

Safer care for patients with adrenal insufficiency: weighing the evidence, balancing risks and acknowledging uncertainties

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ABSTRACT

The National Patient Safety Alert supporting early recognition and treatment of adrenal crisis is a vital new component of care for adults affected by primary adrenal insufficiency. Benefits for patients with secondary and tertiary adrenal insufficiency need to be weighed alongside other considerations such as security of the diagnosis, relative likelihood of adrenal crisis and potential for anxiety and distress from assigning ‘physical dependency’ in relation to glucocorticoid therapy. All clinicians must be vigilant for and responsive to managing risks of adrenal crisis in at-risk patients, while avoiding diagnostic anchoring in the context of acute illness. More research is required to help define who is at greatest risk of adverse outcomes (including avoidance of therapeutic glucocorticoid therapy for fear of adrenal insufficiency) and a cross-specialty approach is advocated.

KEYWORDS: adrenal crisis, glucocorticoids, hypothalamic – pituitary adrenal axis

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A National Patient Safety Alert (NatPSA) to support early recognition and treatment of adrenal crisis in adults is being implemented across England. This was prompted by deaths and incidents of severe harm affecting patients with adrenal

insufficiency (AI) deemed ‘preventable in most, if not all, cases’.^{1,2} The NatPSA is founded upon recent guidance aiming to change the way all healthcare professionals are alerted to AI.² A Steroid Emergency Card has been formulated for issue to patients at risk of adrenal crisis, with additional direction on optimising procedures to identify eligible individuals. In patients affected by primary adrenal insufficiency, the delivery of high-dose glucocorticoid (GC) therapy and saline-containing fluids treats a combined deficiency in cortisol and aldosterone, often to life-saving effect. It is essential that such individuals never miss their steroids and the advice given on the new Steroid Emergency Card is clear in this respect. However, we would like to raise the possibility that application of the NatPSA to other forms of AI can be less straightforward, with the concept of relative risk for adrenal crisis being a central consideration.

In secondary and tertiary AI, pituitary or hypothalamic insufficiency occurs in the presence of intact adrenal glands and mineralocorticoid function (aldosterone secretion from renin-angiotensin activation). This provides a physiological rationale for reduced risk of adrenal crisis due to relatively preserved water and sodium balance compared with primary AI. Studies addressing respective risks are limited but suggest lower crisis rates in secondary AI.^{4–6} Where deficiency of vasopressin (antidiuretic hormone) co-exists with the reduced or absent adrenocorticotrophic hormone (ACTH) secretion of secondary AI (as may occur with more severe pituitary dysfunction), crises are more frequently reported.^{6–8} This raises the possibility of adverse synergies between ‘adrenal crisis’ and inadequately managed cranial diabetes insipidus (CDI). It is noteworthy that CDI was itself the subject of a preceding NatPSA, with which the present alert is competing for clinician ‘bandwidth’ as it emerges into an English NHS coping with the effects of COVID-19.⁹

Relative rates of adrenal crisis are reported least frequently for tertiary AI, in which exogenous GCs suppress the hypothalamic stimulus to cortisol secretion. Limited reporting almost certainly over-estimates risk, due to the small numbers of patients with crises identified and large numbers of GC-treated individuals in the general population who have not had their adrenal reserve assessed.¹⁰ As highlighted by guidance supporting the NatPSA, responses to synthetic ACTH tests may be suboptimal in a significant proportion of patients with high cumulative GC exposure.¹¹ However, robust evidence that this actually translates into a meaningfully increased risk of adrenal crisis is currently lacking.

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These considerations inform our principal concern, that the provision of a Steroid Emergency Card bearing the legend 'THIS PATIENT IS PHYSICALLY DEPENDENT ON DAILY STEROID THERAPY as a critical medicine' may not be appropriate for all patients. Without careful consideration, appropriate caveats and timely reassessment of the decision to issue it, excessive anxiety or distress could arise. As highlighted in supporting guidance, high-dose GCs may be given in a vast array of conditions including systemic vasculitides, haemo- and lymphoproliferative disorders, and for anti-emesis.^{2,11} For patients with asthma receiving inhaled corticosteroids (ICS), fear of AI may present a barrier to adherence. A high proportion of asthma sufferers fail to make adequate use of prescribed ICS and have a correspondingly increased risk for exacerbations, emergency department attendances, admissions and death. In those already struggling to achieve the minimum necessary engagement with prescribed regimens, entrenching non-adherence to ICS (already the largest causes of asthma deaths in the UK) would be a tragedy.¹²

