

Adrenal crisis precipitated by the interaction of apalutamide with corticosteroids



ST JOHN OF GOD
Subiaco Hospital

Author: Christopher Kleemann, BA/BSc MPharm GradDipClinPharm MSHP, St John of God Subiaco Hospital

Background

Primary adrenal insufficiency is the inability of the adrenal glands to produce endogenous cortisol and aldosterone. Patients with primary adrenal insufficiency are reliant on oral replacement of these steroid hormones. Apalutamide is a medication indicated in the treatment of prostate cancer (PC) in both the locally advanced and metastatic setting. It induces CYP enzymes including CYP3A4.⁽¹⁾

Aim

Demonstrate how apalutamide mediated CYP3A4 induction can result in increased metabolism of cortisone and fludrocortisone leading to adrenal crisis

HYPOTHALAMIC PITUITARY ADRENAL AXIS

The HPA axis is a neuroendocrine system that controls the body's reaction to stress and regulates bodily processes such as digestion, immune function, sexual activity, mood and emotions.



Clinical features

PRESENTING COMPLAINT

An 81 year old male with previously stable primary adrenal insufficiency presented to hospital with fatigue, weakness, headaches and light headedness on the background of PC. Recent medication changes include apalutamide with degarelix for PC commencing 3 weeks prior to admission. Other relevant medical history included stable multiple myeloma, renal impairment, single nephrectomy, gout and dyslipidaemia.

Biochemistry	Result	Ref. range
K+	6.1mmol/L	3.5-5.2 mmol/L
BGL	2.6mmol/L	4-7.8 mmol/L
Na+	133mmol/L	135-145 mmol/L
Cortisol	<30 nmol/L @17:00	70-400 nmol/L (PM)
T4	13.8 pmol/L	9-20 pmol/L
TSH	5.25 mIU/L	0.40-4.0 mIU/L

INITIAL MANAGEMENT AND PROGRESS

- Biochemical derangement managed
 - Glucose for hypoglycaemia
 - Calcium resonium for hyperkalaemia
 - IV hydration and hydrocortisone
- No clear cause of adrenal crisis identified
 - No indication of infection – afebrile, normal WCC and neutrophil count, normal CRP, no localising symptoms of infection
 - No recent trauma or surgery
 - No other clear stressors
 - Compliant with steroid replacement

