Tetany in an Extensively Drug Resistant Tuberculosis (XDR-TB) Patient Treated with Capreomycin

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Abstract
- Gross electrolytes disturbances including hypokalemia, hypomagnesemia, and hypocalcaemia have been reported in tuberculosis patients who have been treated with capreomycin. Capreomycin is recommended in the treatment of M. tuberculosis isolates resistant to kanamycin at baseline in multi drug resistant tuberculosis patients (MDR - TB) and treatment of extensively drug resistant tuberculosis (XDR-TB) under programmatic management of drug resistant tuberculosis (PMDT) in India. We report a case of tetany in a extensively drug resistant tuberculosis (XDR-TB) patient treated with capreomycin. She developed hypokalemia after 7 weeks of administration of injection capreomycin intramuscularly daily in dose of 750 mg. Hypokalemia was refractory to intravenous potassium replacement therapy. At 12 weeks during the treatment she developed tetany and hypocalcaemia. Hypomagnesemia was also associated with hypocalcaemia and hypokalemia. Normal level of serum potassium and calcium were achieved with correction of hypomagnesemia.

Introduction
- The national guidelines for programmatic management of drug resistant tuberculosis (PMDT) in India offer an integrated drug resistant treatment algorithm with standard treatment regimen for multi-drug resistant (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). The algorithm also offers scope for modifying the standard regimen for MDR-TB in cases with additional resistance to fluoroquinolones (FQ) or second line injectables (SLI). Although the proportion is small, the number of persons with MDR TB is sizeable in numbers. 1-3% of new and around 12% re-treatment tuberculosis patients are MDR TB. On an average, an estimated 9.7% of patients With MDR TB have XDR TB. As per PMDT guidelines, kanamycin is substituted by capreomycin if drug susceptibility testing results of M. tuberculosis isolates is resistant to kanamycin at baseline or patient is intolerant to same. MDR tuberculosis patient on follow - up, if diagnosed as XDR TB on M. tuberculosis culture report, will also be switched to XDR - TB regimen. The intensive phase of XDR –TB regimen consist of 7 drugs including injection capreomycin for 6-12 months. Capreomycin is a nephrotoxic drug and monitoring of renal function tests and serum electrolytes is required for prolonged use. Nephrotoxicity is most likely to occur in patients with renal impairment, in geriatric patients and in patients receiving other nephrotoxic and/or ototoxic drugs. Electrolyte disturbances are reported rarely with capreomycin. Here, we report a case of dyselectrolytemia presenting as tetany in a young female patient of XDR –TB without prior renal disease treated with capreomycin.

Case Report
- A 21- year, female was admitted in ward on 10th June 2015 as case of extensively drug resistant (XDR) pulmonary tuberculosis (TB), for treatment initiation under programmatic management of drug resistant tuberculosis (PMDT) with Category –V (CAT- V) XDR regimen. She was on treatment for multi-drug resistant (MDR) pulmonary tuberculosis since 2-10- 2014 under PMDT. At the start of MDR TB treatment her sputum test was positive for Mycobacteria tuberculosis complex resistant to Isoniazid and Rifampicin by line probe assay test (LPA), which was resistant to ofloxacin and sensitive to second line injectable drugs (Kanamycin, Amikacin, Capreomycin). 6th month follow – up sputum M. tuberculosis culture was resistant to ofloxacin and second line injectable drugs (Kanamycin, Amikacin). Her treatment was switched over to XDR TB treatment regimen on 17-6- 2015. The following drugs were included in Category-V XDR tuberculosis treatment regimen: Capreomycin, Linezolid, Moxifloxacin, Amoxycillin-clavulanic acid, clofazimine, high dose Isoniazid and Para Amino-salicylic acid after pre evaluation with complete blood count (CBC), liver function test (LFT), kidney function test (KFT) and serum electrolytes. She tolerated antituberculosis treatment (ATT) well for first 1.5 months but developed tingling sensation of lower extremities after 7 weeks of start of XDR treatment regimen. There was no complaint of vertigo, giddiness or tinnitus. She had no history of vomiting, diarrhea or oliguria. Blood examination revealed hyponatremia (Na+ 130 mmol/L) and hypokalemia (K+ 2.9 mmol/L). Normal value for serum sodium and potassium as per the laboratory is 133-145 mmol/ L and 3.8 - 5.5 mmol/ L respectively. She was given intravenous injection Potassium chloride (KCL) with normal saline to correct the deficit (Figure 1). Hyponatremia was improved but hypokalemia persisted. After 5 weeks, she complained of severe abdominal pain and carpopedal spasm (tetany). Serum calcium was 5.05 mg/dl and serum magnesium was 1.19 mEq/l. Normal value for serum calcium and magnesium as per the laboratory is 8.5 – 11.0 mg/dl and 1.3 - 2.50 mEq/L respectively. Inj Magnesium sulphate was given at the rate of 1mEq/ kg over 24 hours followed by 0.5mEq/ kg over 24 hours for next 4 days. Hypokalemia was also corrected with injection potassium chloride infusion.

