Influence of concomitant prednisolone on trimethoprim-associated hyperkalaemia

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Objectives: Trimethoprim–sulfamethoxazole may cause hyperkalaemia by the amiloride-like effect of trimethoprim on sodium channels in the distal nephron. Hyperkalaemia usually occurs after 7–10 days and has been reported in 20%–50% of patients receiving trimethoprim–sulfamethoxazole. Patients with Pneumocystis jiroveci pneumonia and severe hypoxaemia benefit from the use of prednisolone as an adjuvant to trimethoprim–sulfamethoxazole. The addition of prednisolone may lower the incidence of trimethoprim-related hyperkalaemia due, in part, to its mineralocorticoid activity. We studied the effect of concomitant prednisolone on trimethoprim-related hyperkalaemia.

Patients: Thirty patients qualified for inclusion and were reviewed. Patients were divided into two groups: one group received trimethoprim–sulfamethoxazole plus prednisolone (18 patients); and the other group received trimethoprim–sulfamethoxazole alone (12 patients).

Results: The two groups were comparable at baseline, except for the severity of the P. jiroveci pneumonia. Hyperkalaemia developed in seven patients: all in the prednisolone and trimethoprim–sulfamethoxazole group. The greater incidence of hyperkalaemia in this group is surprising and was counter to our expectation.

Conclusions: Although it is possible that there is an unexplained interaction between trimethoprim and prednisolone, we postulate that our observation is a result of the catabolic effect of prednisolone. The patients treated with trimethoprim–sulfamethoxazole plus prednisolone appear to be more likely to develop hyperkalaemia than patients treated with trimethoprim–sulfamethoxazole alone.

Keywords: Pneumocystis pneumonia, HIV, prednisone, glucocorticoid, mineralocorticoid

Introduction

Hyperkalaemia is a common electrolyte abnormality seen in patients with AIDS. The reported incidence of hyperkalaemia among hospitalized patients with HIV ranges from 16% to 21%, which is much higher than the 1.4%–10% incidence of hyperkalaemia among all hospitalized patients.1,2 Factors associated with the development of hyperkalaemia in patients with HIV/AIDS include renal insufficiency, hypoaldosterone states and medications.1,3–6 Hyperkalaemia is a complication of high-dose trimethoprim and as many as 53% of patients receiving trimethoprim-based therapy for Pneumocystis jiroveci pneumonia (PCP)—formerly Pneumocystis carinii pneumonia—have been reported to develop hyperkalaemia.4,5,7,8 Trimethoprim–sulfamethoxazole is the therapy of choice for patients with PCP. A standard adjunctive corticosteroid therapy is used for patients with moderate to severe PCP, and consists of prednisolone at doses of 80 mg/day for 5 days followed by 40 mg/day for 5 days and then 20 mg/day for another 11 days.9

The additive effects of the increased distal delivery of sodium [from a glucocorticoid-related increased glomerular filtration rate (GFR)] and the mineralocorticoid effect exerted on the distal tubule by glucocorticoid therapy result in an acute transient kaliuresis.10 We hypothesized that the adjunctive corticosteroid therapy would ameliorate trimethoprim-associated hyperkalaemia. We evaluated the influence of prednisolone on trimethoprim-induced hyperkalaemia among patients being treated for PCP to determine whether corticosteroid therapy is protective.

Patients and methods

We reviewed the medical records of 135 patients treated with trimethoprim–sulfamethoxazole over 15 months at Harlem

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Prednisolone on TMP-associated hyperkalaemia

Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group 1 (with prednisolone)</th>
<th>Group 2 (without prednisolone)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>12</td>
<td>0.70</td>
</tr>
<tr>
<td>Sex ratio (male:female)</td>
<td>6:12</td>
<td>3:9</td>
<td>0.52</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>49.4 ± 8.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54.2 ± 23.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>22.4 ± 2.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25.2 ± 3.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>134 ± 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>135 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.50</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>3.8 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.1 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.58</td>
</tr>
<tr>
<td>Serum magnesium (mEq/L)</td>
<td>1.8 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.38</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>18 ± 13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 ± 7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.8 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.6</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>22 ± 4.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.8 ± 3.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.017</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.42 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.72</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>24.8 ± 10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23.3 ± 7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.45</td>
</tr>
<tr>
<td>CD4 count (if available) (cells/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>26 ± 16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41 ± 34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.61</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data reported as means ± SD. P values <0.05 were considered significant, as indicated by bold text.

Figure 1. Trend of mean BUN among patients in the two groups.

