# Topiramate in monotherapy or in combination as a cause of metabolic acidosis in adults with epilepsy

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**Aim.** To determine the frequency of metabolic acidosis and its related factors in outpatients taking topiramate in monotherapy or as an adjuvant for the treatment of epilepsy.

**Patients and methods.** Cross-sectional analysis of arterial blood gas test of epileptic patients who received topiramate during 2010 in the Epilepsy Clinic at the National Medical Center '20 de Noviembre' in Mexico. Clinical data regarding epilepsy history and management and the common symptoms of metabolic acidosis were recorded.

**Results.** We studied 32 adults with epilepsy at an outpatient epilepsy clinic who were treated with topiramate in monotherapy or in combination for at least one month. Metabolic acidosis was found in all patients ($HCO_3$ < 22 Eq/L); nine were taking topiramate in monotherapy, and 23 were taking at least two antiepileptic drugs (AEDs). All of the patients were asymptomatic. We found no correlation between bicarbonate levels and the dose of the drug or the duration of treatment. The dose was significantly higher in the monotherapy group, and the bicarbonate level was lower in the patients taking more than one AEDs.

**Conclusions.** The use of concomitant AEDs increases the known effects of topiramate on serum bicarbonate levels and the presence of metabolic acidosis, and these effects appear to be independent of the number of AEDs used.

**Key words.** Adverse event. Antiepileptic drugs. Epilepsy. Metabolic acidosis. Monotherapy. Topiramate.

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Accepted:
05.11.14.

How to cite this paper:
Ruiz-Granados VJ, Márquez-Romero JM. Topiramate in monotherapy or in combination as a cause of metabolic acidosis in adults with epilepsy. Rev Neurol 2015; 60: 159-63.

*Versión española disponible en www.neurologia.com*



## Introduction

Topiramate has been widely used for the treatment of focal and generalized epilepsy since it received FDA approval in 1993. Its broad anticonvulsant properties rely on multiple inhibitory mechanisms, which include voltage-activated sodium channels, L-type high-voltage-activated calcium channels and kainate-evoked currents. In addition to affecting membrane currents, TPM also inhibits isoenzymes I-VI of carbonic anhydrase (CA), which are present in neurons and nephrons [1]. This results in a predisposition to metabolic acidosis that has been widely described in children due to its deleterious effect on the acid-base balance and its associated symptoms such as nausea, headache, diarrhea, hyperventilation, and hypercalciuria, which may lead to nephrolithiasis [2].

Because metabolic acidosis may have adverse clinical consequences, even in its milder forms, we performed this prospective cross-sectional study to assess the severity and prevalence of metabolic acidosis in adults taking topiramate and to attempt to define some factors that determine its presence, specifically if acidosis is significantly associated with drug dose, concomitant drug regimen or with the time that the patient has been taking the drug.

## Patients and methods

The study was approved by the ISSSTE local research and ethics committee, and all patients gave written informed consent. Patients were recruited from the Epilepsy Clinic of the National Medical Center '20 de Noviembre' ISSSTE, in Mexico City, which is a third-level national reference center. We recruited consecutive patients who met the following criteria: willing to participate, aged 18 years or older, had been using topiramate alone or in combination for at least 1 month, and attended regular follow-up visits at the epilepsy clinic. We excluded patients with a concomitant illness or who were taking medications known to cause acidosis.

The recruited patients were asked to provide an arterial blood sample during one of their visits for an arterial blood gas (ABG) test and serum potassium measurement. The ABG test included six parameters: partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide ($PaCO_2$), alveolar-ar-