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Injection calcium gluconate 200mg in 100 ml normal saline was given intravenously over 10 minutes and continued at the rate of 1-2mg/kg/hour for next 10 days till the normalization of calcium level and symptomatic relief. Kidney function tests and liver function tests were within normal limits. Injection Capreomycin was also withheld as a part of treatment for dyselectrolytemia because of reported side effect and there was no other cause for present electrolyte dysfunctions. Injection capreomycin was substituted with injection imipenem and cilastatin with other drugs of CAT- V XDR TB treatment regimen. Serum phosphate was within normal limits and vitamin D3 levels were low. Gradually patient recovered from dyselectrolytemia with normal serum potassium and serum magnesium levels (Figures 1, 2). Later on, oral Calcium was continued along with Vitamin D3 supplementation. No attempt was made to re-introduce injection capreomycin.

**Discussion**

Aminoglycosides and capreomycin cause renal wasting of electrolytes, including potassium, magnesium, and calcium.\(^1\)-\(^3\) Nephrotoxicity of capreomycin is most likely to occur in patients with renal impairment, in geriatric patients and in patients receiving other nephrotoxic and/or ototoxic drugs. Electrolyte disturbances resembling Bartter’s syndrome are reported rarely with capreomycin. The electrolyte disturbances may not be from the toxic levels, but an adaptive immune response to therapy. Autopsy finding of hydropic changes in the epithelial lining of the distal tubules was reported in a patient of electrolyte disturbances suspected due to capreomycin.\(^4\) Caroline bell reported zebra bodies limited to tubules on renal biopsy in a patient of XDR tuberculosis of lymph node due to capreomycin induced acute kidney injury with hypokalemia, hypomagnesaemia and tetany.\(^5\) Zebra bodies are commonly seen with Anderson- Fabry disease, a lysosomal storage disorder of glycosphingolipid catabolism caused by deficiency of a galactosidase. These bodies are lysosomes containing broad transversely stacked myelinoid membranes and also seen in iatrogenic interstitial phospholipidosis (PL) from various pharmacological agents including aminoglycosides.\(^6\)-\(^8\) Drug-induced phospholipidosis is characterized by intracellular accumulation of phospholipids with lamellar bodies, most likely from an impaired phospholipid metabolism of the lysosome. The iatrogenic interstitial phospholipidosis (PL) effects may results from retention of a small, but significant (approx 5%) proportion of administered dose in the epithelial cells of proximal tubules,\(^9\) mainly in endosomal and lysosomal vacuoles.\(^10\)-\(^12\) This results in accumulation of phospholipids in and enlargement of, the lysosomes with inhibition of lysosomal phospholipases. Each cationic, amphiphilic drug (CAD) induces its own phospholipid composition and selectively targets
different organs.13

Gross electrolyte disturbances including hypokalemia, hypomagnesemia and hypocalcaemia have been reported in tuberculosis patients who have been treated with capreomycin. Hypokalemia is reported in 4 to 15% of patients receiving capreomycin therapy for 6 to 26 months.5,14-17 In a large cohort of MDR-TB patients receiving an injectable agent (i.e., streptomycin, amikacin, kanamycin, or capreomycin), forty of the 115 patients (34.8%) were found to have an electrolyte disturbance during the course of therapy.14 The average potassium was 2.85 mEq/L on presentation, with a nadir of 2.65 mEq/L occurring approximately 6 weeks after diagnosis of hypokalemia.14 Hypomagnesemia often accompanied hypokalemia.14 In our patient, hypokalemia reached at nadir of 1.7 mmol/l after 42 days of diagnosis of hypokalemia. Shin et al reported fourteen patients (12.2%) of MDR-TB who had both low potassium and magnesium while receiving an injectable agent.14 The mean duration of therapy at the time of diagnosis of hypokalemia was 5.1 ± 4.0 months.14 Our patient was switched to capreomycin for treatment of XDR TB after 8 months treatment with kanamycin for MDR TB. She developed hypokalemia in seventh week of capreomycin therapy. Electrolyte disturbances did not appear to be related to preexisting renal disease.9 Her renal functions were within normal limits before starting treatment with capreomycin and even with development of electrolyte disturbances she had normal renal functions. Capreomycin and low initial body weight were significantly associated with an increased likelihood of occurrence of hypokalemia.14 Our patient too had low initial body weight 39 Kg (BMI = 15.6 Kg/m²). Use of streptomycin as the choice of injectable was associated with lower rates of hypokalemia in comparison with capreomycin.14 In our patient, M. tuberculosis isolate was also resistant to streptomycin.

