Investigation vignette

A 54 Year old Man with Hypotension, Abdominal pain and Pyrexia

CASE REPORT

A 52 year old man was admitted to a peripheral hospital with nausea, vomiting, diarrhoea and epigastric pain. He was in sinus rhythm, with a heart rate of 126 beats/min, his blood pressure was 80/60 mmHg and his temperature was 38.9ºC. A provisional diagnosis of a ruptured peptic ulcer was made and he underwent a laparotomy. However, the operation revealed no abnormality so he was transferred to our hospital for further management.

On arrival he was sedated and mechanically ventilated with a pulse rate of 138 beats per minute blood pressure of 70/45 mmHg (on a noradrenaline infusion at 60 ug/min).

He had been anuric for the previous 3 hours (despite receiving 1 litre of 4% albumin in 0.9% saline, 1 litre of Gelofusine® and 1.5 litres of 0.9% saline) and had a temperature of 39.2ºC.

A diagnosis of septicaemic shock of unknown aetiology was made and so he was transferred to the intensive care unit (ICU) after venous blood sample had been sent for blood culture, plasma electrolytes, renal function and liver function tests. Intravenous Vancomycin (1 g), gentamycin (320 mg), and metronidazole (500 mg) were administered before the results of the first plasma blood samples were available (Figure 1).

Name	Age	Sex
Mr. B. F.	54	M

Sodium	125	mmol/L	(137 - 145)
Potassium	6.8	mmol/L	(3.1 - 4.2)
Chloride	104	mmol/L	(101 - 109)
Bicarbonate	14	mmol/L	(22 - 32)
Anion Gap	13.8	mEq/L	(8 - 16)
Calc Osmolarity	267	mmol/L	(280 - 300)
Glucose	2.2	mmol/L	(3.0 - 6.0)
Urea	15.2	mmol/L	(3.0 - 8.0)
Creatinine	0.18	mmol/L	(0.05 - 0.12)
Urate	0.35	mmol/L	(0.25 - 0.45)
Phosphate	0.88	mmol/L	(0.70 - 1.25)
Total Calcium	2.62	mmol/L	(2.10 - 2.55)
Albumin	42	g/L	(39 - 50)
Globulins	31	g/L	(22 - 35)
Cholesterol	3.7	mmol/L	(desirable < 5.5)
Total Bilirubin	12	µmol/L	(4 - 20)
GGT	19	U/L	(0 - 50)
ALP	53	U/L	(30 - 100)
LD	210	U/L	(110 - 230)
AST	48	U/L	(10 - 45)

Figure 1. The plasma biochemical profile on admission to the intensive care unit

Diagnosis: Primary adrenocortical insufficiency (Addison's disease)

The hypotension, abdominal pain and pyrexia in this case were caused by adrenocortical failure. The reduced mineralocorticoid effect caused a decrease in sodium reabsorption and decrease in potassium and hydrogen ion secretion at the distal nephron causing a normal anion gap acidosis (type IV renal tubular acidosis), hyponatraemia and hyperkalaemia (with a Na^+:K^+ ratio of < 25:1). The hypoglycaemia was caused by a reduction in glucocorticoid induced gluconeogenesis and the hypercalcaemia was caused by calcium mobilisation from bone,[1] associated with decreased glomerular filtration and increased tubular calcium reabsorption secondary to volume depletion.[2] A short synacthen test was performed, revealing a baseline cortisol of 53 nmol/L, 30 minute cortisol of 55 nmol/L and 60 minute cortisol level of 50 nmol/L, confirming the diagnosis of adrenocortical insufficiency.

Plasma cortisol levels in critically ill patients are usually elevated above 555 nmol/L (i.e., 20 μg/dL) with an associated loss in the diurnal rhythm.[3] However, the range is wide.[3,4] The maximum stress-induced output of cortisol is thought to be up to 555 μ mol/day (i.e., 200 mg/day), with corresponding plasma levels of approximately 1650 nmol/L (i.e., 60 μg/dL).[5] Reports of adrenal hyporesponsiveness in some acutely ill patients with severe inflammation[6,7] or septic shock,[8] and agents such as etomidate (which suppress cortisol synthesis), being associated with increased mortality[9,10] indicate that cortisol secretion is important in the critically ill patient.[11,12] However, the cortisol concentration appropriate for an acute illness is unknown, and there is no correlation between severity of illness and cortisol levels,[13] indicating that the relationship between cortisol secretion and mortality, is far from clear. This uncertainty is even greater in patients who already take glucocorticoid medication.

