Combined therapy with dialysis and glucocorticoids in critically ill renal failure patients

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Introduction

Sepsis syndrome is a significant cause of mortality in the dialysis population, accounting for more than 75% of all deaths from infection [1]. During many acute illnesses, including sepsis, an increase in serum levels of cortisol is an important physiological response that is protective against injury. This response is secondary to increased production of corticotropin-releasing hormone and corticotropin, as well as to a reduction in negative feedback from cortisol [2]. However, in addition to the well-known effect that pre-existing conditions have on the hypothalamic-pituitary-adrenal axis, it has recently been reported that cortisol deficiency occurs during the course of acute illness [3]. This blunting of the physiological response results from elevated cytokine levels, which induce systemic or tissue-specific corticosteroid resistance [4].

Cortisol deficiency in intensive care patients can be difficult to discern clinically, as clinical indicators of the diagnosis are frequently non-specific [3]. In addition, some laboratory findings accompanying this condition in the dialysis population, such as hyperkalaemia and hyponatraemia, can be misleading. In dialysis patients, the persistence of these disturbances even after the initiation of efficient dialysis treatment should raise the suspicion of cortisol deficiency, and more specific laboratory tests should be performed.

In this report, we describe four cases of sepsis syndrome in renal failure patients that, despite dialysis treatment in our intensive care unit, presented persistent hyperkalaemia, hyponatraemia, or both. We found these alterations to be related to cortisol deficiency, confirming that this phenomenon can occur even in the presence of renal failure and showing that aldosterone can act in all cells, mainly in intestinal cells.

Methods

Four septic patients under renal replacement therapy and treatment with vasopressors presented persistently high serum potassium and low serum sodium over an extended period of dialysis treatment. Free cortisol serum levels were measured by radioimmunoassay. Three presented cortisol levels lower than 15 μg/dl. In the one patient presenting a higher cortisol level (27 μg/dl), we performed the low-dose adrenocorticotropic hormone test. An intravenous injection of 1 μg of adrenocorticotropic hormone was given as previously described [5]. In this test, the cortisol level is measured upon administration at 30 and 60 min after administration. Hypoadrenalism is considered likely if the difference between the baseline cortisol level and that seen after administration of the adrenocorticotropic hormone is <9 μg/dl. In three of the four patients, thyroid hormone levels were also determined and were compared to reference values (T4, 4.5–1 μg/dl; T3, 40–180 ng/ml; Free T4, 0.6–1.54 ng/dl; TSH, 0.5–4.2 μU/ml).

Cases

Case 1

A 55-year-old white female kidney transplant patient was admitted to the ICU on the sixth post-operative day following the removal of a rejected kidney. She was in cardiorespiratory arrest due to hyperkalaemia. She had lost one renal graft 4 years before due to chronic graft nephropathy, and a second transplant now had also been rejected. She had been in regular dialysis treatment thrice weekly and had been receiving 5 mg/day of prednisone, which was discontinued after the most recent operation. Since then, despite 4 h of dialysis every other day, she presented serum levels of...
Case 2

A 58-year-old white male patient was admitted to the ICU in septic shock related to pleural empyema. He had high blood pressure, gout, chronic renal failure and coronary heart disease (having undergone coronary bypass surgery 6 years before). A tube thoracostomy was performed, and all infection parameters subsequently improved. However, it was not initially possible to wean the patient from vaso-active drugs. He was under continuous venovenous haemodiafiltration (Q_B = 160 ml/min; Q_D = 1500 ml/h; fluid reposition = 2000 ml/h) using a M100 dialyser (Gambro, Lakewood, CO, USA) on a Prisma machine. However, serum levels of potassium and sodium remained constant at ~7.4 mEq/l and 127 mEq/l, respectively. Thyroid hormone levels were as follows: T4, 5.9 µg/dl; T3, 96 ng/dl; free T4, 0.8 ng/dl; TSH, 3.78 µU/ml. Because the serum cortisol level was 27 µg/dl, an adrenocorticotropic test was performed, as previously described, and the results were positive. Hydrocortisone was started at 100 mg every 6 h and he was weaned from the vaso-active drugs. Serum electrolytes then returned to normal.

Case 3

A 74-year-old black female patient with chronic renal failure, secondary to high blood pressure and renovascular disease was admitted to the hospital for autograft of her right kidney. She subsequently developed infection of the vascular graft and sepsis requiring vaso-active drugs. Sustained low-efficiency haemodialysis (8 h/day) was started using a Fresenius 4008 machine with an F8 polysulphone dialyser at a Q_B of 200 ml/h and a Q_D of 300 ml/h. Despite the dialysis, serum sodium remained low (128 mEq/l), although serum potassium was normal. Random serum cortisol was 14 µg/l. Thyroid hormone levels were as follows: T4, 4.6 µg/dl; T3, 46 ng/dl; free T4, 0.7 ng/dl; TSH, 0.95 µU/ml. After hydrocortisone was started at 300 mg/d, the sodium level normalised, and the condition of the patient improved.

