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Effect of topiramate on acid–base balance: extent, mechanism and effects

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Topiramate is licensed for the treatment of epilepsy and for migraine prophylaxis, but is also used off-licence for a wide range of indications. With the increasing use of topiramate, reports have emerged that topiramate can cause metabolic acidosis in some patients. It does this by impairing both the normal reabsorption of filtered HCO_3^- by the proximal renal tubule and the excretion of H^+ by the distal renal tubule. This combination of defects is termed mixed renal tubular acidosis (RTA). The mechanism involves the inhibition of the enzyme carbonic anhydrase, which is consistent with the fact that genetic deficiency of carbonic anhydrase is associated with mixed RTA. Topiramate-induced RTA can make patients acutely ill, and chronically, can lead to nephrolithiasis, osteoporosis and, in children, growth retardation. There is no proven method for predicting or preventing the effect of topiramate on acid–base balance, but patients with a history of renal calculi or known RTA should not receive topiramate. The utility of regular monitoring of HCO_3^- levels has not been proven and is not routine practice currently. For patients with persistent RTA, topiramate should usually be discontinued as alternative agents are available.

Background

Topiramate is a sulphamate-substituted monosaccharide licensed for the monotherapy and adjunctive treatment of generalized tonic-clonic seizures or partial onset seizures with or without secondary generalization, for the adjunctive treatment of seizures in Lennox–Gastaut syndrome [1], and for migraine prophylaxis [2]. Topiramate is also being used off-label for an ever increasing number of other indications. Several studies have demonstrated the efficacy of topiramate in the treatment of bipolar disorder [3] and in the treatment of post-traumatic stress disorder [4]. Topiramate has also shown promise as an antiobesity agent [5] and in treating alcohol dependence [6]. Investigational uses of topiramate include treatment of bulimia nervosa [7], obsessive-compulsive disorder [8], idiopathic intracranial hypertension [9], neuropathic pain [10], infantile spasm [11] and as an aid in smoking cessation [12].

With the increasing use of topiramate, reports have emerged of serum and urine biochemical derangements induced by this medication (see below). In the present review, we will examine the extent of these derangements and discuss the possible underlying mechanisms and clinical effects.

Topiramate induces metabolic acidosis in some patients

Case reports indicate that topiramate can cause metabolic acidosis in some patients. Burmeister *et al*. [13], for example, reported the case of a 46-year-old prescribed topiramate for vertigo who developed metabolic acidosis with a pH of 7.31 and serum HCO_3^- of 8.9 mM (normal range not provided). Similarly, Ozer and Altunkaya [14] reported the case of a 58-year-old patient on topiramate for refractory temporal lobe epilepsy who developed metabolic acidosis with a pH of 7.29 and serum HCO_3^- of 20 mM. Philippi *et al*. [15] found that metabolic acidosis developed in eight out of nine children after 8–26 days of topiramate treatment with a minimum pH of 7.22 and serum HCO_3^- of 15 mM. At present, there are no published prospective systematic studies of the effect of topiramate on serum pH and there is an important clinical need for studies of this nature.

A number of studies have assessed the effects of topiramate on serum HCO_3^- levels. A low plasma HCO_3^- concentration represents, by definition, a metabolic acidosis. In controlled clinical trials, 32% of adults receiving 400 mg of topiramate daily had a persistent treatment-emergent

reduction in serum HCO_3^- concentrations to <20 mM compared with 1% in placebo-treated patients (see topiramate prescribing information, www.topamax.com, accessed 25 June 2009). More marked lowering of serum HCO_3^- concentrations (<17 mM and >5 mM decrease from pretreatment) was seen in 7% of patients receiving 400 mg of topiramate *vs*. none in the placebo group. Rarely, patients experienced severe decrements to values below 10 mM. In a retrospective cohort study conducted in an outpatient neurology clinic [16], 26 patients out of 54 (48%) had low serum HCO_3^- concentrations (<22 mEq l^{-1}) while on topiramate. Mean serum HCO_3^- concentrations before and during topiramate therapy were 26.8 ± 2.9 mEq l^{-1} and 21.7 ± 3.6 mEq l^{-1}, respectively, with a mean difference of 5.1 ($P < 0.001$). Welch *et al*. [17] compared 32 topiramate-treated subjects and 50 healthy volunteers in a cross-sectional study and found that topiramate-treated subjects had significantly lower serum total carbon dioxide content (23.8 ± 2.0 vs. 26.1 ± 2.1 mEq l^{-1}; $P < 0.001$). The relationship between HCO_3^- concentration and dose of topiramate was not adequately defined in any of the above studies.

