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Intraoperative acidosis related to chronic zonisamide therapy

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Keypoints

1. Zonisamide is a novel anticonvulsant agent used in the treatment of partial and generalized seizures in children and adults. In addition to its anticonvulsant effects, zonisamide inhibits carbonic anhydrase and may result in a chronic, non-anion gap metabolic acidosis.
2. The differential diagnosis of metabolic acidosis can be subdivided into two major categories, normal versus wide anion gap. A wide anion gap acidosis is generally indicative of the presence of an unmeasured acid or anions such as lactic acid. A normal anion gap acidosis is generally the result of bicarbonate loss from the kidneys or the gastrointestinal tract.
3. When intraoperative metabolic acidosis is noted, a review of the patient's current medications is indicated to rule out drug-induced renal tubular acidosis as a contributing factor.
4. Identification of the etiology of the acidosis avoids over-treatment of other potential causes including suspected tissue hypoperfusion or hypovolemia.

Abstract

Zonisamide is a novel anticonvulsant agent used in the treatment of partial and generalized seizures in children and adults. In addition to its anticonvulsant effects, zonisamide inhibits carbonic anhydrase and may result in a chronic, non-anion gap metabolic acidosis. We present an 8-year-old girl with medically intractable epilepsy and Lennox-Gastaut syndrome who presented for a right craniotomy and functional hemispherotomy. Intraoperatively, she was noted to have a metabolic acidosis that was eventually determined to be from chronic therapy with zonisamide. The intraoperative differential diagnosis of metabolic acidosis is presented, an approach for diagnostic investigation presented, and treatment options outlined.

Keywords

Zonisamide, anticonvulsant therapy, metabolic acidosis, anion gap.

Introduction

Zonisamide is an anticonvulsant agent approved as add-on therapy in the treatment of partial seizures in adults with epilepsy.[1] It has also seen increased use as add-on therapy or monotherapy for generalized seizures in adults and children.[2] Zonisamide is a sulfonamide anticonvulsant and a carbonic anhydrase inhibitor, with a chemical structure unrelated to other anti-epileptic drugs.[3] Although its precise mechanism of action is unknown, postulated mechanisms include blockade of both voltage-dependent sodium and T-type calcium channels, and enhancement of gamma-aminobutyric acid (GABA)-

mediated inhibition.[4,5] In addition to its anti-epileptic effects, zonisamide inhibits carbonic anhydrase, which may result in chronic acidosis related to renal losses of sodium bicarbonate.[6] We present an 8-year-old girl who was noted to have a metabolic acidosis during intraoperative care for a craniotomy that was eventually determined to be from chronic therapy with zonisamide. The intraoperative differential diagnosis of metabolic acidosis is presented, an approach for diagnostic investigation presented, and treatment options outlined.