Case 4

A 66-year-old white male patient with persistent high blood pressure and non-dialytic chronic renal failure was admitted to the ICU due to septic shock and decompensated aortic insufficiency. Renal function deteriorated, and the patient required renal replacement therapy. After 40 days of continuous venovenous haemodialysis (Q_B = 150 ml/min; Q_D = 2000 ml/h; Baxter CA210 dialyser), serum potassium was still elevated (6.1–6.9 mEq/l), although serum sodium was normal. At that time, he was receiving vaso-active drugs. Random serum cortisol was 11.8 µg/dl. Hydrocortisone was started at 150 mg 3×/day, and potassium levels subsequently returned to normal. Nevertheless, the patient died 20 days later.

Discussion

Currently, the use of low doses of intravenous hydrocortisone (200–300 mg/day) is recommended for the treatment of septic shock [3]. The rationale for this practice is that relative adrenal insufficiency and peripheral steroid resistance is common in patients with septic shock. The results of various studies suggest that a random cortisol threshold of 15 µg/dl best identifies the patients who would benefit significantly from corticosteroid replacement. In addition, cortisol levels within the 15–34 µg/dl range should prompt a low-dose (1 µg) adrenocorticotropic test, which has been shown to be more sensitive than the 250 µg dose test [3,6].

In renal failure patients, clinical and biochemical data may be misleading. Dialysis usually corrects acid-base and electrolyte disturbances, such as high serum potassium and low serum sodium. The four cases described herein underscore the supposition that the persistence of these electrolyte disturbances after intensive dialysis treatment is a good clinical indicator of underlying cortisol insufficiency.

Glucocorticoids have profound effects on hemodynamics, such as increasing stroke volume, elevating blood pressure and potentiating noradrenaline pressor effects [7]. However, glucocorticoids also provoke widespread stimulation of Na^+–K^+–ATPase activity and increased synthesis of its subunits [8]. Although an important transport enzyme in the renal tubule (mainly in the cortical collecting tubule), glucocorticoid augments renal excretion of potassium and decreases urinary excretion of sodium.

Aldosterone also stimulates sodium transport in the renal collecting duct cells by activating the epithelial sodium channel (ENaC). It has been shown that aldosterone selectively increases abundance of the α-subunit of the ENaC and redistributes it to the apical region of the renal collecting duct cells [9]. In fact, corticosteroids (via glucocorticoid receptors) increase renal sodium transport through similar mechanisms [10].

The ENaC is a pathway for sodium transport across various epithelia, including the renal collecting duct,
lung and distal colon. Its function and regulation are critical points for sodium homoeostasis and blood pressure control. Impairment of its activity is responsible for inherited forms of hypertension (such as Liddle’s syndrome) and renal salt wasting. Sodium transport across epithelia is a two-step process: the ENaC forms a pathway for the cell entry of sodium, as Liddle’s syndrome) and renal salt wasting. Sodium levels of sodium and potassium before and after glucocorticosteroid treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Na/K (mEq/l)</th>
<th>Serum pH</th>
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<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Case 1</td>
<td>117/8.5</td>
<td>135/4.8</td>
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<td>Case 2</td>
<td>127/7.4</td>
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<td>Case 3</td>
<td>128/4.8</td>
<td>139/3.9</td>
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<tr>
<td>Case 4</td>
<td>136/6.9</td>
<td>138/4.2</td>
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In addition, thyroid hormones were normal in three patients. We can assume that the glucocorticoid-enhancing effect on the cell channels (Na$^+$–K$^+$–ATPase and ENaC) resulted in normalization of electrolyte levels. This occurred not only due to potassium loss in the gastro-intestinal tract (coupled with sodium absorption) but also secondary to a shift between the intracellular and extracellular compartments. We therefore, conclude that corticosteroids, mainly aldosterone, play an important role in electrolyte homoeostasis, in healthy individuals and dialysis patients alike. In addition, using dialysis therapy to treat critically ill renal failure patients with persistent hyperkalaemia and hyponatraemia can be challenging. The attending nephrologist and ICU physician should consider the use of glucocorticoids, together with renal replacement therapy, for treating these abnormalities in such patients.

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Conflict of interest statement. None declared.

References

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