Rationale for drug doses used clinically in the management of adrenal insufficiency
Draft for consultation: March 2024: Adrenal Insufficiency

The inclusion of drug doses in the guideline is important to guide non expert clinicians as excess dosing of glucocorticoids can have a significant impact on morbidity and mortality. Dosing as stated in BNF is extrapolated on the basis of glucocorticoid anti-inflammatory action. Endocrine glucocorticoid requirements are lower than BNF doses and this has been quantified. In the early 1990s cortisol product rate was quantified in child and adults using stable isotope methodology showing cortisol production was between 5-10 mg/m^2 body surface area. (Esteban NV et al *J Clin Endocrinol Metab* 1991; Linder BI 1990). In addition cortisol production has a diurnal rhythm, highest levels 6-8am in the range of 200/500nmol/L, and low overnight less than 100nmol/L (Debono M. Eur J Endocrinol. 2009). Endocrinologists have therefore been using much more physiological doses in accord with this.

When given in excess as part of management for inflammatory conditions glucocorticoids can cause significant morbidity from cardiovascular disease as seen in Cushing's Disease such as weight gain, stretch marks, easy bruising, thinning of skin, osteoporosis, hypertension, type 2 diabetes, early cataracts. Whilst the evidence is mainly observational there is a body of data demonstrating increased mortality from glucocorticoids. Einarsdottir (Frontiers Endocrinology 2022) showed increased mortality in people using prednisolone greater than 5mg/day. Cause of death was sepsis and pulmonary embolism whilst Souverain (Heart 2004) and Mebrahtu (CMAJ 2020) demonstrated exogenous glucocorticoid use is associated with increased rate of cardiovascular and cerebrovascular disease. Mebratu et al (JCEM 2019) also looked at mortality and morbidity in an observational study looking at CPRD database. They showed increased mortality in patients taking prednisolone 0.1-5mg a day, and higher mortality again taking prednisolone >7.5mg a day. They reported deaths from glucocorticoid induced adrenal insufficiency and also deaths from glucocorticoid induced Cushing's syndrome (predominantly recorded as sepsis).

Results from short synacthen tests suggest that the accepted endocrine replacement dosing of hydrocortisone is 15-25mg per day and prednisone 3-5mg per day. Doses above this cause an abnormal response, demonstrating suppression of the hypothalamo-pituitary adrenal axis. (Woods C Pet al Eur J Endocrinol. 2015). Equivalent dosing for other glucocorticoid preparations are summarised in this SPS document https://www.endocrinology.org/media/4091/spssfe_supporting_sec_-final_10032021-1.pdf). These doses are supported by published clinical evidence, such as Smith et al 2017 where people with adrenal insufficiency were on a mean dose of either 20.5mg hydrocortisone or 3.7 mg prednisolone and no difference in well-being or cardiovascular parameters such as blood pressure were observed between the two drugs.

Hydrocortisone replacement:
For people taking hydrocortisone as a replacement, Howlett et al 1997 undertook a retrospective survey to identify the appropriate starting dose of hydrocortisone based on the proportion of people achieving 'optimal replacement' to match reasonable physiological cortisol levels. This study showed that a dose of 10 mg on rising, 5mg at lunchtime, and 5mg at evening time, more closely represented a cortisol profile in people without adrenal insufficiency. De Bono et al have shown similar data for 10mg hydrocortisone (Debono: J Clin Endocrinol Metab. 2009) There is an increased mortality for patients taking more than 20mg/day with hypopituitarism (Hammarstrand C EJE 2017)

In clinical practice endocrinologists recommend hydrocortisone dose of 15-25mg per day (split 2-4 times/day with highest dose in the morning)

Prednisolone replacement:

Alrt et al (JCEM 2010) showed that when higher than physiological dosing with prednisolone is given (median 7.5 mg per day), glucocorticoid replacement in CAH is associated with poorer health status, with an increased incidence of obesity, hypertension, osteoporosis and reduced quality of life and fertility. Does as described in the BNF are therefore causing harm. There is data for prednisolone showing that 4mg a day results in physiological replacement serum levels (Williams EL 2016).

In clinical practice endocrinologists recommend prednisolone dose of 3-5mg (usually in a single dose, sometimes split to 2 doses) is the starting dosing for physiological replacement.

Dexamethasone

Dexamethasone is very rarely used in management of adrenal insufficiency- it is only used for a handful of patients with congenital adrenal hyperplasia where it has been difficult to achieve metabolic control. Dexamethasone is very long acting and associated with high rate of symptoms and signs of glucocorticoid excess such as weight gain, hyperphagia, red striae, osteoporosis development of diabetes, avascular necrosis of femoral neck or other bones. s challenging to gain metabolic control. The plasma half-life is 3.5 - 4.5 hours but as dexamethasone binds for a long time to the glucocorticoid receptor the biological half-life is more relevant, which is 36 - 54 hours hence it is not appropriate to use as a physiological replacement glucocorticoid to mimic usual 24-hour diurnal rhythm. Using data from short synacthen testing doses higher than 0.5mg a day have shown suppression of the HPA axis hence the recommending dosing in 0.3-0.5mg a day if used.

Fludrocortisone

Most patients with primary adrenal insufficiency will be adequately replaced with doses of fludrocortisone up to 300mcg/day as stated in the BNF. Some will have report salt craving, postural symptoms and have a low serum sodium and high plasma renin indicative of under replacement of mineralocorticoid, and requirement high doses of fludrocortisone and even salt replacement. This has to be judged on a case-by-case basis.

We would advocate use of these doses for daily replacement as described in this guideline together with sick-day rules dosing to account for increase in cortisol production during physiological and severe psychological stress as the safest way to manage adrenal insufficiency based on the available evidence and expert consensus.

This dosing is also recommended internationally in American Endocrine Society Guidelines. Emergency management is described in the Society for Endocrinology guidance below.

American Endocrine Society Guideline:
Stefan R. Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy, Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 101, Issue 2, 1 February 2016, Pages 364–389, https://doi.org/10.1210/jc.2015-1710

Society for Endocrinology Guidance:
Arlt W; Society for Endocrinology Clinical Committee. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect. 2016