**Table I.** Comparison between patients receiving topiramate in monotherapy or in combination.

| | All | Monotherapy (*n* = 9; 28.1%) | Combination (*n* = 23; 71.9%) | *p* |
|---|---|---|---|---|
| Mean age (years) [a] | 39.75 ± 10.30 | 41.56 ± 8.80 | 39.04 ± 10.90 | 0.54 |
| Female | 23 (71.9%) | 8 (88.9%) | 15 (65.2%) | 0.38 |
| Total daily dose (mg) [b] | 200 (100-400) | 100 (100-400) | 300 (100-400) | 0.03 |
| Months on topiramate [a] | 29.00 ± 17.64 | 20.89 ± 17.30 | 32.17 ± 17.08 | 0.10 |
| Number of concomitant AEDs [b] | 1 (0-3) | – | 2 (1-3) | |
| Arterial pH [a] | 7.39 ± 0.06 | 7.42 ± 0.03 | 7.38 ± 0.06 | 0.08 |
| Serum bicarbonate (mEq/L) [b] | 16 (11-19) | 17 (15-19) | 16 (11-19) | 0.03 |
| $PaCO_2$ (mmHg) [b] | 25 (19-32) | 25 (23-32) | 25 (19-29) | 0.65 |
| Serum potassium (mEq/L) [b] | 3.3 (2.6-4.0) | 3.4 (2.6-3.6) | 3.3 (3.0-4.0) | 0.45 |

AEDs: antiepileptic drugs. [a] Mean ± standard deviation; [b] Median (range).

terial oxygen tension gradient), pH, bicarbonate concentration ($HCO_3$), and standard base excess.

The recorded data included the following: age, sex, the number and types of concomitant anti-epileptic drugs (AEDs), the time in months that the patient had been taking topiramate, the topiramate dosage, and common symptoms of metabolic acidosis (rapid breathing, chest pain, headache, palpitations, muscle and bone pain, muscle weakness, and abdominal pain).

## Statistics

The Shapiro-Wilk test was used to analyze the normality of the continuous variables. The independent samples *t* test and the *U* Mann-Whitney test (when appropriate) were used to test the significance of the differences between patients receiving topiramate alone and in combination. A multiple regression analysis was used to assess the association between serum bicarbonate levels and daily drug dose, treatment duration, the number of concomitant drugs in a continuous form and in a dichotomous form (topiramate alone versus at least one concomitant AED), sex, and age. A *p* value of less than 0.05 in the regression model represented a significantly associated covariate. Pearson's r was used to test for correlations between variables. All analyses were performed with the statistical package SPSS v. 17.

**Table II.** Results of multiple regression analysis.

| | Coefficient | Standard error | *p* |
|---|---|---|---|
| Age | 0.097 | 0.038 | 0.59 |
| Daily dose | 0.054 | 0.004 | 0.78 |
| Number of concomitant drugs | 0.424 | 0.597 | 0.16 |
| Treatment duration | 0.206 | 0.023 | 0.27 |
| Female sex | –0.179 | 0.985 | 0.38 |
| Only topiramate (dichotomous) | –0.806 | 1.247 | 0.004 |