The short synacthen test normally requires the plasma cortisol level to increase two or three times the basal level and be more than 500 nmol/L with stimulation, to reveal a responsive adrenal cortex. Typically, the basal plasma cortisol levels are more than 200 nmol/L rising to 500 nmol/L after administering synacthen. In Addison's disease the baseline cortisol levels are often < 100 nmol/L (if ACTH levels are also measured then they are usually > 200 ng/L), and with stimulation the plasma cortisol does not rise. If secondary (i.e. pituitary) adrenocorticoid insufficiency is suspected (e.g. ACTH level < 10 ng/L), then 1 mg of synacthen is administered intramuscularly daily for 3 days and then 48 hr after the last dose a short synacthen test is performed. If hydrocortisone has been administered, the short synacthen test should be performed after a 24 hr delay.

However, some believe that in the critically ill patient the cortisol rise with the short synacthen test should be at least 250 nmol/L, irrespective of the baseline cortisol level.[14,15] A modification of the short synacthen test, known as the *low-dose corticotropin test*, has been used to detect partial adrenal insufficiency.[16-18] This test requires a baseline plasma cortisol level to be taken before 1 μg synacthen is administered i.v. A plasma cortisol level is taken 30 minutes later, with a normal response being defined as a stimulated plasma cortisol level of > 550 nmol/L.[19] In the critically ill patient a cortisol level < 500 nmol/L, 30 minutes after 1μg of synacthen, indicates impaired adrenal reserve.[20]

With bilateral adrenal failure the serum cortisol levels are usually less than 50 nmol/L and the diagnosis of hypoadrenalism is not in doubt. In critically ill patients (particularly those in whom the baseline cortisol level is less than 414 nmol/L),[21] glucocorticoid replacement (e.g. 200 mg of hydrocortisone/day as a continuous infusion)[21] has been recommended if a short synacthen test does not elicit a rise in serum cortisol of at least 250 nmol/L.[13-15,21]

In critically illness a plasma cortisol level of more than 700 nmol/L (i.e. 25 μg/dL) probably rules out adrenal insufficiency,[22] although one review put the upper level at 938 nmol/L (i.e. 34 μg/dL).[21] In a recent multicentre, placebo controlled, randomised, double blind study of mechanically ventilated, critically ill patients with septic shock, unresponsive to intravenous fluids and catecholamine infusions, 7 days of intravenous hydrocortisone (50 mg 6-hourly) and nasogastric tube instillation of 9-α-fludrocortisone (50 μg in 10 - 40 mL water) significantly reduced the 28 day mortality in patients with relative adrenal insufficiency (i.e. those who had a cortisol rise of < 9 μg/dL or 250 nmol/L at 30 or 60 minute following 0.25 mg of synacthen intravenously).[23] The number needed to treat was 7 patients to save one additional life. Nevertheless, steroid treatment may not be without hazard as this study reported a slight increase in mortality in patients who were adrenal 'responsive' who received cortisol and 9-α-fludrocortisone compared with the placebo group.[23]

The patient who presents with an adrenal crisis can appear to be in 'septic' shock (with high cardiac output and decreased systemic vascular resistance) or hypovolaemic shock (with decreased preload, myocardial contractility and increased systemic vascular

resistance),[11] although the features of eosinophilia and hypoglycaemia are uncharacteristic of a 'septic' or 'hypovolaemic' event. The cardiovascular effects are probably secondary to a reduction in intravascular volume (due to vomiting and chronic salt wasting) and reduction in myocardial contractility and peripheral resistance due to a reduction in adrenoreceptor sensitivity to catecholamines.[12] While the hyperkalaemia may be severe (e.g. > 7 mmol/L) and associated with ECG changes; cardiac arrest from hyperkalaemia due to Addison's disease is rare, probably due to the slow rise in plasma potassium and presence of hypercalcaemia.

In this report, the patient was admitted to the ICU with a diagnosis of 'septic shock' with hypotension resistant to noradrenaline and intravenous fluids. After 4 hours of treatment with hydrocortisone (100 mg as a loading dose, followed by 50 mg intravenously 4-hourly) and intravenous fluids (1 litre of 5% dextrose with 100 mmol sodium bicarbonate in 2 hours followed by 1 litre of 0.9% saline in 6 hours), the noradrenaline was discontinued with a blood pressure of 120/55 mmHg, pulse of 82 beats per minute, temperature of 36.8ºC and a urine output of 230 mL at the 4th hour.

The patient was extubated after 24 hours and discharged to the ward for further management after a 48 hour stay in the ICU.

K. DESHPANDE
Department of Critical Care Medicinet, Flinders Medical Centre, Bedford Park, SOUTH AUSTRALIA

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