Will the routine use of high dose steroids for alcoholic hepatitis result in an increased incidence of clinically significant hypocortisolism in patients with liver cirrhosis?

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Introduction

Recent evidence (the 2015 STOPAH trial[1]) supports the use of high dose steroids for 28 days for acute alcoholic hepatitis. We present a patient with liver cirrhosis treated for acute alcoholic hepatitis, who developed severe hyponatraemia a week after the steroids were abruptly stopped.

Low serum sodium in cirrhotics is common and an independent poor prognostic marker. It usually occurs in the context of portal hypertension, splanchnic vasodilatation and impairment of effective circulating volume, leading to activation of the renin-aldosterone system and vasopressin release that results in ascites and a dilutional hyponatraemia.

However hypocortisolism may already be prevalent (and under diagnosed) in this cohort (51% to 92% in review[2]). With this case report, we provide a clear diagnosis of adrenal insufficiency triggered by the acute withdrawal of 40mg prednisolone after 28 days in a patient with cirrhotic liver disease. We discuss the different causes of hypoadrenalism in this cohort and the salient biochemical features and diagnosis of hypocortisolism in the context of liver disease.

Case Report

A 48 year-old female was admitted under the Liver Team with acute alcoholic hepatitis, on a background of established Childs Pugh C liver cirrhosis, decompensated with encephalopathy and diuretic resistant ascites. She was treated with the usual supportive care and with a non-tapering 28-day course of high-dose (40mg) Prednisolone. Discharge medications included spironolactone 100mg od, rifaxamine 550mg bd, omeprazole 20mg od and propranolol 20 mg BD.

The patient was re-admitted 4 weeks later with severe, symptomatic hyponatraemia. She had remained abstinent since discharge and blood ethanol levels were negative. She was not encephalopathic. She was treated with antibiotics for an E Coli peritonitis diagnosed on (moderate volume) ascitic tap. The spironolactone was discontinued. 2 weeks later her profound hyponatraemia only responded to administration of IV hydrocortisone, given empirically with the diagnosis of possible adrenal suppression in mind.

Endocrine workup and opinion is summarised in the boxes below.

Investigations and management

Based on the biochemical tests below, the patient was diagnosed with suppression of her hypothalamic-adrenal axis, due to the abrupt discontinuation of high dose steroids in the setting of poor adrenal synthetic function due to advanced alcoholic liver disease. Her clinically significant hypocortisolism was treated with hydrocortisone replacement therapy. She was counselled about the importance of her steroid treatment and sick day rules.

Cortisol measurement issues in cirrhosis

Normally, 70% of circulating cortisol is bound to corticosteroid-binding globulin (CBG), 20% is bound to albumin, and the remaining 10% is unbound or “free cortisol” (FC - this is biologically active).

Routine laboratory testing provides a total cortisol result (TC) – that is free plus bound cortisol. Since hepatic protein production is impaired in liver disease, total cortisol results can be misleading.

Proxy markers of FC include salivary cortisol. However, the cortisol index (FCI), which is the serum total cortisol/CBG ratio, has been shown to correlate best with actual serum free cortisol in cirrhotics[3].

Biochemistry

Serum sodium at completion of the course of prednisolone (prior to discontinuation): 131 mmol/L
Serum sodium at readmission, 4 weeks later: 104 mmol/L
Serum sodium following hydrocortisone replacement: 138 mmol/L

Short Synacthen test, 4 weeks following cessation of prednisolone:
ACTH <5 pg/ml
Basal cortisol (09:00am): 44 mmol/L
Cortisol at 30 minutes: 107 mmol/L
Cortisol at 60 minutes: 137 mmol/L (normal peak on local guidelines >450 nmol/L)
Cortisol post-hydrocortisone dose: 764 mmol/L
Serum albumin: 26 g/L
Cortisol-binding globulin (CBG): 43.2 mg/L (normal range 31.0-53.4 mg/L)

The free cortisol index (FCI) is a surrogate marker for free cortisol and is defined as total cortisol (nmol/L)/CBG (mg/L) with a FCI > 12 representing sufficient adrenal reserve[4]. This patient’s peak, post-synachthen FCI was 9.09.

Follow Up

The patient was discharged off spironolactone and on hydrocortisone 10/5/5 mg tds. Spironolactone was gradually reintroduced up to 100mg od to treat her ascites, with no affect on serum sodium. A full pituitary profile revealed normal thyroid function and prolactin levels, although she was amenorrhoeic with low gonadotrophins suggesting an element of pituitary dysfunction as a result of her chronic liver disease.

A repeat long synacthen test reported a baseline cortisol of 770 mmol/L and so her hydrocortisone replacement therapy was stopped. Her sodium dropped from 136 mmol/L to 121 mmol/L and she became confused. It transpired that the patient had actually taken a dose of hydrocortisone the morning of the last synacthen test. It was repeated correctly and her 0 minute sample was 149 mmol/L, staying at 144 mmol/L at 60 minutes. The hydrocortisone replacement therapy was re-started.

Discussion

With this case report we bring to our Endocrine colleagues the following discussion points:

1. **The use of high dose Prednisolone for 28 days in the treatment of alcoholic hepatitis in patients with liver cirrhosis should be used cautiously and be recognised as a risk for subsequent adrenal suppression. Hepatologists should consider adrenal axis interrogation after completion of such courses.**
2. The biochemical diagnosis of hypocortisolism is a particular challenge in such patients and must be done under expert Endocrine guidance.
3. A crucial issue remains to establish whether or when adrenal insufficiency has clinical consequences in cirrhosis, and if so, whether this can be prevented and/or remedied by cortisol supplementation therapy.

References

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Adrenal and steroids
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