Case report

Review of this case and presentation in this format is in accordance with the guidelines of the Institutional Review Board at Nationwide Children's Hospital (Columbus, Ohio). The patient was an 8-year-old, 20 kg girl with medically intractable epilepsy and Lennox-Gastaut syndrome who presented for a right craniotomy and functional hemispherotomy. She developed focal onset seizure activity at 4 months of age, with the eventual diagnosis of right hemispheric cortical dysplasia. Since that time, she had increasing difficulties with control of her seizures despite escalation of anticonvulsant therapy. Other significant past medical history included adenotonsillar hypertrophy with sleep disordered breathing, left hemiparesis, and developmental delay. Current medications included clonazepam 0.5 mg by mouth twice a day, cannabidiol 570 mg by mouth twice a day, lacosamide 11 mg by mouth twice a day, zonisamide 220 mg by mouth once a day, and rectal diazepam as needed to stop seizures. She had been treated with zonisamide for 7 months. Physical examination revealed a young girl in no acute distress. Her airway examination revealed a Mallampati grade I airway. Cardiac and respiratory examination were unremarkable. Neurologic examination revealed a left-sided hemiparesis. Preoperative complete blood count and coagulation function were normal. On the morning of surgery, the patient was kept *nil per os* for 6 hours. She was transported to the operating room where standard American Society of Anesthesiologists' (ASA) monitors were placed. Anesthesia was induced by the inhalation of sevoflurane in nitrous oxide and oxygen. Following the induction of anesthesia, a peripheral intravenous cannula was placed. After effective bag-valve-mask ventilation was demonstrated, neuromuscular blockade was provided by rocuronium 20 mg (0.6 mg/kg). Direct laryngoscopy with a Macintosh 2 blade revealed a grade I view and a 5.5 cuffed endotracheal tube was placed. After anesthetic induction, a second peripheral intravenous cannula and a radial arterial cannula were placed using ultrasound guidance. Maintenance anesthesia included 4-5% inspired desflurane in air and oxygen, a sufentanil infusion (0.1-0.3 µg/kg/hour), and a rocuronium infusion titrated to the train-of-four. Additional anticonvulsant therapy was provided by the administration of levetiracetam (300 mg). The initial arterial blood gas revealed pH 7.28, $PaCO_2$ 36 mmHg, a calculated bicarbonate of 17.2 mmol/L with a base deficit of -9 mmol/L. A serum lactate concentration was 0.6 mmol/L (normal: 0.5-2.2 mmol/L). Following approximately 15-20 mL/kg of isotonic fluids, repeat measurements demonstrated pH 7.31, pCO_2 31 mmHg, pO_2 192 mmHg, and a calculated bicarbonate of 15.7 mmol/L with an unchanged base deficit of -9 mmol/L. Sodium bicarbonate (1 mEq/kg) was administered incrementally during the 14 hours of intraoperative care for a total of 8 doses. Intraoperatively, the base deficit varied from -3 to -8. Repeat lactate concentration remained normal at 0.7 mmol/L. The final arterial blood gas analysis revealed pH 7.37, $PaCO_2$ 36 mm Hg, a calculated bicarbonate of 20.8 mmol/L, and a base deficit of -4 mmol/L. Intraoperative blood loss was 180 mL. Fluids included 1400 mL of isotonic crystalloids, 350 mL of 5% albumin, and one unit of packed red blood cells. At the completion of the surgical procedure, residual neuromuscular blockade was reversed with sugammadex, and the patient's trachea was extubated. She was admitted to the Pediatric Intensive Care Unit for ongoing monitoring. Ongoing arterial blood gas analysis revealed a mild metabolic acidosis (base deficit of -3 to -5) with a normal anion gap. The remainder of her postoperative course was unremarkable.

Discussion

Proper functioning of physiologic and enzymatic systems requires the maintenance of a normal pH in the blood. In simple terms, pH is affected by the intake of buffer or acid in the diet, endogenous production of these compounds, the function of the intrinsic buffering systems, as well as their renal or respiratory elimination. During normal homeostasis, the normal narrow range of pH is maintained by a variety of intrinsic buffering systems within the blood and tissues and ultimately the regulation of PaCO2 by the lungs and hydrogen/bicarbonate elimination by the kidneys.[7]

The endogenous buffer systems are efficient and act rapidly to compensate for small changes in pH. The buffer systems within the blood and plasma include hemoglobin, plasma proteins, phosphate, and the bicarbonate-carbonic acid system. Protein buffers are predominantly responsible for the control of intracellular pH, but also provide buffering mechanisms of the blood. In addition to the protein systems, phosphates and the bicarbonate-carbonic acid system are also involved in the regulation of pH. Phosphates are present in the blood as either a weak acid, sodium dihydrogen phosphate or a weak base, sodium monohydrogen phosphate. The bicarbonate-carbonic acid buffer works in a fashion similar to phosphate buffers. The base, sodium bicarbonate (NaHCO3), combines with HCl forming carbonic acid (H2CO3) and a salt, NaCl. When carbonic acid comes in contact with NaOH, sodium bicarbonate and water are formed. Bicarbonate balance is regulated by bicarbonate reabsorption, mainly in the proximal tubule, and bicarbonate production and excretion in the distal nephron. These systems act to maintain a neutral pH until CO2 can be excreted by the lungs and the bicarbonate/hydrogen ions by the kidneys. The respiratory system contributes to the control of acid-base balance by regulation of PaCO2. CO2 in the blood readily reacts with water to form carbonic acid. The levels of CO2 and carbonic acid in the blood are in equilibrium so that as the PaCO2 increases, the excess CO2 reacts with water to form carbonic acid thereby lowering the pH. Minute ventilation and hence PaCO2 is regulated by chemoreceptors and the respiratory center in the medulla based on the PaCO2 and pH.

