DOI：10.6314/JIMT.202410_35(5).07 內科學誌 2024：35：389-394

Cholestyramine-associated with severe, irreversible, hyperchloremic metabolic acidosis mortality: two related case studies

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Abstract

Cholestyramine, a chlorinated anion exchange resin, acts as a bile acid sequestrant by forming an indigestible compound with bile acids. It effectively reduces diarrhea by sequestering the bile acid salts in the duodenum. However, the chloride ions of cholestyramine can exchange for bicarbonates (HCO_3^-) in the small intestine, which causes the loss of HCO_3^- and the increase level of free chloride reciprocally in the blood. Two elderly patients diagnosed with the stage 3a~4 of chronic kidney disease (CKD) were on the long-term respirator. These two patients suffered from severe diarrhea and were both treated with cholestyramine. A short course of cholestyramine treatment briefly alleviated patients' diarrhea condition but rapidly led to a more serious hyperchloremic metabolic acidosis (HCMA). Because both patients had a pre-existing CKD condition in conjunction with pneumonia, urosepsis, oliguric acute kidney failure (ARF), and chronic respiratory alkalosis due to long-term use of ventilator, the compensatory function for the HCO_3^- resorption in the kidney may be severely perturbed. The dysfunctional kidney function may further aggravate the cholestyramine-induced HCMA in these two patients. Without the renal dialysis, the conditions of these two patients worsened and eventually caused the death of these two patients. In conclusion, the use of cholestyramine for treating severe diarrhea needs to be cautious, especially for the high-risk patients having a pre-existing kidney disease.

Key words: Cholestyramine, Resin, Hyperchloremia, Acidosis, Hyperchloremic metabolic acidosis

Background

Cholestyramine is a positively charged resin that binds bile acids to form a non-digestible complex in gastrointestinal tract. It is commonly used to treat diarrhea associated with bile acid malabsorption, pseudomembranous colitis and pruritis of partial biliary obstruction. The connection between cholestyramine treatment and severe HCMA remains

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unclear. However, the side effect of cholestyramine-associated severe HCMA is rarely fatal and can be alleviated by sodium bicarbonate ($NaHCO_3$) supplementation[1-7].

Objective

We reported two cases of elderly patients under chronic ventilator dependence (CVD), who rapidly developed severe HCMA after a short course of cholestyramine treatment for severe diarrhea. Unexpectedly, the conditions of these two patients showed a limited response to an aggressive $NaHCO_3$ resuscitation and rapidly deteriorated to become the oliguric phase of ARF and sepsis, which eventually caused the death of these two patients.

Case Report

Case 1

A non-diabetic, 86-year-old female patient had had cerebrovascular accident with bedridden and CKD stage 3a showing an estimated glomerular filtration rate (eGFR) of 51 ml/min/1.73m^2. The patient had been under CVD for 4 months before she manifested *Clostridioides difficile*-related pseudomembranous colitis. The 4 gram of cholestyramine powder TID and 250mg of metronidazole Q8H were given per oral for consecutive 7 days.

After cholestyramine treatment, the laboratory results (Table 1) showed the serum Na^+ was at 140.5 mEq/L (normal range, 135 to 148 mEq/L), K^+ was at 5.34 mEq/L (normal range, 3.5 to 5.5 mEq/L), and Cl^- was at 121.3 mEq/L (normal range, 98 to 110 mEq/L). Serum HCO_3^- (normal range, 22.0 to 24.0 mEq/L) has decreased from 24.8 to 8.7 mEq/L and the base excess (normal range, -2 to 3 mmol/L) has also dropped from a baseline level of 1.8 to -13 mmol/L. All these data suggested that the patient was in severe HCMA. During metabolic acidosis, the positive value of urine anion gap (UNa^++UK^+-UCl^-) [2.37 mEq/L] together with urine pH value at 6.5 (>5.0) and low urine osmolal gap at 19.6 mOsm/kg H_2O (<150 mOsm/kg H_2O) indicated a low level of renal acid and urine NH_4^+ secretion. The estimated total body HCO_3^- deficit [0.5×body weight×(24-serum HCO_3^-)] was 252 mEq. An aggressive resuscitation treatment with 238 mEq of HCO_3^- only achieved a partial response of serum level of HCO_3^- from 8.7 to 11.9 mEq/L, which didn't remediate the patient's severe HCMA condition. The hemodialysis was recommended, but was declined by the patient's family. Consequently, the patient developed urosepsis in conjugation with oliguric ARF (a blood urea nitrogen value of 142 mg/dl and a serum creatinine value of 5.04 mg/dl), which eventually caused the death of the patient.

