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CASE REPORT

Acetozolamide induced hyperammonaemia: a case report and review of the literature

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Abstract

Nonhepatic hyperammonaemia is a rare disorder in the ICU. We describe a patient who developed hyperammonaemia after the administration of acetazolamide. Acetazolamide is a frequently used drug in the ICU for the correction of metabolic alkalosis. Acetazolamide-associated hyperammonemia may develop due to interference with the breakdown of ammonia through the urea cycle and through inhibition of the renal excretion of ammonia. Possible treatment options for hyperammonemia have been reviewed. Although the frequency of acetazolamide-induced hyperammonemia is unknown in ICU patients, it is a condition that must be considered when patients treated with acetazolamide show unexplained changes in consciousness.

Introduction

Metabolic alkalosis is a common acid-base disorder in ICU patients and is associated with adverse cardiovascular, pulmonary and metabolic effects.[1-3] By increasing the excretion of bicarbonate, acetazolamide might facilitate discontinuation from mechanical ventilation. Acetazolamide is frequently used in the ICU, and is generally considered to have a favourable safety profile. We describe a patient with severe and recurrent hyperammonaemia upon administration of acetazolamide. We further discuss the literature regarding the underlying mechanisms and treatment options for this condition.

Case

A 73-year-old man was transferred from another hospital to our ICU for analysis of difficult weaning after multiple thoracotomies for pleural empyema. He had a medical history of myocardial infarction, coronary artery bypass surgery with diminished left ventricular function and chronic renal failure with an endogenous creatinine clearance of 60 ml/min. Upon admission,a CT scan of the chest revealed pleural effusions with multiple loculations and adhesions and the patient underwent a rethoracotomy for evacuation of the infected material. During his ICU stay, he developed generalized oedema and was treated with furosemide which resulted in a metabolic alkalosis with a bicarbonate of 44.9 mmol/l. Acetazolamide in a dose of 500 mg daily was started for correction of the alkalosis and to facilitate weaning. On the third day after the start of acetazolamide, his level of consciousness gradually decreased from alert and communicative to stuporous without signs of lateralization. Laboratory analysis revealed a high blood ammonia concentration of 110 µmol/l without signs of liver failure. At that point in time his renal function temporarily decreased to an endogenous creatinine clearance of 37 ml/min. There were no signs of portal hypertension. Because no other medication could be implicated, acetazolamide was stopped and the patient was treated with lactulose to decrease the production and absorption of ammonia in the intestine. The patient regained his normal consciousness after the ammonia level had decreased to normal values in the days that followed. After two weeks, acetazolamide was recommenced in a dosage of 500 mg/day. Again the ammonia concentration increased from 39.9 to 60.4 µmol/l, with no signs of liver or kidney failure. During both episodes, no other metabolic derangements were found that could explain his decreased level of consciousness. After cessation of the acetazolamide and treatment with lactulose, the ammonia concentration decreased and his level of consciousness returned to normal. Ultimately, after 62 days on our ICU, active treatment was withdrawn because of persistent weaning failure.

Discussion

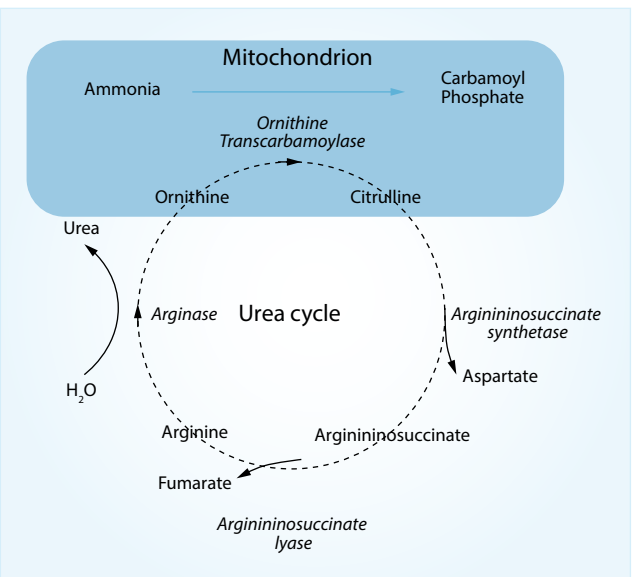
Ammonia is continuously produced during normal metabolism, mainly in the gut, as a by-product of protein digestion and bacterial metabolism. Smaller amounts of ammonia are produced in the kidney, where it is essential for the maintenance of the normal acid-base homeostasis. Ammonium is synthesized in the proximal tubule where

it facilitates the renal excretion of H+ ions. Plasma concentrations of ammonia in the systemic circulation are low, due to an efficient detoxification and elimination process. Hyperammonaemia develops if the ammonia load is high, if portal blood from the intestines bypasses the liver or when there are disturbances in the normal urea cycle.

