TOPIRAMATE AND SEVERE METABOLIC ACIDOSIS

Case report

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ABSTRACT - Topiramate infrequently induces anion gap metabolic acidosis through carbonic anhydrase inhibition on the distal tubule of the nephron - a type 2 renal tubular acidosis. We report on a 40 years old woman previously healthy that developed significant asymptomatic metabolic acidosis during topiramate therapy at a dosage of 100mg/day for three months. Stopping medication was followed by normalization of the acid-base status within five weeks. This infrequent side effect appears unpredictable and should be given careful attention.

KEY WORDS: topiramate, metabolic acidosis, carbonic anhydrase inhibitor.

Acidose metabólica grave por topiramato: relato de caso

RESUMO - Topiramato pode produzir raramente uma acidose metabólica através da inibição da anidrase carbônica no túbulo distal do néfron - acidose tubular renal do tipo 2. Relatamos o caso de mulher de 40 anos previamente saudável que desenvolveu quadro de acidose metabólica assintomática grave, sem outra etiologia identificável, durante uso de topiramato na dose de 100mg/dia por três meses. Este efeito colateral, embora infrequente, parece ser imprevisível e requer atenção cuidadosa.

PALAVRAS-CHAVE: topiramato, acidose metabólica, inibidor da anidrase carbônica.

Topiramate was approved by the FDA (US - Food and Drug Administration) in 1996 for clinical use as an anticonvulsant drug. Since then, other clinical indications have been studied, such as the treatment of bipolar disorder, or neuropathic pain syndromes relief[1,2], and migraine and cluster headache[3-5]. As a consequence, it is likely that clinical use will tend to expand progressively. Initially, significant adverse reactions to topiramate were related to the central nervous system (somnolence, nervousness, psychomotor slowing, memory problems, fatigue), or were gastrointestinal (nausea), ocular (diplopia, nystagmus) and neuromuscular (tremor, paresthesia). Nevertheless, since 1996, when it was approved by FDA, at least twelve reports were made relating metabolic acidosis to the use of topiramate, both in adults and in children[6-17]. Finally, in December 2003, FDA released a note about the risk of metabolic acidosis caused by topiramate usage[18]. Severe metabolic acidosis can occur in patients under topiramate treatment, even when the daily dosage is low. The absence of relevant clinical symptoms renders it more difficult to recognize.

We present a case of severe asymptomatic metabolic acidosis due to topiramate in an adult woman.

CASE

A 46-year old previously healthy white woman came to our hospital with a complaint of intense chest pain for at least 5 days with tenderness on the site of the pain indicating traumatic origin. There were no other symptoms, and physical examination plus X-ray and laboratory evaluation excluded pleural or pulmonary disease. Later, a radiograph of the ribs, a chest CT scan and a radionuclear bone scan showed a small traumatic lesion in the area of the pain. At the hospital entrance, her arterial blood gas analysis revealed metabolic acidosis: pH (7.31), pCO_2 (18.1 mmHg), pO_2 (121.0 mmHg), HCO_3 (8.9 mmol/L), CO_2 (9.5 mmol/L), base excess (-14.1 mmol/L). Renal function was normal (creatinine 0.9 mg/dL), urinary ultrasonography showed two apparently normal kidneys, non-fasting blood glucose was 112 mg/dL, potassium 3.9 mmol/L, sodium 140 mmol/L, chloride 107 mmo/L, serum amylase 54 U/L, AST 12 U/L, serum gamma-glutamyl transferase 12 U/L, prothrombin time 13.2 seconds, alkaline phosphatase 52 U/L, hemoglobin 12.8 g/dL, hematocrit 37.5%, leukocyte count 8400, normal urinalysis with urinary pH

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5.0. Serum anion-gap was 13. We repeated the arterial blood gas analysis after 3 hours: pH (7.31), pCO_2 (24.1 mmHg), pO_2 (134.4 mmHg), HCO_3 (11.8 mmol/L), CO_2 (12.5 mmol/L), base excess (-11.9 mmol/L). Subsequent analysis revealed a normal serum lactate of 1.53 mmol/L, normal serum protein eletrophoresis (with light hypoalbuminemia - 3.05 g/dL), absent cryoglobulins, normal calciuria and phosphaturia.

She had been in use of topiramate as anti-vertiginous therapy for the last 3 months at a daily regular dosage of 100 mg. As vertigo symptoms ceased with this medication, she was reluctant to accept our indication to stop using it. However, on the 5th day of hospitalization we obtained her consent to withdraw the medication. Arterial blood gas analyses or venous serum CO_2 were repeated on the 2nd, 4th, 7th, and 9th days of hospitalization, all with similar acidosis findings.

