



The frequency and severity of metabolic acidosis related to topiramate

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Abstract

Objective: We planned a cross-sectional analysis to determine the frequency and severity of metabolic acidosis in patients taking topiramate while awaiting craniotomy.

Methods: Eighty patients (18 – 65 years) taking topiramate to control seizures while awaiting elective craniotomy were enrolled. Any signs of metabolic acidosis or topiramate-related side effects were investigated. Blood chemistry levels and arterial blood gases, including lactate, were obtained. The severity of metabolic acidosis was defined according to base excess levels as mild or moderate.

Results: Blood gas analysis showed that 71% ($n = 57$) of patients had metabolic acidosis. The frequency of moderate metabolic acidosis was 56% ($n = 45$), while that of mild metabolic acidosis was 15% ($n = 12$). A high respiratory rate was reported in only 10% of moderately acidotic patients.

Conclusions: In patients receiving topiramate, baseline blood gas analysis should be performed preoperatively to determine the presence and severity of metabolic acidosis.

Keywords

Metabolic acidosis, preoperative evaluation, topiramate

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Introduction

Topiramate has been a welcome development for treating patients with refractory epilepsy and has also been proven effective and safe in clinical trials for treating patients with partial seizures.¹ Since then, it has been widely administered to neurosurgical patients, and its clinical use is likely to expand. Thus, anaesthesiologists are increasingly likely to encounter patients

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receiving topiramate therapy during pre-operative evaluations.

Metabolic acidosis is a known infrequent adverse reaction to topiramate therapy.^{2,3} Often, topiramate-related acidosis is asymptomatic, but marked decreases can be expected to occur when patients receiving topiramate undergo surgery.⁴ Craniotomy increases the risk of fluid shift, and therefore requires more anaesthetic drugs for the lengthy surgery.⁵ These factors can in turn increase pre-existing metabolic acidosis. For that reason, in patients taking topiramate and undergoing craniotomy, documenting the metabolic status is important.

Despite the importance of this effect of topiramate on metabolic status, topiramate-related metabolic acidosis has been reported in few adult patients, and there are only limited prospective studies in the literature.^{6–10} Only one of these studies is in neurosurgical patients, and it retrospectively reported the results of blood gas analysis in six patients.¹⁰ Therefore, we designed this prospective cross-sectional analysis to determine the frequency and severity of metabolic acidosis, determined through blood gas analysis, in patients taking topiramate who were being prepared for elective craniotomy.

Patients and methods

We enrolled 80 patients (age range: 18–65 years) who were taking topiramate and planning to undergo elective craniotomy. All patients gave written informed consent, and the study was approved by the institutional ethics committee.

We excluded patients with diabetes mellitus, diabetes insipidus, or hepatic or renal disease, and any patient taking other medications likely to cause metabolic acidosis. The demographic data for each patient were recorded, and any signs of metabolic acidosis or topiramate-related side effects were investigated (e.g., dizziness, drowsiness, headache, somnolence, memory problems,

or paraesthesia). Each patient's respiratory rate was measured at rest and recorded. A high respiratory rate was described as more than 20 breaths per minute at rest. The results of routine blood chemistry tests were also recorded. These included liver and renal function tests, total protein, albumin, electrolytes (sodium, potassium, chloride, magnesium, and calcium), serum osmolality, haemoglobin. Urine analysis results were also recorded. Baseline arterial blood gas levels, including lactate, were obtained at the time of admission (Roche OMNI S, Mannheim, Germany). The severity of metabolic acidosis was defined according to base excess (BE) levels: a BE from -3 to -5 indicated mild acidosis, a BE from -5 to -10 indicated moderate acidosis, and a BE level below -10 indicated severe acidosis.

Patients on topiramate with moderate acidosis were switched to another anti-epileptic drug. If the acidosis resolved within 2–4 days of discontinuing topiramate therapy, patients were scheduled for surgery. If the acidosis did not resolve, the BE was replaced with bicarbonate therapy. Severely acidotic patients with clinical symptoms were treated with bicarbonate.