What is the mechanism of topiramate-induced metabolic acidosis?

The anion gap (AG), which corresponds to the presence of unmeasured anions, allows for the differentiation of two groups of metabolic acidosis. Metabolic acidosis with a high AG is associated with acid accumulation from increased acid production or acid ingestion. Metabolic acidosis with a normal AG is associated with the loss of HCO_3^- from the kidney or gastrointestinal tract, or the failure of the kidney to excrete H^+. When metabolic acidosis occurs without an increase in the anion gap, the chloride concentration is typically increased [18].

A number of case reports have documented that topiramate induces hyperchloraemic normal anion gap [14, 19–21] metabolic acidosis. There are two major causes of this form of metabolic acidosis. The first is HCO_3^- loss from the gastrointestinal tract (most commonly due to diarrhoea), and the second is a selective defect in renal H^+ excretion or HCO_3^- absorption, termed renal tubular acidosis (RTA). Many case reports have also shown that topiramate-induced metabolic acidosis is associated with an alkaline urine [19, 20], and positive urinary anion gap [20]. These findings suggest that the normal-AG metabolic acidosis seen with topiramate use is a result of a defect in the renal regulation of acid–base balance. Taken together with the fact that gastrointestinal disorders that might lead to HCO_3^- loss have been excluded, it seems that topiramate-induced metabolic acidosis is the result of RTA.

More detailed biochemical studies make it possible to differentiate between different types of RTA. Understanding the specific type of RTA induced by topiramate is important as it will allow delineation of the molecular mechanisms underlying this adverse effect and, through this, the development of predictive and preventive strategies.

Elucidating the type of RTA induced by topiramate

Types of RTA

RTA is characterized by acidosis and electrolyte disturbances due to impaired renal H^+ excretion or impaired HCO_3^- resorption. Type 2 (proximal) RTA is due to the inability to reabsorb filtered HCO_3^- in the proximal tubule. Since 85–90% of filtered HCO_3^- is normally reabsorbed in the proximal tubule, this impairment leads to increased delivery of HCO_3^- to the distal portion of the nephron. As the distal tubule is overwhelmed, HCO_3^- spills into the final urine, leading to metabolic acidosis. Type 1 (distal) RTA is characterized by impaired acid secretory capacity in the collecting tubules. This defect leads to inability to excrete the daily acid load, resulting in progressive H^+ retention and a drop in plasma HCO_3^- concentration [18]. Table 1 lists the biochemical features that can be used to differentiate between the types of RTA.

Characteristics of RTA induced by topiramate

A number of case reports have documented that topiramate-induced hyperchloraemic normal anion gap

Table 1

Features of renal tubular acidosis (RTA) syndromes, with those seen in seen in topiramate-induced RTA in bold

	Proximal (type 2)	Distal (type 1)	Study ref.
Urine pH during acidosis	<5.5	**>6.0**	[17]
Urinary HCO_3^- conc.	**Increased**	Normal	[17]
Fractional excretion of HCO_3^-	**>15%**	<5%	[17]
Urinary anion gap	Often negative	**Positive**	[20]
Urinary excretion of citrate	Normal	**Low**	[17, 22]
Urinary excretion of β_2-microglobulin	**Increased**	Normal	[20]

metabolic acidosis is associated with an alkaline urine [19, 20], positive urinary anion gap, low urinary citrate excretion and β_2-microglobulinuria [20]. In the only systematic cross-sectional study of biochemical profiles with topiramate treatment [17], 32 topiramate-treated subjects and 50 healthy volunteers were compared. Serum HCO_3^- levels and urinary citrate excretion were significantly lower with topiramate treatment, whereas urinary pH, urinary HCO_3^- excretion and fractional excretion of HCO_3^- were significantly increased. Similarly, Warner *et al*. [22], in a longitudinal study involving four subjects, found that urinary citrate levels decreased profoundly and quickly after the start of topiramate therapy and continued to decrease with escalating doses. As shown in Table 1, these findings are consistent with impairment of both proximal and distal renal tubular acidification mechanisms. Such a combination of the features of both type 1 and type 2 RTA is referred to as mixed RTA.