Case 2

A non-diabetic, 88-year-old male patient had had complications of chronic obstructive pulmonary disease and stage 4 CKD with an eGFR value of 26 ml/min/1.73m^2 and post-cholecystectomy status. The patient had been under CVD for 11 months before 4 gram of cholestyramine powder BID per oral was given for consecutive 22 days to treat chronic diarrhea caused by bile acid malabsorption.

Table 1. Laboratory results of two patients with cholestyramine-associated hyperchloremic metabolic acidosis

Age	eGFR ml/min/1.73m^2 (≧60)	HCO_3^- mEq/L (22.0-24.0)	Cl^- mEq/L (98-110)	pCO_2 mmHg (35-45)	pH (7.35-7.45)	UAG mEq/L	HCO_3^- deficit mEq/L	Indication of Cholestyramine	Underlying diseases
86	51	8.7	121.3	14.8	7.389	2.37	252	Pseudomembranous colitis (*C.difficle*)	CKD 3a, Oliguric ARF, CVD, urosepsis
88	26	8.2	123.5	15.4	7.343	54.1	413	Diarrhea, post-cholecystectomy status	CKD 4, Oliguric ARF, CVD, nosocomial pneumonia

UAG: urine anion gap = UNa^++UK^+-UCl^- (a positive UAG during metabolic acidosis suggests a low urine acid and low NH_4^+ excretion); Total body HCO_3^- deficit (mEq/L)=[0.5 x body weight x (24-serum HCO_3^-)]; CKD: chronic kidney disease; ARF: acute renal failure; CVD: chronic ventilator dependence

After administration of cholestyramine, laboratory results (Table 1) showed a serum Na^+ was at 145.4 mEq/L, K^+ was at 3.68 mEq/L, and Cl^- was at 123.5 mEq/L. The serum HCO_3^- level decreased from 19.5 to 8.2 mEq/L and the base excess dropped from a baseline level of -3.4 to -14 mmol/L. All these numbers indicated that the patient was in a severe HCMA. During metabolic acidosis, the positive [54.1 mEq/L] urine anion gap with a urine pH value at 6.0 (> 5.0) indicated a low urine acid secretion. The estimated total body HCO_3^- deficit was 413 mEq. An aggressive HCO_3^- supplement with a total amount of 765 mEq was prescribed for the treatment of severe HCMA. As a result, the serum level of HCO_3^- partially elevated from 8.2 to 14.5 mEq/L, but couldn't ease the patient's severe HCMA condition. The hemodialysis was recommended, but was turned down by the patient's family. The patient was later contracted with nosocomial pneumonia and developed the oliguric ARF with a blood urea nitrogen value at 133 mg/dl and a serum creatinine value at 5.2 mg/dl, which ultimately resulted in the death of the patient.

Discussion

The daily biliary secretion is about 1 liter and contains ~3 gram of total bile acids, which are pooled together from 4~12 cycles of enterohepatic circulation. The cholestyramine resin (Figure 1) contains the binding sites of chloride (Cl^-), which can be exchanged with bile acids in the duodenum to form an irreversible and non-absorbable complex. Each gram of cholestyramine contains 4 mEq of chloride[6]. The release of Cl^- from cholestyramine resin can further exchange with HCO_3^- through Cl^-/HCO_3^- antiport and results in duodenal HCO_3^- loss and Cl^- gain. In the present study, the calculated overall Cl^- load was at 336 mEq and 704 mEq in Case 1 and 2, respectively.