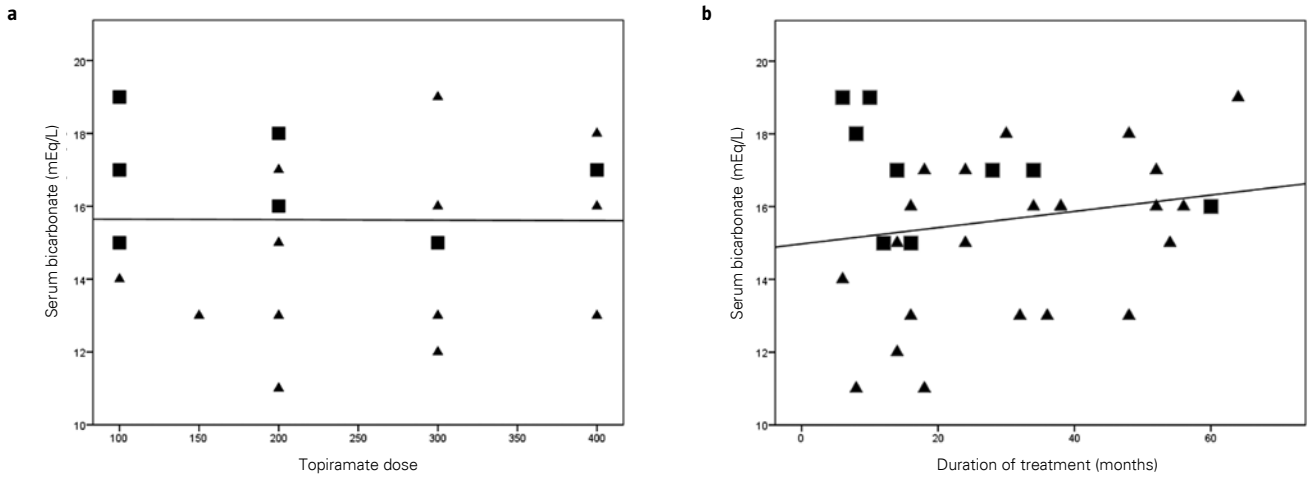
## Results

From January 1 to December 31, 2010, 32 patients (23 females) were recruited. Nine patients (28%) were on topiramate alone. The daily topiramate doses ranged from 100 to 400 mg and were significantly higher in patients taking additional AEDs (Table I). In the combination therapy patients, the median number of concomitant AEDs was 2 (range: 1-3), and the most commonly associated AEDs were valproic acid, levetiracetam and lamotrigine. All patients self-reported the absence of common symptoms of metabolic acidosis.

The mean pH was 7.39 ± 0.06 (range: 7.19-7.48). All patients had absolute hypocarbia ($pCO_2$ < 35 mmHg). The median $pCO_2$ was 25 mmHg (range: 19-32 mmHg). Metabolic acidosis was identified in all patients, as defined by a low serum $HCO_3$ (normal range: 22-26 mEq/L), and was uncompensated (presence of pH < 7.36) in three patients (9.4%). All cases of uncompensated metabolic acidosis were identified in patients receiving combination therapy. pH and serum $HCO_3$ were lower in patients receiving concomitant AEDs, but only the difference in $HCO_3$ reached statistical significance (Table I).

The multiple regression analysis showed a significant association between serum bicarbonate and the use of combination therapy when the number of AEDs was transformed into a dichotomic variable, but the association was not significant when the number of AEDs was represented as a continuous variable (Table II). Because the topiramate doses significantly differed between the groups, we used a correlation analysis to assess the relationship between these two values within the groups (Figure). We found a weak negative correlation in the

**Figure.** Data from patients receiving topiramate alone (squares) and in combination (triangles) show lack of association between serum bicarbonate and topiramate dose (a) or duration of the treatment (b). Scatter plots show bicarbonate values for topiramate daily doses, months of treatment, and trend lines.




group receiving topiramate alone (Pearson's $r$ = –0.305; $p$ = 0.42) and a weak positive correlation in the group taking at least two AEDs (Pearson's $r$ = 0.299; $p$ = 0.16). Concerning the duration of treatment we found no correlation (Pearson's $r$ = 0.098; $p$ = 0.59).

## Discussion

Although abnormally low serum bicarbonate levels and pH have been previously described in pediatric patients taking topiramate [3], the reports in adults are more scarce and have primarily been described in patients undergoing surgery [4-6]. In the outpatient population, the study by Mirza et al [7] involved ABG analysis in 64 patients taking topiramate and 16 patients taking zonisamide. They found that 29% of the patients taking topiramate had low serum bicarbonate levels, and they found no correlation between bicarbonate levels and the dose of the drug or the duration of treatment. Similarly, we also found no impact of drug dose or duration of treatment on the development of metabolic acidosis, but the prevalence of metabolic acidosis that we found was much higher. In another study involving 320 neurosurgical patients taking topiramate, only four patients were reported to be free of metabolic acidosis (a prevalence of 98.75%), which is more concordant with the 100% prevalence found in our patients [6]. Nevertheless, in a study by Garris et al of 54 patients taking topiramate, the prevalence of low serum bicarbonate levels was 48% [8].