The patient was discharged from hospital on the 12th day - seven days after stopping topiramate - with the following arterial blood gas results: pH (7.36), pCO_2 (18.7), pO2 (134.0), HCO_3 (10.3) and CO_2 (11.0 mmol/L), base excess (-11.8mmol/L) - metabolic acidosis with partial respiratory compensation. She returned 30 days later (five weeks after topiramate withdrawal), when a normal complete arterial blood gas result was found - pH (7.44), pCO_2 (35.0 mmHg), pO_2 (124.0 mmHg), HCO_3 (23.0 mmol/L) and CO_2 (24.0 mmol/L), base excess (zero). She was no longer on topiramate.

DISCUSSION

Metabolic acidosis in adults may be caused by increased acid generation (as in ketoacidosis and in lactic acidosis), by loss of bicarbonate (diarrhea or type 2 renal tubular acidosis - RTA) or by diminished renal acid excretion (as in renal failure or in type 1 RTA). Type 1 and type 2 RTA are uncommon disorders, particularly in adults[19], but in the absence of clear clinical evidence as in ketoacidosis, lactic acidosis or diarrhea, the presence of RTA should always be considered in any patient with otherwise unexplained normal anion gap metabolic acidosis[20].

RTA refers to the development of metabolic acidosis because of a defect in the ability of the renal tubules to perform their normal response to acidemia: reabsorption of all the filtered bicarbonate and increased hydrogen excretion, the latter leading to regeneration of bicarbonate in the plasma. The type 1 RTA (distal) is characterized by impaired acid secretory capacity in the collecting tubules. This defect leads to an inability to excrete the daily acid load, resulting in progressive hydrogen ion retention and a drop in plasma bicarbonate concentration. In adults, this type 1 RTA is caused by some autoimmune disease (e.g., Sjögren's syndrome) or by some other condition associated with chronic hyperglobulinemia, none related to our patient. Type 2 RTA (proximal) originates from the inability to reabsorb filtered bicarbonate in the proximal tubule normally. Since this reabsorption occurs in the proximal tubule (85 to 90% of the filtered load), this disturbance leads to an increased delivery of bicarbonate to the distal portion of the nephron. As the distal tubule is initially overwhelmed, there is bicarbonate spill into the final urine, leading to metabolic acidosis.

Type 2 RTA may occasionally present as an isolated defect or as part of Fanconi syndrome, a generalized proximal tubular dysfunction with bicarbonaturia, glucosuria, phosphaturia, uricosuria, aminoaciduria, and tubular proteinuria. In adults, the most common causes of Fanconi syndrome are the excretion of light chains due to multiple myeloma (which may be latent); and the use of a carbonic anhydrase (CA) inhibitor (as acetazolamide). In our patient, proteinuria, glucosuria and phosphaturia were absent, stepping aside the possibility of Fanconi syndrome.

On the other hand, topiramate has been demonstrated to be an effective inhibitor of some CA isoenzymes[14,21], this being the mechanism assigned to the development of metabolic acidosis during its use[8,9,12,14,15]. A slight reduction in serum CO_2 by topiramate has been demonstrated as relatively common and generally asymptomatic[12,17], but marked decreases appear unusual, and are expected to occur when topiramate is associated to other acidogenic conditions, such as renal disease, diarrhea, ketogenic diet or surgery[12]. It was surprising that no other condition besides topiramate ingestion could be attributed to our patient. Anyway, the question remains why some people on topiramate may develop such a significant deficit of serum bicarbonate[9,10,15,17] and others[12,17] not. As topiramate has a different power of inhibition over each CA isoenzyme[21], it seems reasonable to assume that differences between CA isoenzymes activity expression in different people could exist. Maybe this could explain the apparent diversity of susceptibility to metabolic acidosis in different persons.

Another difference is the time required for serum CO_2 to return to normal. Fakhoury et al.[8] reported two patients who attempted suicide by taking a topiramate overdose. Their metabolic acidosis returned to normal after 5-6 days. Stowe et al.[13] observed the normalization of mental status (previously altered, in a patient with metabolic acidosis due to topirama-

te) 48 hours after drug withdrawal. When our patient was discharged from hospital seven days after topimarate withdrawal, she had an arterial serum CO_2 of 11.0 mmol/L. Normalization was detected 30 days later, but there was no opportunity for further laboratory evaluation during this period.

On the other hand, metabolic acidosis usually provokes some clinical manifestation such as hyperventilation and, when severe, mental confusion. In our patient, despite an initial pH of 7.31 and serum bicarbonate of 8.9 mmol/L, there were no clinical manifestations.

Since metabolic acidosis, when low-grade, may induce multiple endocrine and metabolic dysfunctions, and when severe may be a life-threatening condition, and also considering that its onset during topiramate therapy appears unpredictable, it would be a good practice to measure serum CO_2 or serum bicarbonate in a venous blood sample previously and at regular intervals when this drug must be administered to any patient.

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