In colon, malabsorption of bile acids can cause diarrhea via several mechanisms (Figure 2): (1) the increase of intracellular mediator [cAMP] to enhance Cl^- secretion, (2) the reduction of occludins to enhance permeability and motility, (3) the stimulation of cholinergic neurons via neurocrine-mediated secretion, (4) the increase of serotonin release to increase mucus and fluid secretion and (5) the decrease of Na^+/K^+-

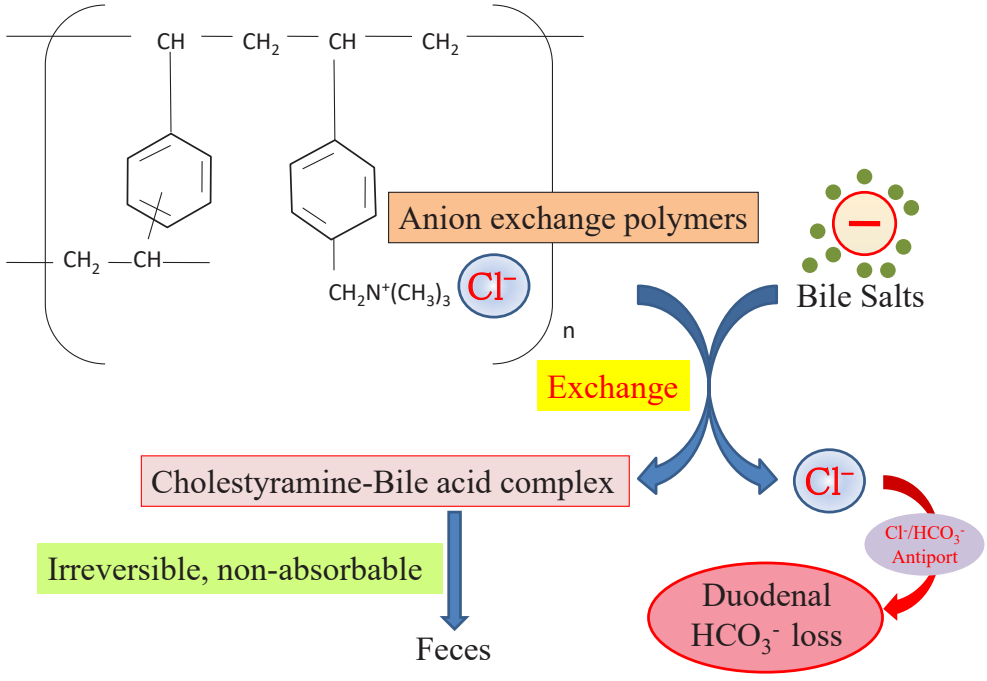

Figure 1. The cholestyramine anion-exchange polymer forms a complex with negatively charged bile salts and causes the loss of duodenal HCO_3^- via Cl^- / HCO_3^- antiport.

ATPase activity to reduce salt and water reabsorption. The cholestyramine-bile acid complex obstructs the above mechanisms and demonstrates an anti-diarrhea effect[8].

The loss of duodenal HCO_3^- can be compensated by normal renal function. However, the chronic respiratory alkalosis in CVD patients have a problem in replenishing the level of HCO_3^- from renal proximal tubules and collecting ducts (Figure 3)[9]. Retrospectively, in the present case report, the two patients under CVD and chronic respiratory alkalosis showed a gain of Cl^- in conjunction with the loss of duodenal HCO_3^- in oliguric ARF of chronic kidney disease. All these results suggest that the cholestyramine may impede the renal rejuvenation of HCO_3^- together with the secretion of H^+ and Cl^-, and gives rise to severe HCMA and ultimately irreversible clinical complications.

The cholestyramine-associated severe HCMA attributes to several risk factors: the renal failure, concurrent spironolactone use, volume depletion, low body mass index (BMI) or small body weight, chronic respiratory alkalosis, impaired renal HCO_3^- regeneration, impaired urinary acidification and impaired Cl^- secretion (Figure 2 and 3).

Conclusion

The elderly patients in the long-term bedridden condition usually have multiple organ disorders and are at a higher risk for ARF. Therefore, they are more prone to development of severe metabolic acidosis in septicemia. The geriatric CVD patients with the oliguric ARF after receiving a short-term treatment of cholestyramine can rapidly turn into a more severe HCMA. Our study suggests that cholestyramine treatment should be carefully monitored or avoided