Pathophysiology of mixed RTA

The HCO_3^- reabsorptive defect in type 2 (proximal) RTA may be produced by one of a number of molecular defects. For example, an inherited defect in the gene for the Na^+-HCO_3^- cotransporter (SLC4A4) results in autosomal recessive type 2 RTA [23], and defective carbonic anhydrase activity has been described among patients with type 2 RTA (see below). On the other hand, the defective H^+ secretion in type 1 (distal) RTA is caused by impairment of a distinct set of factors. For example, impaired function of the Cl^--HCO_3^- exchanger due to gene mutations leads to autosomal-dominant [24] RTA type 1.

How can the proximal and distal tubular defects seen in mixed RTA be explained? An autosomal recessive form of osteopetrosis (marble brain disease) provides a clue that helps in answering this question. This condition is characterized by fractures, short stature, mental retardation, dental malocclusion, and visual impairment from optic nerve compression. Basal ganglia calcification may develop. RTA with the characteristics of both proximal and distal tubular dysfunction usually accompanies marble brain disease, according to reported case studies [25–27]. In a detailed study of a single patient with this disease, both proximal and distal renal tubular acidification defects were verified with alkali and acid loading [28]. Sly *et al*. [29] identified loss of carbonic anhydrase II (CAII) as the biochemical defect. To date, more than 50 cases have been reported worldwide. However, the majority of patients come from North Africa and the Middle East, with nearly 75% being of Arabic descent. There are 12 described mutations of the CAII gene. However, three mutations (His107Tyr, 2971G3a and 744delA) account for >90% of the reported patients with CA type II deficiency [30]. Lack of CA therefore can induce mixed RTA.

Table 2

Inhibition of carbonic anhydrase (CA) II, IV and XII assayed by spectrophotometric methods based on the CO_2 hydrase activity of topiramate by Supuran's group [32]

CA	Ki* (nM)
II	10
IV	4900
XII	3.8

*Ki refers to the dissociation constant for binding of topiramate to CA with low Ki indicating high affinity.

Table 3

Inhibition of carbonic anhydrase type II by topiramate according to different assay methods

Method	Ki	Ref
pH shift method (Supuran's group)	10 nM	[34]
pH shift method (Maryannoff's group)	500 nM	[33]
Esterase assay	430 nM	[33]
ThermoFluor assay	500 nM	[47]

Renal carbonic anhydrase and inhibition by topiramate

CA catalyses the conversion of carbon dioxide to HCO_3^- ion and H^+. Sixteen different CA isozymes are presently described in humans, each differing by their relative hydrase activity, tissue distribution, subcellular localization and susceptibility to inhibition. CA type II predominates in human kidneys. CA type II plays an essential role in the reabsorption of ultrafiltered HCO_3^- by the proximal tubule and the urinary acidification by the distal tubule. CA type II accounts for 95% of CA activity in the kidney. Most of the remaining 5% of renal CA comprises CA type IV and CA type XII [31].

Studies of inhibition of CA by topiramate have produced conflicting results. Although Supuran's group [32] found that topiramate behaves as a very potent inhibitor of human CA types II and XII and a medium potency inhibitor of type IV (Table 2), Maryannoff *et al*. found topiramate to have only submicromolar activity against CA II [33].

A number of methods have been used to assay the inhibition of CA isoenzymes (Table 3). These include spectrophotometric methods based on the CO_2 hydrase activity of these enzymes (the 'pH shift' method), spectrophotometric methods based on the esterase activity of these enzymes, and a ThermoFluor method, which monitors the protein thermal stability in the presence of various concentrations of ligands investigated as inhibitors in the presence of fluorescent dyes. All methods have advantages

and disadvantages. The esterase method is easy to execute, but its main disadvantage is that most CAs are quite weak esterases [32]. The ThermoFluor method is not yet validated for assaying CA inhibitors as it has been tested only on a very restricted number of compounds [32]. The pH shift method is the preferred method as it monitors the real physiological reaction that these enzymes catalyse: CO_2 hydration to HCO_3^- and protons, and its inhibition by various classes of compounds. However, even using the pH shift method, Supuran's and Maryannoff's groups have produced conflicting data for the inhibition of CA II by topiramate (Table 3).

