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Chronic impact of topiramate on acid-base balance and potassium in childhood

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ABSTRACT

Topiramate, which is commonly prescribed for seizure disorders and migraine prophylaxis, sometimes causes metabolic acidosis and hypokalemia. Since the effects of topiramate on acid–base balance and potassium levels have not been well explored in children, acid–base balance, anion gap and potassium were assessed in 24 patients (8 females and 16 males) aged between 4.6 and 19 years on topiramate for more than 12 months and in an age-matched control group. Plasma bicarbonate (21.7 versus 23.4 mmol/L; $P < 0.03$), carbon dioxide pressure (39.7 versus 43.2 mm Hg; $P < 0.05$), and potassium (3.7 versus 4.0 mmol/L; $P < 0.03$) were on the average lower and chloride (109 versus 107 mmol/L; $P < 0.03$) higher in patients treated with topiramate than in controls. Blood pH, plasma sodium and the anion gap were similar in patients on topiramate and in controls. In patients on topiramate no significant correlation was observed between the dosage of this agent and plasma bicarbonate or potassium as well as between topiramate blood level and the mentioned electrolytes. In conclusion long-term topiramate treatment is associated with a mild, statistically significant tendency towards compensated normal anion gap metabolic acidosis and hypokalemia.

1. Introduction

Topiramate is commonly prescribed for the management of seizure disorders and for migraine headache prophylaxis.[1–3] Several case reports describe the association between topiramate treatment and the development of metabolic acidosis and hypokalemia. Metabolic acidosis and hypokalemia are mostly precipitated by factors such as surgery, diarrhea, respiratory disease or infection, underlying renal disease, and ketogenic diet.[4–6]

The effects of topiramate on acid–base balance and potassium level have not been well explored in children and adolescents on long-term treatment. This circumstance prompted us to address this question in a cross-sectional analysis.

2. Patients and methods

Twenty-four consecutive patients aged between 4.6 and 19 years (Table 1) with either generalized or partial epilepsy on

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Table 1 – Demography of 24 epileptic patients on long-term management with topiramate (administered in two divided doses) included in the study. Data are given either as median (with interquartile range between brackets) or as relative frequency.

Age, years	14 [9.9–16]
Gender, females:males	8:16
Duration of topiramate treatment, months	23 [19–50]
Underlying epileptic condition	
Partial, N	12
Generalized, N	12
Antiepileptic management	
Topiramate dose, mg/kg body weight daily	2.8 [1.7–4.9]
Topiramate trough level, μmol/L	15.0 [7.8–18.9]
Monotherapy, N	17
Polytherapy, N	7[a]

a Valproic acid ($N = 4$); carbamazepine ($N = 1$); lamotrigine ($N = 1$); levetiracetam ($N = 1$).

medication with topiramate, who were on regular follow-up at the Department of Pediatrics, Ospedali Bellinzona and Mendrisio, Switzerland, entered the study between February 2008 and May 2009. They met the following inclusion criteria: treatment with topiramate for more than 12 months, stable drug management and absence of seizure activity for more than 4 months, no infections during the preceding 6 weeks, absence of chronic kidney disease, and age-adapted diet (with an adequate intake level for potassium). Patients on alkali therapy, on supplementation with potassium or on ketogenic diet were not included. The study, which had been approved by the Institutional Review Board, was also concurrently performed in an age-matched control group of 24 non-pharmacologically treated children and adolescents with idiopathic childhood nephrotic syndrome cured for 2 or more years ($N = 5$) or functional voiding disorders ($N = 19$). They were 13 male and 11 female subjects aged between 4.1 and 18, median 14 years.

Both in patients on topiramate as well as in controls a morning blood specimen was taken after a light breakfast, according to our standard procedure.[7] Venous blood was collected anaerobically with minimal stasis and without movement of the forearm for determination of pH, carbon dioxide pressure, potassium, chloride and sodium. In patients blood was also drawn before the morning dose of antiepileptic drugs for the determination of topiramate level. Undiluted blood samples were used for the triplicate determination of pH, carbon dioxide pressure, potassium, chloride and sodium within 10 min after collection by means of direct electrodes.[7] Plasma bicarbonate was calculated from pH and carbon dioxide pressure using the Henderson–Hasselbalch equation and the anion gap from the difference between measured cations (sodium and potassium; mmol/L) and anions (bicarbonate and chloride; mmol/L).[7] The topiramate level was determined by means of a fluorescence polarization immunoassay.

Considering the small sample size, nonparametric techniques were used to analyze the data. Values are expressed either as individual data or as median and interquartile range, which extends from the value at the 25th to that at the 75th centile and includes half of the data points. For analysis the two-tailed Mann–Whitney–Wilcoxon test for two independent samples and simple regressions with the Spearman rank order correlation coefficient r_s were used. Statistical significance was defined as a P value of <0.05.

3. Results

Information on the 24 epileptic patients on long-term management with topiramate is given in Table 1. Plasma bicarbonate (21.7 [20.0–23.5] versus 23.4 [22.4–24.6] mmol/L; $P < 0.03$), carbon dioxide pressure (39.7 [37.8–40.5] versus 43.2 [38.5–45.0] mm Hg; $P < 0.05$), and potassium (3.7 [3.6–3.9] versus 4.0 [3.9–4.1] mmol/L; $P < 0.03$) were lower and chloride (109 [107–111] versus 107 [105–108] mmol/L; $P < 0.03$) higher in patients treated with topiramate than in controls, as given in Fig. 1. Blood pH (7.36 [7.33–7.38] versus 7.36 [7.35–7.40]), plasma sodium (140 [139–142] versus 140 [139–141] mmol/L) and the anion gap (13 [12–14] versus 12 [9–14] mmol/L) were similar in patients on topiramate and in controls. Plasma bicarbonate, carbon dioxide pressure, potassium and chloride were not statistically different in 17 patients on monotherapy and in 7 on polytherapy.

In patients no significant correlation was observed between the dosage of topiramate and plasma bicarbonate or potassium as well as between topiramate blood level and the mentioned electrolytes (Fig. 2). No significant correlation was also noted between the duration of medication with topiramate and plasma bicarbonate or potassium.

4. Discussion

This simple cross-sectional analysis explored the effect of topiramate for more than 12 months on acid–base profile and potassium level in children and adolescents. The results demonstrate that in these patients long-term topiramate treatment is associated with a mild, statistically significant tendency towards a compensated normal anion gap metabolic acidosis and hypokalemia.

Topiramate inhibits the carbonic anhydrase that is expressed in proximal renal tubular cells with an activity level that is many times less than that of acetazolamide.[1–3] This inhibition of carbonic anhydrase, which is considered unrelated to its antiepileptic effect, may result in normal anion gap renal tubular acidosis and hypokalemia.[8] Acidosis and hypokalemia initially were felt to be a rare adverse reaction in children treated with topiramate with case reports that document their occurrence while undergoing surgical procedures,[4,6] and especially approximately one week after beginning topiramate[5] or after an increase[5] in its dose.

The novelty of the present report is that patients were on topiramate for more than 12 months. The results obtained in the patients likely reflect a chronic compensated stage that may be different from studies where acid–base balance and potassium level were assessed at a more acute stage. Our data indicate that in childhood compensated metabolic acidosis and hypokalemia are a more frequent side effect of topiramate than previously anticipated with both plasma