Case Report

Refractory Hyperkalaemia Due to Trimethoprim, Successfully Treated with Fludrocortisone

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Abstract

We report a case of intractable hyperkalaemia in an elderly patient with myeloma, who received conventional dose of trimethoprim-sulfamethoxazole and hyperkalaemia resolved following therapy with fludrocortisone. We recommend monitoring of serum potassium in high-risk patients receiving conventional doses of trimethoprim-sulfamethoxazole for 5 or more days. ©

INTRODUCTION

Trimethoprim-Sulfamethoxazole (TMP-SMZ) is extensively used in clinical practice to treat a variety of infections of which urinary tract infections, respiratory tract infections and *Pneumocystis carinii* pneumonia (PCP) are the commonest. Higher doses TMP-SMZ are used to treat PCP. TMP-SMZ is known to produce several untoward renal reactions, such as acute interstitial nephritis and crystalluria causing acute renal failure. Hyperkalaemia is a rare, potentially life-threatening complication of trimethoprim especially when used in high doses.2

We report a case of intractable hyperkalaemia secondary to TMP-SMZ in an elderly patient with multiple myeloma, which resolved after administration of fludrocortisone.

CASE REPORT

A 65 year old man was admitted to hospital with complaints of backache and generalized weakness of two months duration and fever of one week duration. He was detected to be a diabetic six months previously. The physical examination revealed pallor, mild dehydration and tenderness over twelth thoracic and fourth lumbar vertebrae. He was afebrile, pulse rate was 82/minute and blood pressure was 130/85 mm Hg. The examination of respiratory, cardiovascular, nervous systems and abdomen was unremarkable. Investigations at the time of admission were: hemoglobin- 8.1gm/dl, WBC count- 6900/c.mm. (neutrophil- 81%, lymphocyte- 9%, eosinophil- 6%, monocyte- 4%), platelet count- 3,20,000/c.mm, ESR- 150mm at 1 hour, blood urea- 95mg/dl, serum creatinine- 2mg/dl, serum sodium- 122mEq/L, serum potassium- 3.6mEq/L, serum chloride- 87mEq/L, serum bicarbonate- 18mEq/L, serum protein- 7.2gm/dl, serum albumin- 2.6gm/dl, serum globulin- 4.6gm/dl, serum calcium- 8.0mg/dl, serum uric acid- 6.8mg/dl, serum LDH- 300IU/L and serum alkaline phosphatase- 1375 IU/L.

Urine examination showed albuminuria (1+), 4 to 5 RBC’s/hpf and glycosuria. Urine for Bence-Jones protein was positive. Bone marrow study showed 15.5% plasma cells. Serum protein immunoelectrophoresis showed monoclonal IgG kappa light chain. X-ray of the skull showed multiple punched out osteolytic lesions. X-ray of the spine showed compression fracture of twelth thoracic and fourth lumbar vertebrae. Diagnosis of multiple myeloma with acute renal failure secondary to cast nephropathy and intravascular volume depletion was made.

Dehydration was corrected with intravenous saline. Azotaemia improved (serum creatinine 1.5mg/dl) with correction of dehydration. He was started on chemotherapy consisting of intravenous methyl prednisolone 250 mg daily for 3 days and intravenous cyclophosphamide 800 mg. He developed fever following chemotherapy. In view of high prevalence of *Stenotrophomonas maltophilia* infection among subset of patients with malignancy receiving chemotherapy during that period in the hospital, he was given prophylactic Bactrim DS (trimethoprim 160mg, sulfamethoxazole 800mg) one tablet twice daily. Five days later he developed hyperkalaemia (serum potassium-5.6 mEq/L) and TMP-SMZ was stopped after 7 days therapy.

Hyperkalaemia continued to worsen and was refractory to 72 hours of intensive anti-kalaemic therapeutic measures consisting of dextrose-insulin infusion, intravenous saline to increase distal delivery.
of sodium, nebulization with β2 agonists and retention enema with potassium binding resin. Serum potassium level reached a peak of 6.5mEq/L and serial serum potassium readings are depicted in Fig. 1.

Several possible causes of persistent hyperkalaemia were considered. Renal failure alone was the unlikely cause, as estimated GFR by MDRD formula was 40ml/min, at which level hyperkalaemia is unlikely to develop. Arterial blood gas analysis did not show metabolic acidosis and there was no evidence of tumor lysis syndrome (serum calcium-9.4 mg/dl, serum phosphorous-4 mg/dl and serum uric acid-2.4 mg/dl). Trans-tubular potassium gradient (TTKG) was done to assess the distal tubular potassium secretion. Urine and serum potassium were 7 and 5.5 mEq/L respectively and urine and serum osmolality were 302 and 309 msom/kg respectively. Calculated TTKG was markedly low at 1.3 confirming the decreased distal tubular secretion of potassium. In the final analysis TMP-SMZ was thought to be the cause of persistent hyperkalaemia. As hyperkalaemia was intractable, fludrocortisone 0.1 mg/day was started and continued for 3 days. Response was gradual but sustained. Serum potassium normalized after 36 hours and remained so subsequently.

**DISCUSSION**

Hyperkalaemia, potentially a life-threatening complication of trimethoprim was detected only 25 years after being in clinical use. Many physicians are not aware of this potentially dangerous side effect of trimethoprim. Trimethoprim-induced hyperkalaemia is dose-dependent. Earlier reports of trimethoprim-induced hyperkalaemia were in acquired immunodeficiency syndrome (AIDS) patients, in whom higher doses are used to treat PCP infection. However subsequently it was discovered that hyperkalaemia can occur even when used in conventional doses especially in elderly, patients with mild renal insufficiency and hyporeninemic states. Alappan et al analyzed 80 patients who had no renal insufficiency and had no other causes of altered potassium homeostasis, who were treated with conventional doses of TMP-SMZ for at least 5 days. There was a mean rise of serum potassium of 1.2mEq/L, from 3.9 to 5.1mEq/L and peak effect occurred at 4 to 5 days. Clinically significant hyperkalaemia (serum potassium ≥ 5.5mEq/L) occurred in 21% of patients.

Trimethoprim produces hyperkalaemia by blocking the amiloride sensitive epithelial sodium channels (ENaC) of principal cells in cortical collecting duct (CCD), thus producing a state of pseudohypaldosteronism. By blocking ENaC, trimethoprim inhibits generation of electrical gradient (potential difference) required for potassium secretion in CCD. Aldosterone acts on principal cells of CCD by activating basolateral Na-K ATPase, as well as by inserting amiloride sensitive sodium channel (ENaC) and K+ channel on the luminal membrane. By giving mineralocorticoid in supraphysiologic dose in our patient, we hypothesize that new ENaC were inserted which were unaffected by trimethoprim as drug was already discontinued. To the best of our knowledge this is the first report, were in fludrocortisone was used successfully to treat trimethoprim induced resistant hyperkalaemia.

To conclude, we report a case of intractable hyperkalaemia in an elderly patient who received conventional dose of trimethoprim-sulfamethoxazole, which resolved following therapy with fludrocortisone. We recommend monitoring of serum potassium in high-risk patients receiving conventional doses of TMP-SMZ for 5 or more days.

**REFERENCES**