The role of concomitant medications has not previously been addressed, and we believe that the most important finding of our study is that, in patients taking topiramate, the use of concomitant AEDs increases the effect of topiramate on the serum bicarbonate level and pH. Although we did not identify a correlation between the number of concomitant AEDs and the presence of metabolic acidosis, the results of the multiple regression analysis show that combination therapy has a role on the development of acidosis. The mechanisms underlying this finding most probably involve complex pharmacokinetic drug interactions that are always present in epileptic patients receiving more than one AED [9]. Unfortunately, our sample size was small, and the number of patients in the combination therapy group did not allow a stratified analysis based on the different AEDs used, which constitutes one important limitation to our study. Therefore, we believe that a future study with a larger sample size would allow the further analysis of the AED combinations, which may identify the degree at which each concomitant medication exacerbates the acidosis.

Another limitation of our study is that we were not able to obtain serum concentrations of topira-

mate, and using daily dose as the sole measure for drug exposure is sub-optimal since it is known that up to 40-60% of epilepsy patients are non-compliant with their treatment [10], this could have reduced the likelihood of finding a correlation between the studied variables, nevertheless it has been demonstrated that topiramate shows linear pharmacokinetics and that, therefore, its concentration in plasma increases linearly with increasing dose [11]. Likewise, topiramate is prone to drug interactions [12], and gender, age and pharmacogenetics also have an impact on its serum concentrations. All these factors should be addressed in future studies. However, the study also has some strengths. For example, because of the known unreliability of venous blood sampling to adequately assess blood gasses and pH [13], we used an ABG analysis, which yields a more accurate measurement.

Additionally, the patients were specifically questioned about the known symptoms of acidosis. In this respect, our study found that all patients were asymptomatic despite their serum pH and bicarbonate levels. This finding may be clinically relevant for patients taking topiramate who are surveyed for surgery without an ABG analysis and therefore face an increased risk of developing severe intraoperative hyperchloremic metabolic acidosis [6].

Our findings lead us to believe that patients on topiramate could benefit from been screened for metabolic acidosis, because most are asymptomatic and there are many serious consequences of chronic metabolic acidosis, particularly in children, in patients with renal and respiratory impairment and in those suffering from any acute pathological condition that may result in high metabolic responses [14].

In conclusion, this study shows that, in addition to the known association between topiramate use and the presence of metabolic acidosis, the concomitant use of AEDs further increases this effect irrespective of the number of drugs used. Additionally, neither the topiramate dose nor the treatment duration appears to play a role in the development or severity of metabolic acidosis.

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## Topiramato en monoterapia o en combinación como causa de acidosis metabólica en adultos con epilepsia


**Objetivo.** Determinar la frecuencia de acidosis metabólica y sus factores relacionados en pacientes tratados con topiramato solo o como adyuvante para el tratamiento de epilepsia.

**Pacientes y métodos.** Análisis transversal de la gasometría arterial de pacientes epilépticos que recibieron topiramato durante 2010 en la clínica de epilepsia del Centro Médico Nacional 20 de Noviembre en México. Se registraron datos clínicos concernientes a la epilepsia y su tratamiento, así como de los síntomas comunes de acidosis metabólica.

**Resultados.** Se estudiaron 32 adultos con epilepsia, quienes recibieron topiramato en monoterapia o en combinación por lo menos durante un mes. Se encontró acidosis metabólica en todos los pacientes ($HCO_3$ < 22 Eq/L); nueve tomaron sólo topiramato y 23 tomaron por lo menos dos fármacos antiepilépticos (FAE). Todos los pacientes fueron asintomáticos. No se encontró correlación entre los niveles de bicarbonato y la dosis del medicamento o la duración del tratamiento. La

dosis fue significativamente mayor en el grupo de monoterapia y el nivel de bicarbonato fue más bajo en los pacientes que tomaban más de un FAE.

**Conclusiones.** El uso concomitante de FAE incrementa los efectos conocidos del topiramato sobre los niveles séricos de bicarbonato y la presencia de acidosis metabólica; estos efectos parecen ser independientes del número de FAE utilizados.

**Palabras clave.** Acidosis metabólica. Antiepilépticos. Efecto adverso. Epilepsia. Monoterapia. Topiramato.