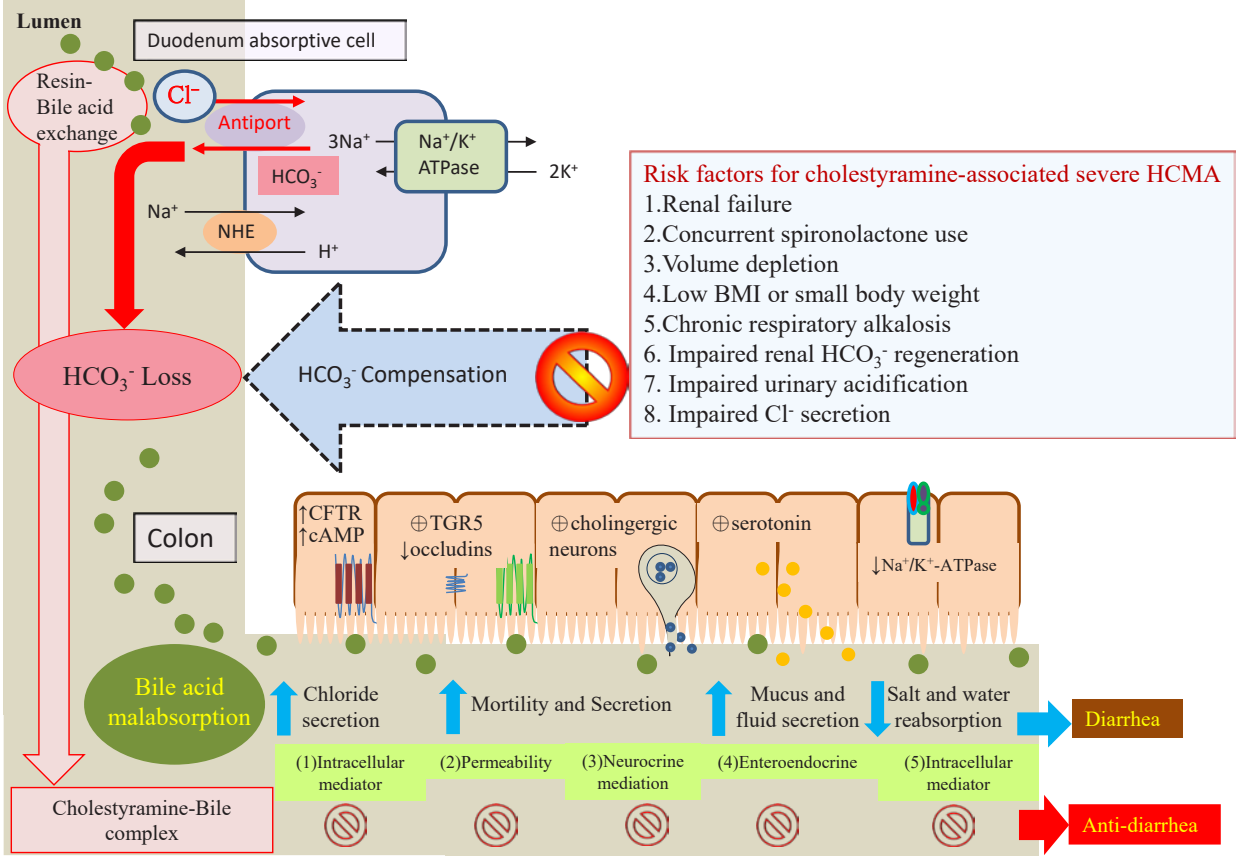

Figure 2. Cholestyramine-Bile complex reduces the bile acid malabsorption and alleviates diarrhea condion. The compensation mechanism for the loss of duodenal HCO_3^- can be interrupted by the above risk factors.