Normalization of electrolyte values may take up to four months after cessation of the offending agent.16 Approximately 86% of those with hypokalemia went on to normalize, with a mean duration of potassium disturbance of 6.6 ± 3.9 months.14 Hypokalemia may be refractory to treatment if hypomagnesemia is present and not addressed. In a multivariable model; factors associated with earlier time to hypokalemia resolution were male gender and absence of hypomagnesemia.14 Magnesium serves as a cofactor in the adenosine Triphosphatase dependent mechanism for active transport of sodium and potassium across the cell membrane, further potassium wasting occurs as a consequence of resultant intracellular magnesium deficiency. Decreased cell magnesium may open potassium channels in the luminal membrane of the loop of Henle and increase in membrane permeability may lead to potassium leakage out of the cells and increase potassium excretion.16-19 Spironolactone (100 to 300 mg/day) may also aid in the normalization of serum potassium and magnesium.5,20 However the use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride) was not associated with resolution of hypokalemia in a cohort of MDR TB patients receiving treatment.14 Caution should be used when potassium-sparing diuretics are administered in conjunction with potassium supplements, since hyperkalemia or orthostasis can result. In our patient hypokalemia was refractory to potassium replacement therapy till hypomagnesemia was corrected. (Figure 1). Aquinas et al reported recurrence of hypokalemia on resuming capreomycin in two patients with resolution on discontinuation of the injectable. We did not try to re-introduce capreomycin in our patient; however Caroline had re-introduced capreomycin successfully at a lower drug dose.

Hypomagnesemia, though infrequently looked for, is present in up to 12 % of hospitalized patients.3 Few studies have documented the association of hypomagnesemia in patients with tuberculosis and is multifactorial in origin such as malnutrition, malabsorption, and therapy induced renal loss.5-6 There is also evidence that the use of aminoglycosides (AMG) and capreomycin causes renal wasting of electrolytes, including potassium, magnesium, and calcium.7-9 Capreomycin is thought to induce secondary hyperaldosteronism leading to urinary loss of potassium and magnesium.16,21-22 Hypomagnesemia is believed to cause impaired synthesis or secretion of parathyroid hormone which results in decrease serum calcium levels24. The symptoms of hypocalcaemia include muscle spasm, tetany and seizure. In our patient hypocalcaemia was suspected with the presentation of abdominal cramps and Carpopedal spasm (tetany). In our patient Hypomagnesemia was also associated with hypocalcaemia which did not resolve until the magnesium deficiency was corrected. Normal level of serum magnesium and calcium level was achieved after administration of intravenous magnesium sulphate along with calcium gluconate. In the presence of hypocalcaemia, tetany can occur during the administration of magnesium-sulfate if calcium is not supplemented, as ionized calcium levels can drop acutely due to complex formation with sulfate ions and increased urinary excretion.24

Monthly estimations of the serum electrolytes was proposed when prolonged capreomycin therapy is necessary for the treatment of patients with pulmonary tuberculosis and to stop the drug when hypokalaemia or hypomagnesemia develop.6 The implementation of a program wide protocol appeared to shorten the time to diagnosis of hypokalemia and improve rates of electrolyte resolution.14 Magnesium deficiencies presented on average 2.7 months after diagnosis of hypokalemia in a cohort of MDR TB patient on treatment.14 In our patient, hypomagnesemia was detected 5 weeks after diagnosis of hypokalemia when patient developed Carpopedal spasm. Monitoring serum potassium alone is sufficient for electrolyte abnormalities.14 PMDT guidelines recommends monthly estimation of serum creatinine and serum electrolytes during the period injection capreomycin is administered.4 Serum magnesium and calcium levels may be checked in hypokalemic and/or symptomatic individuals. In areas where serum magnesium and/or calcium levels are not available, empiric repletion of magnesium and calcium is a reasonable alternative.14

Conclusion

Iatrogenic interstitial phospholipidosis (PL) results from retention of small but significant (approx 5%) proportion of administered dose in the epithelial cells of proximal
tubes with cationic, amphiphilic drug (CAD). There are few reports of capreomycin induced iatrogenic interstitial phospholipidosis presenting as hypokalemia, hypocalcaemia and hypomagnesaemia. Our patient developed hypokalemia after 7 weeks of therapy of capreomycin. The hypokalemia was refractory to intravenous potassium replacement therapy. On presentation of tetany at 12 weeks she was diagnosed to have hypokalemia associated with hypocalcaemia and hypomagnesaemia. Normal level of serum potassium and calcium were achieved with correction of hypomagnesaemia. A high level of suspicion of hypomagnesaemia is warranted in patient developing hypokalemia on prolonged therapy with capreomycin. Serum magnesium and calcium levels may be checked in hypokalemic and/or symptomatic individuals.

References