Acidosis, defined as an arterial pH less than 7.35, may be primarily respiratory or metabolic. Respiratory acidosis results from an increased $PaCO_2$ and a secondary decrease in pH, while metabolic disturbances are those that involve the bicarbonate system. The differential diagnosis of metabolic acidosis can be subdivided into two major categories, normal versus wide anion gap. A wide anion gap acidosis is defined as one in which the calculated anion gap $[Na^+ - (Cl^- + HCO_3^-]$ is greater than 10 mEq/L. A wide anion gap acidosis is generally indicative of the presence of an unmeasured acid or anions. These anions are frequently either ingested toxins or byproducts of endogenous metabolism. Common causes of wide anion gap metabolic acidosis include carbon monoxide inhalation, ketoacidosis, toluene inhalation, alcohol poisonings (ethylene glycol, propylene glycol, methanol), uremia, salicylate ingestion, or cyanide inhalation. Acidosis may also be related to lactic acidosis due to tissue hypoperfusion intraoperatively or during critical illness. Alternatively, a normal anion gap acidosis is generally the result of bicarbonate loss. This is usually through gastrointestinal losses (diarrhea) or renal wasting (renal failure, renal tubular acidosis). Renal losses of bicarbonate may occur from primary renal diseases or associated drug therapy, as was the case in our patient, related to the inhibition of carbonic anhydrase.[8,9]

In our patient, the acidosis was noted incidentally on routine intraoperative blood gas analysis using point-of-care testing. As this device does not measure serum electrolytes other than sodium, potassium, and calcium, it was not feasible to rapidly calculate the anion gap although the metabolic acidosis with an associated base deficit was noted. To rule out tissue hypoperfusion, a point-of-care test for serum lactate was obtained, which was normal. Another common cause of intraoperative acidosis is dilutional acidosis related to volume resuscitation with non-buffer containing isotonic fluids such as normal saline.[10]

Dilutional acidosis occurs as the endogenous buffer system is diluted by non-buffer containing intravenous fluids, thus resulting in a hyperchloremic metabolic acidosis. In our patient, the acidosis was noted prior to the administration of significant amounts of isotonic crystalloid thereby eliminating this as the etiology. Subsequent evaluation of the preoperative medication list identified zonisamide as the likely etiology of the acidosis.

Anecdotal reports have suggested the potential association of zonisamide with renal tubular acidosis.[6,11,12] Inoue et al. reported a 7-year-old boy treated with zonisamide who, similar to our patient, developed metabolic acidosis. A work-up resulted in the diagnosis of renal tubular acidosis, which resolved when zonisamide was replaced with phenytoin. Mizra et al. measured electrolytes and genotyped single nucleotide polymorphisms (SNPs) in the main renal carbonic anhydrase isoenzymes (II, IV and XII) in 70 patients, treated with either topiramate (n=55) or zonisamide (n=14) or both (n=1).[12] Twenty-six percent of the patients had a metabolic acidosis (serum bicarbonate <20 mmol/L). There was no association between serum bicarbonate and the dose of the drug or the duration of treatment. Serum bicarbonate levels were associated with SNPs in the carbonic anhydrase isoenzymes. In February 2009, the FDA issued a warning that zonisamide was known to cause metabolic acidosis, and recommended routine monitoring of serum bicarbonate levels prior to initiating therapy and during therapy with zonisamide.

Treatment options should be focused toward identifying and correcting the etiologic factor, which in this case, involves stopping the causative drug if the acidosis is severe. Identification of the etiology of the acidosis avoids over-treatment of other potential causes including suspected tissue hypoperfusion or hypovolemia.[14] As the acidosis is chronic, acute treatment with sodium bicarbonate is unlikely to be necessary during intraoperative care. Chronic metabolic acidosis can result in hyperventilation, non-specific symptoms including fatigue and anorexia, and more severe end-organ effects including cardiac arrhythmias or altered mental status. Long term adverse effects on the kidneys and bones can result in growth retardation and renal calculi in children. In such patients, chronic supplementation with oral bicarbonate can be used to prevent the effects of chronic acidosis.

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