SPSS for Windows version 16.0 was used for statistical analysis, and the results were expressed as the mean \pm standard deviation (SD). All variables were tested for normal distribution using the Shapiro–Wilk test. Correlations between the variables were analyzed with Spearman's rho correlation test and one-way analysis of variance. A P -value < 0.05 was considered statistically significant.

Results

The demographic characteristics, topiramate dosages, concomitant antiepileptic therapies, topiramate-related side effects, and surgical pathologies appear in Table 1. Blood chemistry results were within the normal range in all patients, but blood gas

Table 1. Patient characteristics, antiepileptic drugs, topiramate dosages and side effects, and surgical pathology ($n = 80$).

	Normal acid–base status $n = 23$ (28.7%)	Mild acidosis $n = 12$ (15.0%)	Moderate acidosis $n = 45$ (56.2%)
Age, years	42 ± 14	44 ± 10	39 ± 13
Gender, males/females, n	19/4	5/7	22/23
ASA status I/II, n	15/8	10/2	25/20
Weight, kg	71 ± 14	58 ± 9	67 ± 12
Topiramate dosages, n (%)			
2 × 50 mg	14 (17.4)	11 (22.0)	26 (32.5)
2 × 100 mg	9 (11.2)	1 (1.2)	19 (23.7)
Duration of use, months	19 ± 6	17 ± 9	15 ± 11
Concomitant antiepileptic medications, n (%)			
Carbamazepine	9 (11.2)	10 (6.2)	23 (28.7)
Lamotrigine	3 (3.7)	4 (5.0)	1 (1.2)
Levetiracetam	4 (5.0)	3 (3.6)	12 (15.0)
Lamotrigine + Levetiracetam	–	–	10 (6.2)
Surgical pathology, n			
Meningioma/glioma/MTS	5/10/8	4/3/5	9/23/13
Topiramate-related side effects, n (%)			
Headache	4 (5.0)	3 (3.7)	7 (8.7)
Sleepiness	7 (8.7)	4 (5.0)	14 (17.4)
Dizziness	2 (2.5)	1 (1.2)	3 (3.6)
Paraesthesia	1 (1.2)	1 (1.2)	2 (2.5)

Data presented as mean ± SD.

ASA, American Society of Anesthesiologists; MTS: mesial temporal sclerosis.

analysis showed metabolic acidosis in 71% ($n = 57$) of patients. Moderate metabolic acidosis was observed in 56% ($n = 45$) of patients, while mild metabolic acidosis was seen in 15% ($n = 12$).

Mean arterial blood gas values were reported as pH: 7.34 ± 5 , carbon dioxide partial pressure (PaCO₂): 29 ± 5 mmHg, bicarbonate (HCO₃⁻): 18 ± 2 mmol.L⁻¹, BE: -6.3 ± 2 mmol.L⁻¹, chloride (Cl⁻): 111 ± 3 mmol.L⁻¹, and lactate: 0.9 ± 0.2 mmol.L⁻¹; furthermore, serum potassium was 3.4 ± 2.1 mEq.L⁻¹ and urinary pH was 4.0 ± 1.3 in patients with metabolic acidosis ($n = 57$).

Ten percent of patients with metabolic acidosis had a high respiratory rate. Headache ($n = 14$), sleepiness ($n = 25$), dizziness ($n = 6$), and paraesthesia ($n = 3$) were topiramate-related side effects observed in

patients. There was no correlation between the frequency of these side effects and the severity of metabolic acidosis ($p > 0.05$), or between the duration of topiramate use and the severity of metabolic acidosis ($p > 0.05$).

For patients with moderate acidosis ($n = 45$), topiramate therapy was discontinued and the side effects resolved in 2–4 days.

Discussion

In this study, the frequency of topiramate-related metabolic acidosis was 71%. Among these patients with metabolic acidosis, 56% had moderate acidosis that resolved 2–4 days after the discontinuation of topiramate therapy.

Metabolic acidosis is a life-threatening complication of the perioperative period.⁵

It can cause decreased cardiac output, electrolyte imbalance, surgical bleeding, and neurological complications, even coma and death, in surgical patients.¹¹ Neurosurgical patients have a potentially higher risk of acidosis than patients undergoing other surgeries because of the longer duration of surgery, greater risk of fluid shift, and increased requirements for anaesthetic drugs. Thus, documenting a patient's metabolic status before surgery is critical in this group. The 71% frequency of topiramate-related metabolic acidosis that we observed is a high percentage for surgical patients. Patients with mild acidosis present no symptoms, however, and this absence of relevant clinical symptoms renders it more difficult to recognize the problem without blood gas analysis.