Hospital Center. Exclusion criteria were a baseline renal insufficiency (serum creatinine >1.5 mg/dL), medications known to influence serum potassium levels, including diuretics and angiotensin-converting enzyme inhibitors, trimethoprim dose <320 mg/day, and/or duration of therapy with trimethoprim <7 days. Patients with moderate to severe infection (PaO<sub>2</sub> < 70 mmHg, Aa gradient >35 mmHg) received trimethoprim–sulfamethoxazole with adjunctive prednisolone (Group 1) and were compared with patients with mild infection who received trimethoprim–sulfamethoxazole alone (Group 2).

Data reviewed included information on height, weight, medications, clinical findings, laboratory results, including serum electrolytes, hepatic profile, arterial blood gas and CD4 count (if available), and the dose of trimethoprim–sulfamethoxazole that the patients received. Information collected at the time of admission/initiation of therapy was included. We reviewed the serum chemistries for the duration of inpatient therapy. P values <0.05 were considered significant.

Results

Thirty patients met the inclusion criteria and were included [mean age of 51.3 years, mean body mass index (BMI) of 23.5 kg/m<sup>2</sup> ± 3.2, mean baseline serum creatinine of 0.9 ± 0.3 mg/dL, blood urea nitrogen (BUN) of 15 ± 11 mg/dL and serum potassium of 4.0 ± 0.5 mEq/L]. The patients were divided into two groups based on the therapy they received (Table 1) and the incidence of hyperkalaemia in the two groups was compared using the Fisher exact test. Hyperkalaemia occurred in seven patients—all in the group that received concomitant prednisolone and none in the group that received only trimethoprim–sulfamethoxazole (P=0.024). The two groups did not differ at baseline with respect to age, gender distribution, severity of HIV disease (measured by CD4 count), nutritional status (i.e. BMI and serum albumin), renal function (estimated by BUN and serum creatinine) or serum electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Cl<sup>-</sup>). Higher BUN concentrations developed over time in patients receiving prednisolone (Figure 1). There was a difference in the serum bicarbonate concentration between the two groups (22 ± 4.8 versus 26.8 ± 3.2 mEq/L, P=0.017), with no significant difference in the blood pH between the two groups (7.43 ± 0.05 versus 7.42 ± 0.05, P=NS). The lower mean serum bicarbonate in Group 1 in the absence of a significant difference in the blood pH between the two groups is likely to be the result of a greater hypoxaemia and respiratory alkalosis among patients in Group 1 and is unlikely to have influenced transcellular potassium shifts.

Discussion

Trimethoprim is structurally related to the potassium-sparing diuretic agent amiloride. This structural similarity allows trimethoprim at high concentrations to block amiloride-sensitive sodium channels and function like a potassium-sparing diuretic. Glucocorticoid administration has been reported to cause an acute transient kaliuresis that is thought to be a direct result of an increased GFR and the resultant increased sodium delivery to the distal nephron. This kaliuresis could possibly ameliorate the potassium-sparing effect of high-dose trimethoprim. Surprisingly, our results indicate that the addition of glucocorticoids potentiates, rather than ameliorates, the risk of hyperkalaemia.
Potassium and nitrogen are found within muscle cells in a fixed ratio of 2.7 mEq of potassium for each gram of nitrogen.\textsuperscript{14} As a result, protein breakdown in catabolic states results in the release of both nitrogen (in the form of urea) and potassium into the extracellular compartment in a predictable and proportional manner.\textsuperscript{15,16} Glucocorticoid excess-induced catabolic protein breakdown results in potassium release into the extracellular compartment. This release coupled with the potassium-sparing effect of high-dose trimethoprim may be the underlying mechanism for the increased incidence of hyperkalaemia that we observed in Group 1.

The BUN concentration on the eighth day among patients in Group 1 was significantly higher than in Group 2 (30 versus 11.8 mg/dL, \(P<0.05\); Figure 1). This finding correlates well with earlier studies of glucocorticoid-related catabolism, which suggest that the peak BUN excretion occurred on the eighth day.\textsuperscript{15} The expected concomitant increase in the extracellular nitrogen and potassium caused by glucocorticoid-induced catabolism may explain the significantly higher risk of hyperkalaemia among patients who receive trimethoprim–sulfamethoxazole with prednisolone.

Our study has several limitations, including the small sample size, the use of retrospective data extracted from medical charts and the absence of urinary findings, including direct measurement of potassium and urea nitrogen excretion rates.

Conclusions

The use of adjuvant prednisolone with trimethoprim–sulfamethoxazole appears to increase the risk of developing hyperkalaemia. The cause of the hyperkalaemia may be related to the catabolic effect of the concomitant glucocorticoid therapy in the setting of patients with trimethoprim-impaired potassium excretion. Additional prospective studies are required to determine whether the use of combination therapy predisposes patients to hyperkalaemia or only identifies high-risk patients.

Acknowledgements

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This study was conducted as part of our routine work.

Transparency declarations

None to declare.