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Acetazolamide therapy for hypokalemic alkalosis in Bartter syndrome

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There is no information available on the efficacy of acetazolamide on the management of severe hypokalemic alkalosis refractory to the standard therapy. A benefit from acetazolamide appears to be apparent in the management of hypokalemic alkalosis in patients with Barter syndrome.

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Editorial

Bartter syndrome is an autosomal recessive kidney disorder characterized by hypokalemia, metabolic alkalosis, and normal blood pressure (1). The syndrome is associated with mutations in Na^+, K^+, 2 Cl^- system also called as the Na^+-K^+-2Cl^- cotransporter in the tick ascending loop of Henle (2). Under normal conditions, once the Na^+, K^+, 2Cl^- is transported into the apical membrane of the tubule cells, Na^+ is transported by active Na^+/K^+/ATPase, and Cl^- is passed by diffusion across the basolateral Cl^- channels. However, K^+ ions, is transported back through the apical K+ into the lumen, establishing a positive charge between the interstitial compartment and tubule lumen. This charge gradient is necessary for the reabsorption of both Ca^{++} and Mg^{++} ions.

Impaired operation of any component of this reabsorption system can result in clinical manifestation of Bartter syndrome. Inactivation of this transport system can lead to reduced K^+, and Cl^-, and Na^+ reabsorptions in the ascending loop of Henle, as well as impaired renal ability to concentrate urine, leading to significant polyuria and potential for severe life-threatening dehydration specially in infants and toddlers if do not receive adequate water. Furthermore, the increased Na^+ delivery to distal nephron and collecting duct promotes K^+ and H^+ ions excretion into the lumen by principal cells in exchange for Na^+ reabsorption, leading to hypokalemia and metabolic alkalosis (3).

To date, five types of Bartter syndrome have been identified through genetic analysis. The neonatal Batter syndrome is associated with mutations in *SLC12A1 (NKCC2)* (type 1) (4,5) or *ROMK/KCNJ1* (type 2) (6,7) protein genes and is manifested during neonatal period by polyuria, severe dehydration, polydipsia, hypokalemic alkalosis, hypercalciuria, nephrocalcinosis, kidney stones, and may progress to renal failure.

Classic Bartter syndrome (type 3) is due to mutations in *CLCNBK* gene, located in the thick ascending limb of the Henle (7). Patients with classic Bartter syndrome usually presents during school age with symptoms that are similar to those patients receiving furosemide diuretic. Patients with type 3 Bartter syndrome also have polydipsia and polyuria, hypokalemia, alkalosis, normal blood pressure and failure to thrive, but or mildly elevated urinary Ca^{++} excretion without the tendency to develop nephrolithiasis. The diagnosis is established by increased plasma renin activity (PRA), aldosterone levels and over production renal prostaglandins. High urinary K^+, Na^+, Cl^-, Ca^{++} and Mg^+ levels despite of low serum Na^+, K^+, and Cl^- and Mg^{++} values are usually found. The hypercalciuria in Bartter syndrome is secondary to impaired furosemide-delicate transport system in the ascending loop of Henle.

The increased PRA and aldosterone level is secondary to hyperplasia of the juxtaglomerular apparatus (6,8).

Type 4 Batter syndrome is caused by mutations in gene *BSND* is also associated with sensorineural deafness (9) while type 5 Bartter syndrome is caused by mutations in gene *CASR* and is associated with autosomal dominant hypokalemia (10).

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Gitelman syndrome, which is a subset of classic Bartter syndrome is caused by mutations in the *SLC12A3* gene resulting in an impaired function of the thiazide-Na^+-Cl^- transport mechanism also known as *NCCT*, located in the distal convoluted tubules, which is responsible for the transport of Na^+, K^+, Cl^-, Ca^{++}, and Mg^{++} (11-14).

Clinical signs of Gitelman syndrome include hypokalemic alkalosis with normal blood pressure, hypomagnesemia, and hypocalciuria. The hypercalciuria in Gitelman syndrome is influenced by defective thiazide-finely tuned transport system in the convoluted tubules (15,16).

Early diagnosis and appropriate treatment of fluid-electrolyte disorders in infants and young children may improve growth and prevent or retard the disease progression to kidney failure.

The standard therapy includes KCL supplementation, prostaglandin E inhibitors (NSAIDS), angiotensin-converting enzyme inhibitors (ACEI) such as enalapril, and aldosterone antagonists such (spironolactone or amiloride) (17-21).

However, hypokalemic alkalosis persists in majority of patients despite of combination therapy with K^+ sparing diuretics, angiotensin-converting enzyme inhibitors (ACEI), and nonsteroidal anti-inflammatory drugs (NSAIDs). Acetazolamide, a carbonic anhydrase inhibitor, has been used frequently and effectively for the management of hypokalemic alkalosis as a result of loop diuretics administration, especially in critically ill patients with congestive heart failure (22-25).

There is no information available on the efficacy of acetazolamide on the management of severe hypokalemic alkalosis refractory to the standard therapy. A benefit from acetazolamide appears to be apparent in the management of hypokalemic alkalosis in patients with Barter syndrome. Acetazolamide, prevents reabsorption of sodium bicarbonate in the proximal tubule, thereby causing bicarbonate wastage (26).

The low cost, limited side effects and the ease of administration are compelling evidence to consider acetazolamide for the treatment of hypokalemic alkalosis in patients with Batter syndrome unresponsive to the conventional therapy.

Author's contribution

FA is the single author of the paper.

Conflicts of interest

The author declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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