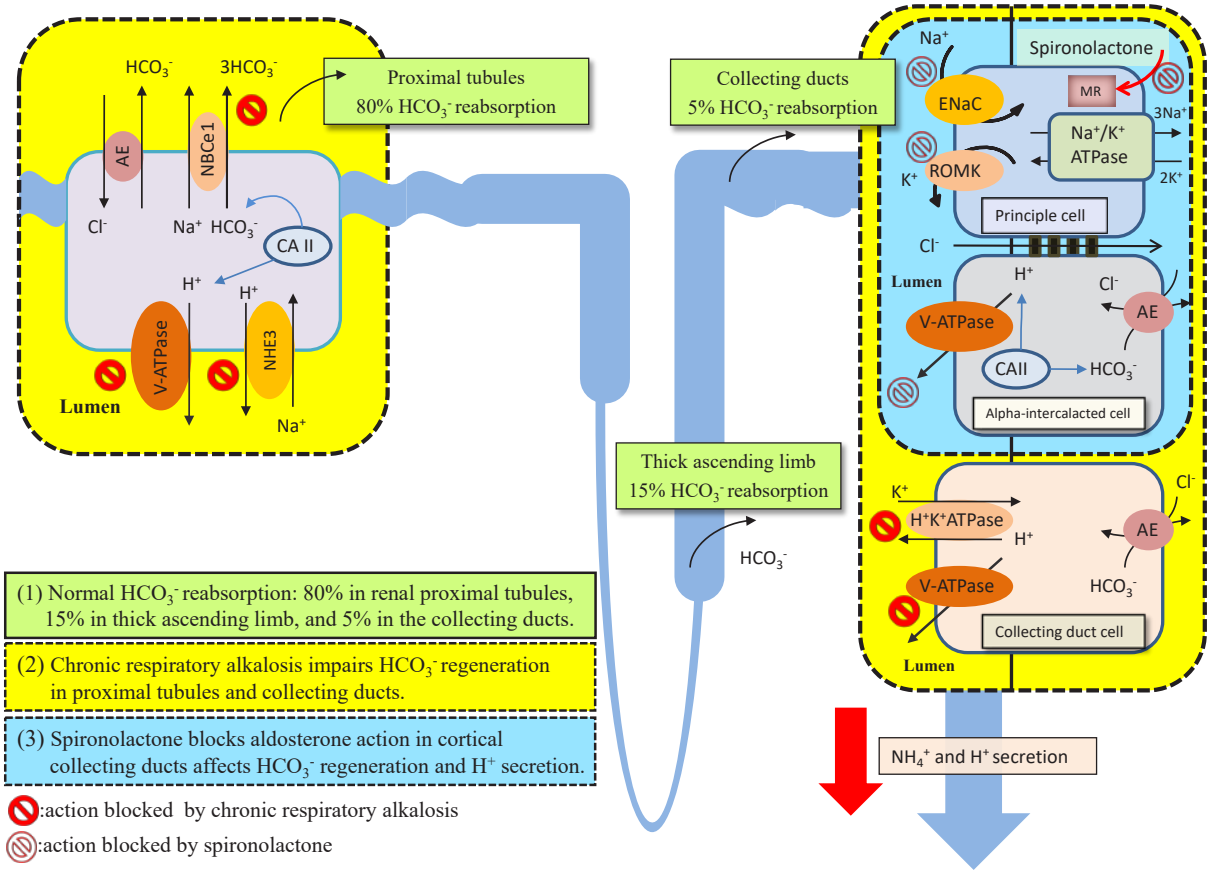

Figure 3. The metabolism of HCO_3^- in the kidney.

in patients with a higher risk for ARF to prevent the patients from the unwanted fatal outcomes.

Acknowledgement

The authors greatly thank Professor Lin, Shih-Hua for his insightful advice and invaluable guidance for the study.

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可利舒Cholestyramine引起嚴重不可逆高血氯代謝性酸中毒死亡：兩個相關病例的研究報告

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摘要

可利舒（cholestyramine）是含氯離子 (Cl^-) 的交換樹脂，會在十二指腸結合膽酸形成不可分解的化合物，經由降低膽酸的作用而止瀉，而後經糞便排泄。可利舒的氯離子經由小腸吸收，而交換出碳酸氫根離子 (HCO_3^-)，使人體流失 HCO_3^- 而增加血中氯。慢性腎臟病 stage3a~4 期且長期呼吸器依賴的兩位老年病患發生嚴重腹瀉，在短期使用可利舒止瀉後，發生嚴重高血氯代謝性酸中毒。因慢性腎臟病且合併長期呼吸器依賴產生的呼吸性鹼中毒，加上後來病患得到院內感染肺炎、泌尿道感染致敗血症併發寡尿性急性腎衰竭等種種因素，讓正常腎臟 HCO_3^- 代償機制嚴重受阻，而使可利舒引發的嚴重高血氯代謝性酸中毒更難以大量碳酸氫鈉來中和。因病患久病而家屬拒絕洗腎，最後病患回天乏術。使用可利舒治療需小心謹慎及避免使用在高風險族群，特別是慢性腎臟病患者。