Hepatic failure is the most common cause of acute severe hyperammonemia in adult ICU patients.[4] Non-hepatic hyperammonaemia is a less recognized cause of hyperammonaemia in ICU patients. It can result from increased ammonia production that exceeds the liver's excretory capacity, resulting for instance from increased protein metabolism as seen after gastrointestinal haemorrhage and steroid use. Ammonia production can also increase after infection with urease splitting bacteria or after urinary diversion when (urease-producing) bacteria in the colon degrade the nitrogenous compounds excreted in the urine with formation and adsorption from ammonia into the systemic circulation.[5] Decreased ammonia elimination is caused by portosystemic shunting, or interference with the normal urea cycle. Ammonia is metabolized in the liver to urea through the urea cycle. This hepatic urea synthesis is controlled by a large number of enzymatic processes and is important for both the removal of the toxic ammonium ions and for the removal of bicarbonate (*figure 1*).[6,7]

Acetazolamide may induce hyperammonaemia in two ways. First, carbonic anhydrase activity is essential for hepatic urea synthesis from ammonium ions. Carbonic anhydrase inhibitors such as acetazolamide can inhibit this urea synthesis. This inhibition of urea synthesis occurs proximally in the urea cycle, at a step prior to citrulline formation,[8,9] thus causing hyperammonaemia.

Figure 1. Schematic presentation of urea production from ammonia through the urea cycle.



Acetazolamide can also interfere with the normal production and excretion of ammonia from the kidney. Normal kidney cells produce free ammonium ions that are either excreted into the urine or released into the renal vein. The release of ammonia into the renal vein represents a major source of the normal ammonia concentration in blood.[10,11] Acetazolamide acts through changes in the acid-base balance and by a direct effect on the kidney. The total amount of ammonia produced by the kidney and its partition into the renal vein or the urine is modified in response to the acid–base balance, potassium status and kidney function.[12,13] Acidosis induces an increase in the total kidney ammonia production and a significant rise in the urinary excretion of ammonia. In contrast, metabolic alkalosis is associated with a marked reduction in urinary ammonium excretion and a rise in the ammonium released into the kidney's venous blood. In the kidney, carboxic anhydrase is located on the brush border of the tubular cells, where it promotes hydrogen ion loss and reabsorption of bicarbonate. Acetazolamide mainly acts on the proximal tubule of the kidney and induces a metabolic acidosis by inhibiting bicarbonate re-uptake. Acetazolamide also reduces the urinary excretion of ammonium by shifting the ammonia from the urinary compartment to the renal vein,[14] thus further contributing to the hyperammonaemia – as seen in our patient. As acetazolamide is mainly excreted by the kidney, patients with renal failure are at risk for acetazolamide accumulation resulting in hyperammonaemia.[15]

Untreated hyperammonaemia can result in encephalopathy, brain oedema and intracranial hypertension, with high morbidity and mortality rates in ICU patients. Ammonia is metabolized by astrocytes to form glutamine. Increased intracellular glutamine concentrations act as an active osmolyte causing movement of water into the astrocytes, inducing swelling of the astrocytes and brain oedema. Ammonia also changes GABA-mediated neurotransmission which reduces the normal level of consciousness.[16] During the course of hyperammonaemic encephalopatic neuroinflammatory processes, disruption of the blood-brain-barrier and oxidative stress may also contribute to the brain damage.[17]

The first step in the treatment of hyperammonaemia is the identification and correction of the precipitating cause. Laxatives such as lactulose and other non-absorbable disaccharides are generally used as first line treatment in most institutions. Scientific evidence for the use of non-absorbable disaccharides is poor. One systematic review found no significant effect of non-absorbable disaccharides on acute or chronic hepatic encephalopathy when compared to placebo.[18] Antibiotics such as vancomycin and neomycin reduce ammonia absorption from the gut by decreasing bacterial ammonia production in the intestinal tract and can be used as

a second line treatment in hyperammonemia. These antibiotics are statistically superior to non-absorbable disaccharides in improving hepatic encephalopathy and lowering blood ammonia concentrations.[18] The efficacy and safety of rifaximin plus lactulose vs. lactulose alone for treatment of hyperammonaemia was recently studied.[19] Although the combination of lactulose plus rifaximin was more effective than lactulose alone, the results of this trial are difficult to interpret due to the high mortality in both groups.[20] Probiotics have been suggested as ammonia lowering therapy. Although probiotics decreased plasma ammonia concentrations compared to placebo, no advantage was found in all-cause mortality, number of adverse events, or quality of life.[21] In patients with urea cycle disorders, ammonia scavengers can be used.[22] The ammonia scavengers such as sodium benzoate act by conjugation of benzoate with glycine to generate hippurate. These conjugates are then excreted in the urine.

Hyperammonaemia may be caused by both hepatic and non-hepatic disorders. Acetazolamide is a frequently used drug that may induce hyperammonaemia by interfering with the urea cycle and renal ammonium handling. Hyperammonaemia must be considered in ICU patients with unexplained changes in consciousness who are treated with acetazolamide.

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