In a systematic review of topiramate use, Dell'Orto and colleagues concluded that topiramate is associated with mild to moderate hypochloraemic metabolic acidosis.¹² Topiramate can weakly inhibit carbonic anhydrase, which may lead to hypochloraemic metabolic acidosis, most likely from renal tubular acidosis rather than from a more central mechanism.^{9,12} Only three studies (with small sample numbers) and a few case reports have documented the frequency of topiramate-related metabolic side effects (maximum 55 patients) to date.^{9,10} Despite the many reports describing the phenomenon in paediatric patients, the literature includes only one report of metabolic acidosis related to topiramate therapy in adult neurosurgical patients.¹⁰ That study included only six blood samples after the induction of anesthesia.¹⁰ The authors retrospectively reported that metabolic acidosis occurred in 60% of patients taking topiramate in their case series. However, they collected the data retrospectively, after anaesthesia, and their series is a small sample size. They recommend that patients who take topiramate should be asked about symptoms during the preoperative evaluation and that blood gas analysis should be

routinely performed before patients undergo surgical procedures.¹⁰ To date, our series is the largest to document metabolic disturbances related to topiramate in a surgical population.⁶⁻¹⁰

Although increased respiratory rate is a sign of acidosis, it appears only in patients with moderate to severe acidosis and cannot be detected easily. There are different reports of the time required for serum carbon dioxide levels to return to normal after topiramate is discontinued.⁹ In our series, 10% of patients had increased respiration and blood gases normalized in 2–4 days in most patients after topiramate was discontinued, a finding that reflects those reported in the literature.⁹

In conclusion, the results of this prospective study suggest that, in patients receiving topiramate, preoperative evaluation should include the consideration of metabolic acidosis. Baseline blood gas levels can be obtained to confirm the presence and severity of metabolic acidosis.

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Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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References

1. LaRoche SM and Helmers SL. The new antiepileptic drugs: scientific review. *JAMA* 2004; 291: 605–614.

2. Tschoner A, Engl J, Laimer M, et al. Metabolic side effects of antipsychotic medication. *Int J Clin Pract* 2007; 61: 1356–1370.
3. Faught E, Wilder BJ, Ramsay RE, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD study group. *Neurology* 1996; 46: 1684–1690.
4. Montenegro MA, Guerreiro MM, Scotoni AE, et al. Predisposition to metabolic acidosis induced by topiramate. *Arq Neuropsiquiatr* 2000; 58: 1021–1024.
5. Waters JH, Miller LR, Clack S, et al. Cause of metabolic acidosis in prolonged surgery. *Crit Care Med* 1999; 27: 2142–2146.
6. Groeper K and McCann ME. Topiramate and metabolic acidosis: a case series and review of the literature. *Paediatr Anaesth* 2005; 15: 167–170.
7. Ko CH and Kong CK. Topiramate-induced metabolic acidosis: report of two cases. *Dev Med Child Neurol* 2001; 43: 701–704.
8. Ozer Y and Altunkaya H. Topiramate induced metabolic acidosis. *Anaesthesia* 2004; 59: 830.
9. Stowe CD, Bollinger T, James LP, et al. Acute mental status changes and hyperchloremic metabolic acidosis with long-term topiramate therapy. *Pharmacotherapy* 2000; 20: 105–109.
10. Rodriguez L, Valero R and Fàbregas N. Intraoperative metabolic acidosis induced by chronic topiramate intake in neurosurgical patients. *J Neurosurg Anesthesiol* 2008; 20: 67–68.
11. Schulman P and Mako J. Acidosis, lactic/metabolic. In: Fleisher LA, Roizen MF (eds) *Essence of anesthesia practice*, 3rd ed. Philadelphia: Elsevier Saunders, 2011, p. 5.
12. Dell’Orto VG, Belotti EA, Goeggel-Simonetti B, et al. Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. *Br J Clin Pharmacol* 2014; 77: 958–964.