The differences observed in inhibition data between Supuran's and Maryannoff's groups may be attributable to limitations in enzyme assays used by the latter to test inhibitors, as rather high amounts of reducing agents, such as dithiothreitol, were present in their buffer. These agents have now been shown to influence strongly the binding of inhibitors to CA isoenzymes. In one study, enzyme inhibitor affinity for all investigated CAs diminished by orders of magnitude with increasing concentrations of these agents in the assay system [34]. Dithiothreitol and similar derivatives should not be added to the assay buffers used in monitoring CA inhibition, as they lead to underestimation of the binding constants.

Finally, X-ray crystallography studies [35] have revealed a very tight association between bound topiramate and the active site of CA II, with a network of eight strong hydrogen bonds with critical amino acids side chains from the cavity fixing topiramate within the active site, consistent with topiramate's very potent inhibitory activity against CA II.

Clinical effects of carbonic anhydrase inhibition

Effects of metabolic acidosis

Some manifestations of metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, and more severe sequelae such as cardiac arrhythmias or coma. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in children may also reduce growth rates.

A number of case reports have documented the clinical impact of topiramate-induced metabolic acidosis. Stowe *et al*. [21] reported the case of a 20-year-old man taking topiramate 400 mg daily for 9 months, in addition to phenytoin and valproic acid for epilepsy. The patient presented with acute mental status changes consisting of disorientation, somnolence, agitation and headache for 2 weeks. His serum HCO_3^- concentration was noted to be 8 mEq l^{-1} and the chloride 122 mEq l^{-1}. A continuous infusion of sodium bicarbonate was started and topiramate was tapered over a 5-day period. The metabolic acidosis and mental status changes resolved within 48 h. A 47-year-old woman taking topiramate 150 mg daily for 12 months for migraine is reported to have suffered weight loss, joint pains and muscle weakness [20]. Laboratory data revealed a serum HCO_3^- concentration of 19 mEq l^{-1} (reference range not provided). The authors reported that all laboratory data were normal before the initiation of topiramate but did not report any follow-up laboratory data after discontinuing topiramate. Tartara *et al*. [36] reported a 22-year-old man who developed metabolic acidosis after 4 months of taking topiramate 800 mg daily for Lennox–Gastaut syndrome. The patient had symptoms of fatigue, lethargy, hypotonia and hyperventilation. His arterial blood gas revealed a pH of 7.3 (reference range 7.35–7.45), and his serum HCO_3^- concentration was 19 mEq l^{-1} (reference range 22–26 mEq l^{-1}). The metabolic acidosis resolved after withdrawal of topiramate.

The metabolic adverse effects of topiramate have been well documented in children. For example, Phillipi *et al*. [15] treated seven infants aged 5–7 months and two toddlers aged 1.5 and 2.3 years with topiramate for epilepsy after failure of standard antiepileptic drug treatment. The blood gases were normal before treatment with topiramate in all nine patients. Metabolic acidosis developed in eight children after 8–26 days (median 14 days) of topiramate treatment with a minimum serum HCO_3^- between 15 and 18 mM (median 17 mM), and pH between 7.22 and 7.40 (median 7.35). Four of nine children showed clinical signs of hyperventilation and received oral sodium HCO_3^-.

Nephrolithiasis

Topiramate use is associated with a 10-fold increase in risk of nephrolithiasis. The incidence of stone formation in the general population is thought to be 0.15–0.2% [37]. Analysis [38] of a total of 1183 patients in topiramate clinical trials showed that 18 patients (1.5%) developed 21 episodes of renal calculi.

