

Review Article

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Renal Injury in Calcium-Alkali Syndrome

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Abstract

Calcium-alkali syndrome is characterized by hypercalcemia, renal injury and metabolic alkalosis. Calcium-alkali syndrome caused by calcium carbonate and vitamin D has been increasing in association with their growing use for the treatment and prevention of osteoporosis. Renal injury is the most critical factor determining the severity and prognosis of this syndrome. This review focuses on the mechanism and clinical aspects of renal injury in calcium-alkali syndrome.

Introduction

Calcium-alkali syndrome is characterized by hypercalcemia, renal injury and metabolic alkalosis. Calcium-alkali syndrome was previously called milk-alkali syndrome because it was first reported in a patient who was treated for gastric ulcer using milk and alkaline powders that consisted of magnesium and sodium bicarbonate for neutralization of stomach acidity [1]. Renal injury in milk-alkali syndrome is considered a severe complication because approximately one-third of cases resulted in permanent renal impairment [2]. The incidence of milk-alkali syndrome declined with the development of new drugs such as histamine H₂ blockers and doxycycline for treatment of gastric ulcer. However, resurgence of this syndrome occurred in the 1990s as a result of increased osteoporosis awareness and common use of calcium carbonate, which supplied both calcium and absorbable alkali, and vitamin D for treatment and prevention of osteoporosis [2,3]. Since the “milk” in milk-alkali syndrome no longer reflects the etiologic origin of the modern version of this syndrome, it was recommended that its name be changed to calcium-alkali syndrome [4]. Calcium-alkali syndrome is now considered one of the most common causes of hypercalcemia [5,6]. Renal injury in calcium-alkali syndrome is the most critical factor determining its severity and prognosis. In this review, we focus on the mechanism and clinical aspects of renal injury in calcium-alkali syndrome.

Diagnosis of Calcium-Alkali Syndrome

The diagnosis of calcium-alkali syndrome requires a history of taking such drugs as calcium carbonate, vitamin D or thiazides and finding of hypercalcemia, metabolic alkalosis, and variable degrees of renal insufficiency. The symptoms such as nausea, vomiting, anorexia, headache, dizziness, vertigo, and confusion may occur within a few days. Muscle aches, psychosis, tremor, polyuria, polydipsia, pruritus, and abnormal calcification are chronic symptoms [4]. Severe hypercalcemia is always present, and combination of an elevated serum bicarbonate and high pH level in the presence of renal failure are differential diagnosis. Level of 1, 25-OH vitamin D and intact PTH are generally suppressed. The intact PTH level may need to be measured to exclude primary hyperparathyroidism. Malignancy should be excluded, because it is one etiology of hypercalcemia.

Subtypes of Renal Injury in Calcium-Alkali Syndrome

As shown in Table 1, calcium-alkali syndrome has been categorized into acute, subacute and chronic types [7,8]. The acute type develops within a few days to weeks after the initiation of treatment with calcium carbonate. Recovery from this type of renal injury occurs

rapidly after cessation of calcium carbonate ingestion. The sub acute type occurs during therapy with calcium carbonate that has been used intermittently for years. In contrast to the acute type, there is less rapid improvement and recovery of renal function is slower. The chronic type occurs after a long history of ingestion of large amounts of calcium carbonate. The renal insufficiency of this type does not show complete recovery.

Physiology and Pathology of Renal Injury in Calcium-Alkali Syndrome

As mentioned below, although the basic mechanism of acute, subacute and chronic type of renal injury in calcium-alkali syndrome is not considered to be different, the duration and severity of pathological changes in kidney determine the acute, subacute and chronic stages by inducing subsequent calcium depositions and infiltration of inflammatory cells that contribute to chronic renal changes such as renal fibrosis or tubular atrophy.