As national uptake of the NatPSA proceeds, patients stand to benefit from greater recognition at point-of-interface with healthcare systems. Increasing use of electronic record systems should mean that correct coding results in more patients with AI receiving enhanced GC therapy for elective surgery, critical illness or trauma. However, we are also concerned that the presentation of the Steroid Emergency Card does not lead to misdirected medical management. Akin to challenges arising in the implementation of NatPSA processes for wrong-site surgery, potential pitfalls include diffusion of responsibilities around patient care, increased hazard signalling (struggling to 'see the wood for the trees') and clinical haste in assigning a diagnosis and acting on it.¹³ With diagnostic anchoring, delayed treatment of other acute disorders that mimic adrenal crisis is a possibility (eg sepsis, pulmonary embolism or myocardial infarction).

In dealing with risk, a balance of benefits and harms to patients must be sought. We suggest that the significant risk of crisis in patients with primary AI merits the fullest interpretation of available guidance. We propose that the risks of crisis need to be expressed in relative terms for patient groups expected to mount greater physiological responses to stress and critical illness, ie some secondary AI and perhaps most tertiary AI diagnosed on exogenous steroid exposure alone. Clinical discussions with individual patients may need to encompass greater diagnostic and prognostic uncertainty, especially for tertiary AI, where resources for formal adrenal reserve assessment are outweighed by the potentially enormous number of patients 'at risk'.

We applaud the efforts that have gone into the development of the guidance underpinning the NatPSA. This sets the stage for a wider discussion of how best to tackle these issues in an integrated fashion. Acknowledging the present uncertainties, it is

now beholden on the community of clinicians enfranchised across specialties to build the evidence base in this area. With careful coordination, the best possible balance of informed benefits should be achievable for all patients, wherever they may fall on the spectrum of risk for adrenal crisis. ■

References

- 1 NHS. *Steroid Emergency Card to support early recognition and treatment of adrenal crisis in adults: 13 August 2020: NatPSA/2020/005/NHSPS*. NHS, 2020.
- 2 Simpson H, Tomlinson J, Wass J, Dean J, Arlt W. Guidance for the prevention and emergency management of patients with adrenal insufficiency. *Clin Med* 2020;20:371–8.
- 3 Ahmed AB, George BC, Gonzalez-Auvert C *et al*. Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by glucocorticoids. *J Clin Invest* 1967;46:111–23.
- 4 Arlt W, Allolio B. Adrenal insufficiency. *Lancet* 2003;361:1881–93.
- 5 Hahner S, Loeffler M, Bleicken B *et al*. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *Eur J Endocrinol* 2010;162:597–602.
- 6 Hahner S, Spinnler C, Fassnacht M *et al*. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *J Clin Endocrinol Metab* 2015;100:407–16.
- 7 Broersen LHA, van Haalen FM, Kienitz T *et al*. The incidence of adrenal crisis in the postoperative period of HPA axis insufficiency after surgical treatment for Cushing's syndrome. *Eur J Endocrinol* 2019;181:201–10.
- 8 Omori K, Nomura K, Shimizu S, Omori N, Takano K. Risk factors for adrenal crisis in patients with adrenal insufficiency. *Endocr J* 2003;50:745–52.
- 9 NHS England. *Patient safety alert: Stage One: Warning: Risk of severe harm or death when desmopressin is omitted or delayed in patients with cranial diabetes insipidus*. NHS, 2016.
- 10 Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. *Clin Endocrinol (Oxf)* 2016;84:17–22.
- 11 Specialist Pharmacy Service. *Guidance on issuing the Steroid Emergency Card in adults*. SPS, 2021. www.sps.nhs.uk/articles/advice-on-issuing-the-steroid-emergency-card-update-23rd-december-2020
- 12 Royal College of Physicians. *Why asthma still kills: The National Review of Asthma Deaths (NRAD): Confidential Enquiry report*. London: RCP, 2014.
- 13 Rhodes P, Giles SJ, Cook GA *et al*. Assessment of the implementation of a national patient safety alert to reduce wrong site surgery. *Qual Saf Health Care* 2008;17:409–15.

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