agents, the old treatments are still the best

Anjali Amin *clinical research fellow*, Amir H Sam *senior lecturer in endocrinology*, Karim Meeran *professor of endocrinology*

Imperial Centre for Endocrinology, Imperial College London, UK

Steroids are among the most commonly prescribed drugs. Synthetic glucocorticoids such as prednisolone and dexamethasone are commonly used as anti-inflammatory or immunosuppressive agents in supra-physiological doses and have longer half lives than the naturally occurring hydrocortisone.

Patients with primary adrenal insufficiency require replacement of both mineralocorticoid, in the form of fludrocortisone, and glucocorticoid. All healthcare professionals should know how to manage patients with hypocortisolaemia, some of whom will be at risk of life threatening adrenal crises.[1]

In the United Kingdom, hydrocortisone is the most commonly prescribed glucocorticoid for replacement therapy in both primary and secondary hypocortisolaemia. Other glucocorticoids are more often used for other conditions. Dexamethasone is the most potent and is mainly used in intracranial and oncological conditions. Prednisolone is the standard treatment for most inflammatory conditions. Prednisone is also available as a delayed release preparation and is converted to active prednisolone by first pass metabolism in the liver.

In healthy humans, cortisol is secreted from the adrenal glands in a distinct circadian rhythm, with peak levels in the early morning, dropping to undetectable levels during the night.[2 3] Hydrocortisone replacement therapy is tailored to mimic this diurnal pattern. Hence, conventional treatment with hydrocortisone for hypocortisolaemia is generally divided into three daily doses, with a larger proportion of the total dose taken in the morning.

In 2012 an oral modified release formulation of hydrocortisone, Plenadren, was licensed in the UK. What are its advantages?

The basis for the licensing decision was a single non-blinded crossover trial of 64 patients.[4] In the trial, participants were randomised to receive either a single daily dose of modified release hydrocortisone or a standard immediate release formulation in three divided doses for 12 weeks, followed by a switch to the other formulation for a further 12 weeks. The study showed that patients taking the once daily formulation had a lower body weight, blood pressure, and glycated haemoglobin concentration at 12 weeks compared with those taking conventional doses of hydrocortisone. This was unsurprising, however, as the doses of hydrocortisone were not comparable: the 24 hour cortisol exposure was lower with the modified release formulation than with the standard doses. Lower hydrocortisone doses than the 20-30 mg daily usually prescribed may therefore result in similar benefits to those seen with the modified release formulation at a fraction of the cost.

Although Plenadren has been marketed as a convenient once daily formulation and patients prefer a once daily formulation to multiple daily doses, adherence did not differ between the two formulations. Neither did quality of life scores.[4]

The cost of drugs is a consideration. Patients with adrenal insufficiency are often young and will require lifelong replacement treatment. Currently, Plenadren costs almost four times as much as standard hydrocortisone (£224 (€283; $380) compared with £60.70 for 28 tablets (20 mg)).[5]

If slow release formulations bring advantages then glucocorticoids with longer half lives offer possible alternatives in the treatment of hypocortisolaemia. Prednisolone has an ideal half life, allowing once daily treatment,[6] and patients with adrenal insufficiency derive the same subjective benefit from equivalent doses of prednisolone and hydrocortisone.[7] Prednisolone costs £1.31 for 28 tablets at the 5 mg dose; data on overtreatment with once daily prednisolone remain inconclusive.[8-10]

Prednisone, an inactive drug precursor converted to active prednisolone in the liver, offers no obvious added benefit to prednisolone, and the modified release preparation is expensive. Soluble prednisolone is also available, but at £39.93 for 28 tablets at the 5 mg dose[5] is about 40 times more expensive than standard prednisolone tablets. Dexamethasone is less commonly used because of its longer duration of action.

We now need long term randomised clinical trials looking at the efficacy and side effects of the available glucocorticoids in the management of hypocortisolaemia. A further study comparing truly equivalent doses of hydrocortisone, prednisolone, and modified release hydrocortisone is required.

Current formulations of hydrocortisone do not fully replicate the normal circadian rhythm of cortisol.[11] Several centres

Correspondence to: K Meeran, Endocrinology Department, Charing Cross Hospital, London W6 6RF, UK k.meeran@imperial.ac.uk

measure levels of cortisol in patients who are taking hydrocortisone and use these data to titrate dose and timing of treatment. As a result some patients follow three times daily regimens while others (presumably slower metabolisers) have twice daily dosing. Other centres do not measure levels but treat patients empirically.

Centres that titrate doses will want to measure levels of prednisolone, and assays are being developed to enable this. At present, however, there is no evidence of any difference between the three replacement options, so it is logical to use the most cost effective, which is prednisolone. Plenadren is the least cost effective and hence has no current place in the treatment of adrenal insufficiency. Hydrocortisone was the most cost effective option until 2008, when its price increased 60-fold,[12] but prednisolone should now be the first line option for glucocorticoid replacement therapy.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. *BMJ* 2012;345:e6333.
2 Krieger DT, Allen W, Rizzo F, Krieger HP. Characterization of the normal temporal pattern of plasma corticosteroid levels. *J Clin Endocrinol Metab* 1971;32:266-84.
3 De Lacerda L, Kowarski A, Migeon CJ. Diurnal variation of the metabolic clearance rate of cortisol. Effect on measurement of cortisol production rate. *J Clin Endocrinol Metab* 1973;36:1043-9.
4 Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. *J Clin Endocrinol Metab* 2012;97:473-81.
5 Joint Formulary Committee. *British National Formulary*. 2014. www.medicinescomplete.com.
6 Al-Habet S, Rogers HJ. Pharmacokinetics of intravenous and oral prednisolone. *Br J Clin Pharmacol* 1980;10:503-8.
7 Bleicken B, Hahner S, Loeffler M, Ventz M, Allolio B, Quinkler M. Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens. *Eur J Endocrinol* 2008;159:811-7.
8 Valero MA, Leon M, Ruiz Valdepenas MP, Larrodera L, Lopez MB, Papapietro K, et al. Bone density and turnover in Addison's disease: effect of glucocorticoid treatment. *Bone Miner* 1994;26:9-17.
9 Jodar E, Valdepenas MP, Martinez G, Jara A, Hawkins F. Long-term follow-up of bone mineral density in Addison's disease. *Clin Endocrinol* 2003;58:617-20.
10 Koetz KR, Ventz M, Diederich S, Quinkler M. Bone mineral density is not significantly reduced in adult patients on low-dose glucocorticoid replacement therapy. *J Clin Endocrinol Metab* 2012;97:85-92.
11 Debono M, Ross RJ. What is the best approach to tailoring hydrocortisone dose to meet patient needs in 2012? *Clin Endocrinol (Oxf)* 2013;78:659-64.
12 Joint Formulary Committee. *British National Formulary* 2008;55.

Cite this as: *BMJ* 2014;349:g4843