Inhibition of renal tubular CA has been implicated in topiramate-associated urolithiasis. Topiramate-induced CA inhibition leads to RTA and decreased urine citrate concentrations (see above). Urinary citrate is a well-known inhibitor of urolithiasis. This hypocitraturia, as well as decreased acidification of urine in the distal tubule, contribute to an environment that is favourable for calcium phosphate stone formation. Welch and colleagues [17] recently investigated the relationship between topiramate treatment and propensity for kidney stones in a study comprising a cross-sectional arm and a short-term longitudinal arm. The results showed that serum HCO_3^- levels were lower with topiramate treatment. Furthermore, topiramate treatment increased urinary pH, urinary HCO_3^- excretion, and fractional excretion of HCO_3^-, whereas topiramate significantly reduced urinary citrate excretion ($P < 0.001$). The relative saturation ratio for stone-forming salts increased with topiramate treatment ($P < 0.001$). Urinary saturation of undis-

sociated uric acid decreased with topiramate treatment ($P < 0.001$). Lamb *et al*. [39] reported renal stones in three adult patients who were treated with topiramate for epilepsy. The authors evaluated the biochemical risk factors for developing nephrolithiasis in these and eight additional topiramate-treated patients who had not developed renal stones. The authors noted high penetrance of the biochemical risk factors for nephrolithiasis. The most consistent feature was inadequate urinary acidification: most patients failed to produce a urinary pH less than 6.1. Nine patients demonstrated hypocitraturia; in some cases citrate was undetectable.

Bone health

Congenital deficiency of CA II (marble brain disease) is known to cause osteoporosis [26]. Furthermore, osteomalacia in adults, and rickets and growth retardation in children, are recognized features of both distal (type 1) and proximal (type 2) RTA [18]. It is very likely therefore that prolonged RTA due to topiramate use will have a detrimental effect on bone health. However, the effect of topiramate on long-term bone health has not been studied. This is a particularly important area, as there is increasing realization that patients with epilepsy are at increased risk of osteoporosis [40]. Although poor bone health has largely been ascribed to the use of enzyme-inducing anticonvulsants, there is increasing evidence that non-enzyme-inducing anticonvulsants can impair bone health in both men [41] and women [42] through a variety of mechanisms.

Management

Topiramate, through its inhibition of CA, predisposes to the development of RTA, kidney stones and osteoporosis. Ideally, patients should have their risk of developing these complications assessed before commencing topiramate. Unfortunately, apart from excluding patients with a history of renal calculi and RTA from receiving topiramate, there are no other predictive risk factors that can be used in clinical practice. Adequate hydration whilst using topiramate should be encouraged as it can reduce the risk of developing renal stones. Clinicians must also remain vigilant to the clinical manifestations of metabolic acidosis. A possible strategy for detection could involve the measurement of serum HCO_3^- levels, but the utility of this has not been investigated. We would therefore recommend that this be evaluated in a systematic manner so that stringent criteria for monitoring drug treatment can be met [43].

For patients who develop RTA on topiramate, there are no evidence-based or universally accepted management strategies. For patients with persistent severe RTA, discontinuation of the drug should be considered if feasible; otherwise, therapy centres on the administration of alkali to achieve a normal or near-normal plasma [HCO_3^-]. Alkali therapy allows the resumption of normal growth in children and the correction of bone disease in adults [44]. Urinary calcium excretion is reduced while urinary citrate excretion increases with an attendant improvement in nephrocalcinosis and of the risk of new stone formation [45]. Various alkali replacement preparations are available; oral sodium citrate and citric acid are usually well-tolerated HCO_3^- precursors.

Conclusions

Clinicians prescribing topiramate must remain vigilant to the possible adverse effects produced as a result of its inhibition of carbonic anhydrase. Patients who experience these adverse effects usually require discontinuation of treatment with topiramate, as alternatives are available. However, if discontinuation is not possible, remedial therapy in the form of alkali replacement should be considered. There is a need for further research in this area, particularly in terms of identifying other potential risk factors, the long-term consequences of the acid–base imbalance (especially in relation to bone health) and in defining the utility of routine serum HCO_3^- levels in monitoring treatment with topiramate. Finally, it is clear from the epidemiological data that not all patients develop acidosis with topiramate. Dose may clearly be one susceptibility factor, as evidenced by the occurrence of acidosis in patients who have taken an overdose of topiramate [46]. However, most patients develop metabolic acidosis within the recommended therapeutic dosages – it is possible that genetic polymorphisms in the genes for CA isoenzymes II, IV or XII may be predisposing factors, but this needs to be evaluated in a robustly phenotyped cohort of patients on topiramate.

Competing interests

A.G.M. has received reimbursement from Janssen-Cilag for attending a symposium.

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