Pharmacist literature review

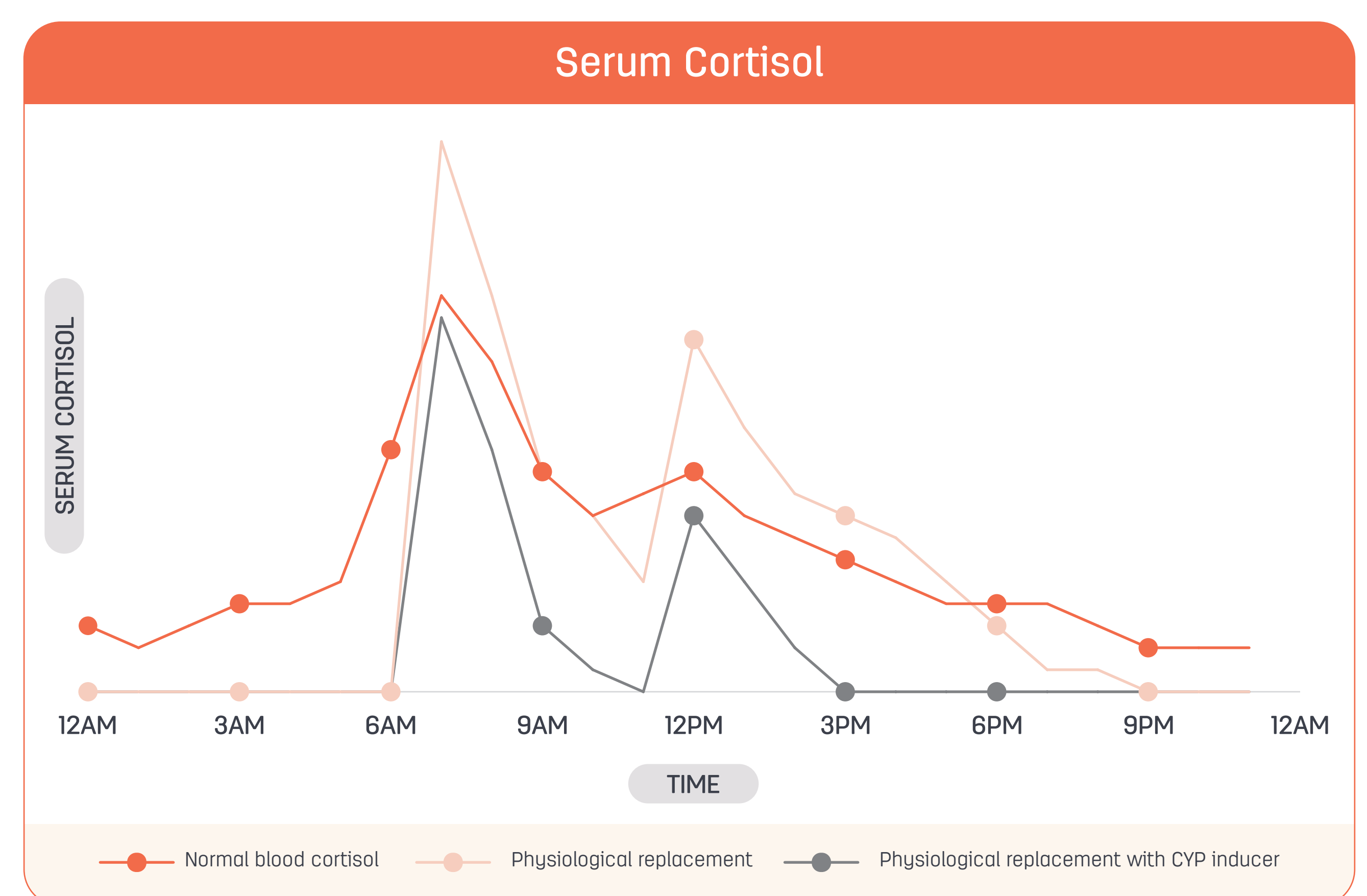
APALUTAMIDE

Apalutamide is a non-steroidal androgen receptor inhibitor used in the treatment of PC. It may be given with or without a gonadotrophin-releasing hormone antagonist such as degarelix. Apalutamide is a known strong CYP3A4 inducer based on manufacturers data.⁽¹⁾

CORTISONE AND FLUDROCORTISONE

Cortisone acetate and fludrocortisone are commonly used in Australia for physiologic replacement of cortisol and aldosterone in patients with adrenal insufficiency.

Corticosteroids are metabolised by CYP3A4.⁽²⁾ The interaction between apalutamide and corticosteroids has been theorised based on case reports with other strong CYP3A4 inhibitors such as phenytoin, carbamazepine and rifampicin.⁽³⁾ The specific interaction between apalutamide and corticosteroids has not been described in vivo or vitro.



Outcome

The interaction between apalutamide and corticosteroids was identified and brought to the attention of the treating team. Apalutamide was ceased, endocrinology consulted, and fludrocortisone dose increased from 100mcg daily to 200mcg daily.

Following the increase in fludrocortisone dose symptoms improved, serum electrolytes normalised, no further hypoglycaemic episodes occurred, and the patient was discharged after 5 days in hospital.

Conclusion

This case demonstrates the clinically relevant drug interactions corticosteroids can have, especially in the context of patients with adrenal insufficiency.

It highlights the strong CYP3A4 induction capabilities of apalutamide and the care that must be taken in assessing concurrent medications for interactions.

REFERENCES

- Australian Medicines Handbook 2020 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2020 July. Accessed: 2 Oct 2023. Available from: <https://amhonline.amh.net.au/>
- Dennis MW. Clinical Pharmacology of Corticosteroids. Respiratory Care [Internet]. 2018 Accessed: 2 Oct 2023; 63(6):655 p.]. Available from: <http://rc.rcjournal.com/content/63/6/655.abstract>
- Lexicomp® Drug Interactions (n.d.). UpToDate. Accessed: 2 Oct 2023. Available from: www.uptodate.com/drug-interactions/