

Novel medications inducing adrenal insufficiency

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Emerging evidence demonstrates that an increasing number of novel medications have considerable potential to induce adrenal insufficiency. This condition might lead to acute adrenocortical insufficiency, which is potentially fatal; however, the condition could be avoided if clinicians are more aware of the new findings and their implications.

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An adequate adrenal stress response is essential to maintain the vital functions of the human body in health and disease¹. However, iatrogenic suppression of the hypothalamic–pituitary–adrenal (HPA) axis is an increasing challenge for clinicians². One important factor is the widespread use of novel steroid medications to manage chronic diseases in an ageing society^{1,3}. Novel drugs targeting common disorders (for example, hypertension or cancer) interfere with adrenal steroid synthesis or metabolism and have the potential to induce adrenal suppression. Here, we comment on evidence and mechanisms related to medications that induce adrenal insufficiency. Furthermore, we suggest steps to be taken to tackle this problem.

Steroid hormone synthesis inhibitors

Common malignancies, such as prostate or breast cancer, are treated with hormonal deprivation therapy. However, in tumours refractory to the standard treatments, novel selective steroid hormone synthesis inhibitors show promise. For example, 17 α -hydroxylase (CYP17A1) inhibitors (abiraterone for prostate cancer) can suppress androgen production but also induce cortisol deficiency⁴. Patients treated with these inhibitors require glucocorticoid replacement therapy to avoid adrenal crisis, to lower progesterone and aldosterone accumulation and to decrease hypertension. However, such replacement therapy (up to 10–20 mg prednisone) exposes patients to excess glucocorticoids and the risk of acute adrenal crisis⁴.

In the future, more potent inhibitors of androgen production might be developed. For example, in 2018, a phase I clinical trial was commenced to investigate novel selective cholesterol side-chain cleavage inhibitors for prostate cancer⁵. However, this drug will induce a complete blockade of the production of all major steroids, including cortisol, aldosterone and androgens. All treated patients will require hormone replacement therapy and should be trained in prevention of adrenal crisis.

Aldosterone synthase (CYP11B2) inhibition has the potential to prevent metabolic, cardiac and renal dysfunction in patients with the metabolic syndrome⁶. However,

at higher doses, these compounds induce a general inhibition of 11 β -hydroxylase activity, which lowers aldosterone and cortisol production. Once these medications enter widespread clinical use, adrenal function, particularly during stress, should be monitored (BOX 1).

Checkpoint inhibitors

Many patients with advanced skin tumours and other solid tumours as well as haematological malignancies are now being treated with immune checkpoint inhibitors (ICIs; antibodies that block key immune checkpoint proteins, such as CTLA4 or PD1). However, it has become apparent that ICI-induced endocrinopathies are a frequent adverse effect of these medications. Over 50% of these endocrinopathies involve an impairment of HPA axis function⁷ (BOX 1). Of note, appropriate immune–endocrine crosstalk is crucial for the function of the adrenal stress axis¹. For example, inflammatory cytokines (such as IL-1, IL-6 and TNF) regulate the HPA axis. Immune cells interact directly with corticotrophs as well as adrenal cells. In addition, adrenal cells express Toll-like receptors and chemokine receptors that facilitate the immune–adrenal response during inflammation¹.

Inflammation, sepsis and autoimmune disease are known to induce adrenal insufficiency¹. Unsurprisingly, ICIs can also have a major effect on HPA axis function. The HPA axis might also be disrupted by inflammation of the pituitary gland, which blunts adrenocorticotrophic hormone (ACTH) release, or, less commonly, ICIs might directly impair the adrenal gland^{1,7}. The mechanisms of HPA axis dysregulation are not fully explored. However, data suggest that blocking expression of CTLA4 on endocrine cells (for example, by ipilimumab treatment) leads to site-specific deposition of complement components, pituitary infiltration and hypophysitis⁷.

Alarmingly, an increase has occurred in the number of reports of adrenal crisis in patients treated with ICIs^{1,7}. The first onset of symptoms can occur as early as 1 week or as late as 416 weeks after treatment with ICIs, requiring constant clinical vigilance. Furthermore,

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“patients on these medications ... should be equipped with an emergency identification card and a kit for self-treatment of adrenal insufficiency”

the drug's adverse effect profile might change during its life cycle and patients might have additional predisposing factors that increase the risk of adrenal crisis. Finally, ICIs might affect other endocrine organs, such as the thyroid gland⁷. If hypothyroidism is treated before steroid replacement, then severe adrenal crisis might occur.