Hypercalcemia is caused when the calcium input by dietary intake and intestinal absorption exceeds the calcium output by primarily renal excretion. Factors that can increase calcium input include increased dietary calcium intake, ingestion of supplemental calcium with enhanced intestinal absorption of calcium from stimulation by vitamin D. Since hypercalcemia has a natriuretic and diuretic effect, conceivably by activating the calcium-sensing receptor (CaSR), it leads to intravascular depletion and thereby decreases the glomerular filtration rate (GFR), which reduces the filtration of calcium [9,10]. The use of diuretics such as thiazides may accelerate the decrease of calcium excretion by inhibiting the thiazide-sensitive sodium chloride co-transporter and may contribute to hypercalcemia and hypovolemia [11]. This hypovolemia increases the reabsorption of calcium and bicarbonate in the proximal convoluted tubules. Hypercalcemia also causes renal vasoconstriction leading to decreased GFR and reducing the amount of calcium and bicarbonate excretion [8,12]. Then, elevation

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Received January 31, 2012; Accepted February 27, 2012; Published February 29, 2012

Citation: Yoshizawa H, Morishita Y, Kusano E (2012) Renal Injury in Calcium-Alkali Syndrome. J Nephrol Therapeutic S3:006. doi:10.4172/2161-0959.S3-006

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| | Acute and Sub acute type | Chronic type |
|----------------------------------|---|--|
| Duration period | Weeks or Months | Years |
| Drugs and risk factors | CaCO ₃ , VitD3, Thiazides, osteoporosis | CaCO ₃ , VitD3, Thiazides, chronic kidney disease, osteoporosis |
| Renal histologic findings | Calcium deposition in renal tubules and interstitial tissue is mild to moderate. Interstitial fibrosis or inflammatory change is also mild. | Calcium deposition in renal tubules and interstitial tissue is moderate to severe. Interstitial fibrosis and inflammatory cell infiltration are moderate to severe. Tubular atrophy. Glomerulus hyalinization, Thickening of Bowman's capsule. |
| Treatment | Hydration with saline and cessation of suspected drugs. | Hydration with saline and cessation of suspected drugs. Dialysis. |
| Renal outcome | Recovery from renal insufficiency occurs rapidly in a few days or weeks. | Complete recovery from renal insufficiency does not occur. Dialysis is sometimes required. |

Table 1: The histology and outcomes of renal injury in calcium-alkali syndrome.

of bicarbonate levels by ingestion of alkali and decreased bicarbonate excretion produces alkalemia, which enhances calcium reabsorption.

An alkalotic environment is known to facilitate calcium precipitation [13,14]. Several histological observations of kidney in calcium-alkali syndrome have been reported. Burnett and Commons [15] reported nephrocalcinosis from a single autopsy. Other autopsy reports described parietal to complete glomerulus hyalinization, thickening of Bowman's capsule, tubular atrophy and diffuse lymphocytic infiltration [16-18]. Extensive calcification of convoluted renal tubular cells and the tubular lamina was described as a striking feature [11]. Scholz and Keating [19] reported a case of focal calcification in the renal tubules. Randall et al. [20] reported tubular epithelium degeneration and granular material (presumably calcium-laden) in and around the collecting tubules, as well as hyalinization of several glomeruli and thickening of the basement membrane. In these reports, some correlation was found between the amount of calcium deposition and renal prognosis. The two cases with persistent renal impairment had more prominent calcium deposition, as well as interstitial fibrosis, and larger area with inflammatory changes [21]. It is noted that calcium deposition in the kidney is not usually seen radiographically.

Treatment and Prevention

The main therapy for calcium-alkali syndrome is volume expansion with saline and cessation of calcium carbonate ingestion to break the malignant cycle induced by exposure to calcium and alkali. Acute kidney injury is also reversible by this therapy in most cases. In refractory cases, hemodialysis may occasionally be necessary. Furosemide may be used to enhance calciuresis.

In order to prevent this syndrome, the patients taking calcium carbonate and vitamin D should be need close monitoring of serum calcium level and renal function.

Conclusion

Calcium-alkali syndrome is resurgent owing to the use of calcium carbonate and vitamin D. Since it may cause serious renal injury, healthcare practitioners should bear this syndrome in mind when using these agents.

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