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Drug-Induced Endocrine and Metabolic Disorders

In the excellent review of drug-induced endocrine and metabolic disorders by Ma et al.,[1] many agents were not included in the authors' list of medications that cause hypokalaemia. Large doses of benzylpenicillin (penicillin) G may promote urinary potassium excretion by acting as non-reabsorbable anions in the distal renal tubule. They enhance sodium delivery to the distal nephron leading to the secretion of potassium and hydrogen ions, resulting in hypokalaemia and metabolic alkalosis.[2,3] Other classes of penicillin, such as penicillinase-resistant penicillins (for example, oxacilline and dicloxacillin) and piperacillin, can also cause severe hypokalaemia, even when serum creatinine levels remain normal. Aminoglycosides and capreomycin can induce renal potassium wasting by inducing depletion of magnesium.[4,5] The frequency of hypokalaemia ranges from 4% to 15% of patients receiving capreomycin therapy for 6–26 months. In a recent cohort, 30 (68.2%) of 44 patients taking capreomycin developed hypokalaemia (defined as serum potassium <3.3 meq/L).[5] Capreomycin-induced hypokalaemia seems to be more common in patients with low initial body weight or malnutrition. The exact mechanism of the urinary loss of potassium and magnesium due to aminoglycoside is not entirely elucidated. It may be due to aminoglycoside-induced hyperaldosteronism and tubular toxicity. Chou et al.[6] hypothesise that gentamicin, an aminoglycoside, induces the action of calcium-sensing receptor on the thick ascending loop of Henle and distal tubule to cause renal wasting of potassium, sodium and magnesium. It may be useful to recommended close monitoring of serum potassium in patients who receive aminoglycoside, especially capreomycin and/or high doses of penicillins.

Sirolimus, an immunosuppressive macrolide antibiotic, has been shown to cause hypokalaemia due to excessive urinary excretion of potassium, probably secondary to a mild tubular dysfunction.[7] However, the exact mechanism is still unclear. Potassium deficit can occur without associated metabolic acidosis, hyperaldosteronism or Fanconi syndrome. Hypokalaemia is mild and seems to be dose dependent. Patients with sirolimus-induced hypokalaemia respond well to either potassium supplements or reduced dosing of sirolimus.

A number of antifungal agents can induce hypokalaemia. Amphotericin B promotes renal-potassium wasting through a toxic effect on the renal tubule. It causes inhibition of the secretion of hydrogen ions by the collecting duct cells as well as causing magnesium depletion. Amphotericin B-induced hypokalaemia is dose dependent and generally occurs before renal insufficiency. A retrospective study suggests that amiloride may be beneficial in patients treated with amphotericin B, by decreasing total potassium requirements and supplementation as well as increasing serum potassium concentrations.[8] Caspofungin, a new antifungal agent, can also lead to hypokalaemia. However, hypokalaemia is significantly less common among patients treated with caspofungin compared with patients treated with amphotericin B.[9] Itraconazole can cause excessive urinary loss of potassium with severe hypokalaemia.[10] Hypokalaemia is also seen with oral fluconazole.[11] Patients who are treated with these antifungal drugs should have their serum potassium levels monitored.

Gossypol, a male contraceptive agent, can cause or contribute to hypokalaemia in 1% of users.[12,13] Hypokalaemia seems to be dose dependent. Some patients were reported to have chronic persistent hypokalaemia long after cessation of gossypol treatment. Gossypol-induced hypokalaemia is related, in part, to the inhibition of 11 β-hydroxysteroid dehydrogenase that causes an apparent mineralocorticoid excess leading to excessive potassium excretion and sodium resorption.

We believe that these drugs, frequently prescribed in daily practice, should be added to the authors' list of agents that can cause hypokalaemia.

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