Multiple drug interactions

Novel medications that might have a low or moderate risk of inducing full adrenal insufficiency in patients with an intact HPA axis have the risk of causing substantial damage in patients with a partially or subclinically impaired adrenal stress response. For example, in our ageing society, it is reported that >5% of the population have been exposed to glucocorticoid treatment and will have suppressed HPA axis function¹.

The most common cause of HPA axis failure is systemic glucocorticoid administration. For example, data confirm a clear dose dependency of iatrogenic glucocorticoid excess and adrenal insufficiency³. By contrast, co-prescribing of low dose steroids (for example, inhaled fluticasone) together with medications inhibiting CYP3A4 (for example, ritonavir) substantially potentiates exposure to steroids and might induce long-term secondary adrenal insufficiency. Drugs that lower

cholesterol (the substrate for steroid biosynthesis) levels (for example, statins or the potent PCSK9 inhibitors) do not affect adrenal steroidogenesis under normal conditions. However, they might contribute to adrenal insufficiency under stress or in combination with other drugs that affect steroid metabolism⁸.

Patients with hepatitis or liver disease have impaired adrenal function. For example, a substantial proportion of patients with alcoholic liver disease have impaired adrenal function, as do patients with chronic infections (for example, viral hepatitis, HIV or *Mycobacterium tuberculosis*)¹. In addition, up to 30% of patients receiving opioids have a suppressed HPA axis⁹. Opioids exert a tonic inhibition on the HPA axis, blocking hypothalamic corticotropin-releasing hormone (CRH) release and subsequent ACTH and cortisol production. Finally, we are beginning to learn more about environmental endocrine disruptors and chemicals that block adrenal steroid production and predispose to an impaired HPA axis¹⁰ (BOX 1).

What needs to be done?

First, we should raise awareness about this problem among the endocrine community and among health-care professionals. Second, patients on these medications (BOX 1) should be equipped with an emergency identification card and a kit for self-treatment of adrenal insufficiency. Education and training of patients, their carers and relatives (as required for patients with Addison disease) should be offered. Third, we should develop appropriate test systems to explore the effects of novel medications on HPA axis function. Finally, we suggest the development of a digital application using a machine learning algorithm to help health-care professionals assess risk for adrenal insufficiency in their patients.

Box 1 | Examples of medications causing or predisposing to adrenal insufficiency

Steroids (systemic, intra-articular or inhaled)

- Cause adrenal suppression through negative feedback on hypothalamus and pituitary

CYP3A4 inhibitors (HIV drugs (for example, ritonavir), antifungal drugs (for example, fluconazole) and antidepressants (for example, fluvoxamine))

- Adrenal suppression occurs in combination with low dose steroids (intranasal or inhaled, for example, fluticasone)
- Potentiating exposure to steroids, which enhances adrenal suppression through negative feedback

Opioids (morphine, fentanyl, tramadol, methadone or mixed opioids)

- Tonic inhibition on the hypothalamic–pituitary–adrenal (HPA) axis blocking hypothalamic corticotropin-releasing hormone (CRH) release

Immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab and avelumab)

- Hypophysitis due to pituitary infiltration of lymphocytes, leading to adrenocorticotrophic hormone (ACTH) deficiency
- Less commonly, direct impairment of adrenal cortex

Lipid-lowering therapies (statins, PCSK9 inhibitors and LDL apheresis)

- Under normal conditions may be safe in humans
- Based on data in animal models and in state of very low cholesterol availability or impaired liver function, adequate synthesis of cortisol may be impaired

Anti-prostate cancer drugs (abiraterone or novel steroid blocking agents, for example ODM-208)

- Inhibition of steroid synthesis at multiple levels (for example cholesterol side-chain cleavage enzyme, 17-hydroxylase and 21-hydroxylase) will induce various degrees of decreased cortisol production

Aldosterone synthase inhibitors (for example, LCI699)

- Inhibition of 11-hydroxylase activity (CYP11B2) at higher doses will decrease both aldosterone and cortisol synthesis

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Competing interests

The authors declare no competing interests.