Osteocalcin suppression may be a useful marker for steroid exposure.

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Background

Hydrocortisone is currently the first-line treatment for glucocorticoid replacement in patients with adrenal insufficiency[1]. The treatment regimes have been designed to mimic the physiological diurnal variation of endogenous cortisol in a healthy individual, peaking in the morning with two additional peaks corresponding with meal times (Figure 1). This requires hydrocortisone to be taken three time daily.

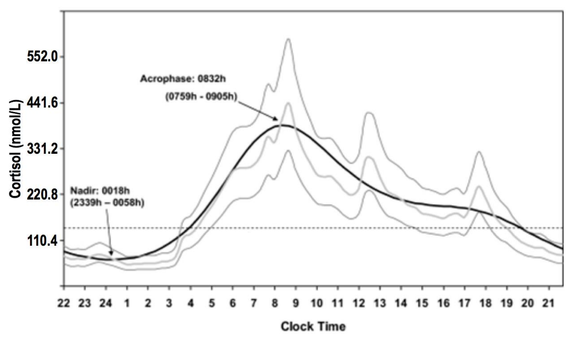

Figure 1: Circadian cortisol profile. *Figure adapted from Debono et al[2].*
The graph illustrates the geometric mean (±2SD) of 33 healthy individuals at various times, representing the mean physiological circadian cortisol profile. The nadir is the trough cortisol concentration, while the acrophase is the peak cortisol concentration.

Prednisolone is an alternative treatment in adrenal insufficiency[1]. It is structurally analogous to hydrocortisone, with the exception of a double bond between the first and second carbon atoms in ring A of the molecule[3] (Figure 2). This structural difference confers a longer half-life and higher potency[4]. Thus, prednisolone can be taken once daily. The bioequivalence ratio between hydrocortisone and prednisolone is commonly quoted to be 4:1[1], reflected by the clinically prescribed doses of 20mg (10mg-5mg-5mg) of hydrocortisone and 5mg of prednisolone. However, the clinical application of prednisolone has been limited due to reports that it has greater deleterious effects on bone turnover compared to hydrocortisone[4,5].

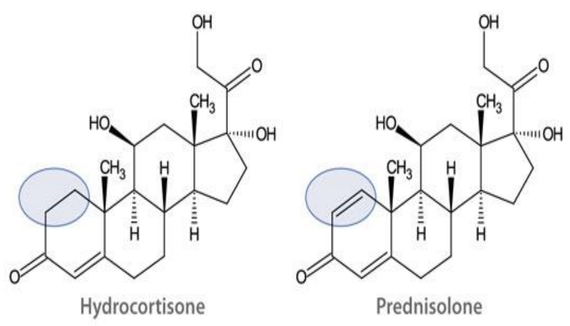

Figure 2: Structure of hydrocortisone and prednisolone. *Figure from Sigma-Aldrich[4].*
Prednisolone has a double bond between carbon 1 and carbon 2 in ring A, while hydrocortisone has a single bond. The structural difference accounts for the variation in potency between the two molecules.

Recent evidence from Caldeto et al. suggests that the bioequivalence ratio between hydrocortisone and prednisolone is 6-8:1[6], instead of 4:1. Using this ratio, 5mg of prednisolone would equate to a higher dose of glucocorticoids compared to 20mg of hydrocortisone. This offers a potential explanation as to why studies have found that prednisolone has more adverse effects on bone compared to other glucocorticoids, as an over-replacement of glucocorticoids has been demonstrated to be associated with osteoporosis[7].

Therefore, more research has to be conducted to compare the effects of lower, more physiological doses of prednisolone with hydrocortisone on bone turnover.

Case study

Mrs. M is a 66 year old female who has had adrenal insufficiency for many years. This was diagnosed after Synacthen tests revealed complete adrenal suppression due to high-dose prednisolone treatment for pulmonary eosinophilia. She has since been on a 10mg-5mg-5mg hydrocortisone regime, with occasional recurrences of eosinophilia treated by restarting high-dose prednisolone.

Mrs. M has recently developed osteoporosis. Concerned about her condition, she was interested to find out which treatment had a greater deleterious effect on bone turnover. She experienced no difference in symptoms of withdrawal between the two treatments.

Conjugated osteocalcin (Gla-OC) is an osteoblast-specific product, and is therefore considered to be a marker of bone formation. We decided to measure Mrs. M's Gla-OC levels on two separate days, whilst she was on 20mg of hydrocortisone and 3mg of prednisolone respectively.

Methods

Samples were acquired when Mrs. M was taking 10mg-5mg-5mg of hydrocortisone. After which, she suspended hydrocortisone and began treatment with 3mg of prednisolone. Samples were then collected after 2 weeks of consistent prednisolone treatment for comparison.

To account for the diurnal variation of Gla-OC, concentrations were measured 2, 4, 6 and 8 hours after the morning dose of hydrocortisone and prednisolone. Gla-OC concentrations were also measured 9 and 10 hours after the morning dose of hydrocortisone.

Levels of Gla-OC were quantified using commercially available assays (TaKara Osteocalcin (Gla-OC) EIA kit, TaKara Bio Europe/Clontech, Saint-Germain-en-Laye, France).

Results

There was no significant difference between the mean Gla-OC concentration measured 2, 4, 6 and 8 hours after the morning dose of prednisolone (8.25ng/ml) and hydrocortisone (7.73ng/ml). Gla-OC was also measured 9 and 10 hours after the morning dose of hydrocortisone (Table 1).

	Gla-OC (ng/ml)	
Time after morning dose (hours)	Prednisolone	Hydrocortisone
2	9.0	7.8
4	7.2	7.5
6	8.4	7.8
8	8.4	7.8
9		7.3
10		9.3

Table 1: Comparison of Gla-OC concentrations after prednisolone or hydrocortisone treatment.

Conclusion

From these results, it appears that there is no significant difference between the effect of hydrocortisone and prednisolone on osteoblast production of Gla-OC. Mrs. M chose to remain on 3mg due to its convenient once daily dose.

This case study demonstrated that Gla-OC levels have the potential to be used to monitor bone formation in patients treated with glucocorticoids, guiding the choice of medication. Long-term follow-up of the patient's bone mineral density would be necessary to investigate the correlation between suppression of Gla-OC and osteoporosis.

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