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Topiramate induces type 3 renal tubular acidosis by inhibiting renal carbonic anhydrase

Sir,

We report a case of mixed (type 3) renal tubular acidosis (RTA) associated with the anti-convulsant drug topiramate used for migraine prophylaxis. A 47-year-old woman treated with topiramate (150 mg/day) since 12 months for invalidating migraine was referred for a metabolic acidosis evidenced in a routine blood sampling. She complained of muscle weakness and bone pain. Clinical examination showed weight loss (−6 kg in 4 months) and joint sensitivity. Blood analyses confirmed a mild hyperchloraemic metabolic acidosis (plasma HCO_3^-, 19.0 mEq/l; plasma anion gap, 8 mEq/l) with hypokalaemia (3.2 mEq/l) and normal renal function. Plasma HCO_3^- before topiramate administration was normal. The urine pH was 6.0 with a positive urinary anion gap (UAG, +39 mEq/day), positive β_2-microglobulinuria (2.1 mg/l) and a low urinary citrate excretion (0.7 mM/24 h). Serology and auto-immune markers were negative. Echography showed no kidney calcifications. The hyperchloraemic metabolic acidosis with normal glomerular filtration rate (GFR) and positive UAG indicates RTA, associated with both proximal (β_2-microglobulinuria) and distal (hypocitraturia) tubular dysfunction. The normal blood analyses before the introduction of topiramate suggests that these disorders result from tubular dysfunction caused by inhibition of carbonic anhydrase (CA).

Type II CA (CAII) plays an essential role in the reabsorption of ultrafiltered HCO_3^- by the proximal tubule (PT) and the net urinary acidification by α-type intercalated cells of the distal nephron (Figure 1). It also provides the H^+ for extracellular acidification during bone resorption by osteoclasts. Deficiency in CAII, either inherited (marble brain disease; OMIM #259730) or acquired (e.g. acetazolamide-induced), is associated with a mixed proximal and distal RTA (type 3 RTA), without evidence for generalized PT dysfunction [1,2]. Topiramate is a sulfamate-substituted monosaccharide that is structurally related to acetazolamide (Figure 1). As such, it inhibits CAII more effectively than other isoforms [3]. Long-term inhibition of CAII by topiramate may thus disturb the homeostasis of both the

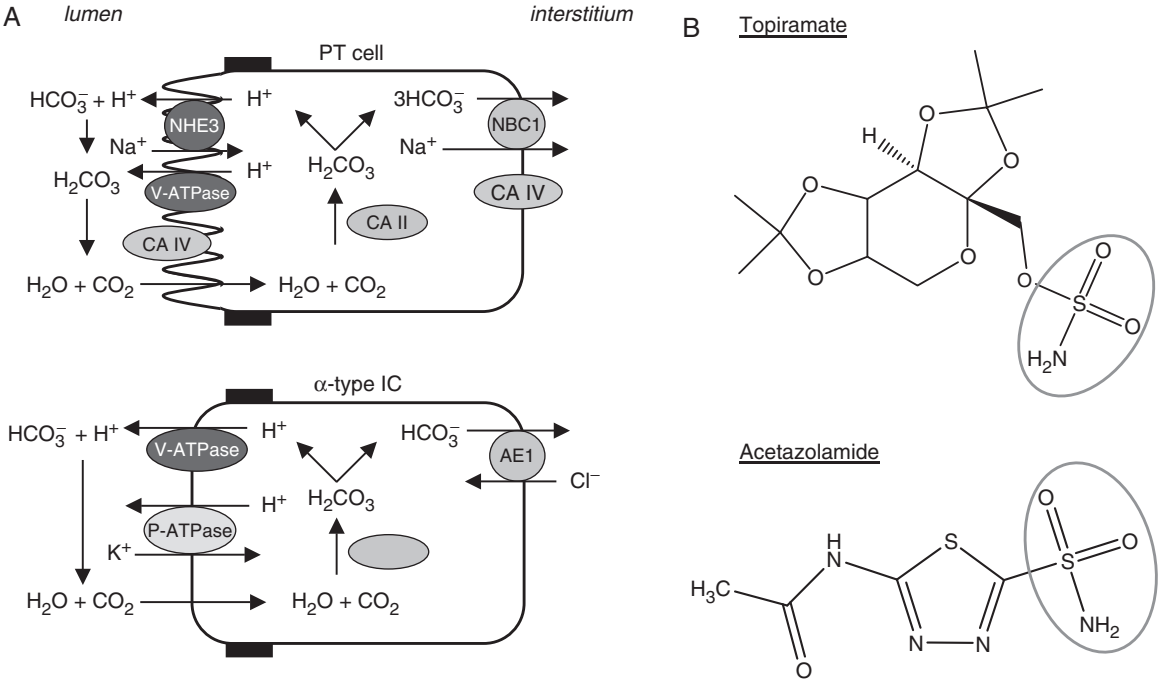

Fig. 1. Role of CA isoforms in the kidney and structure of topiramate. (**A**) Pathways involved in HCO_3^- reabsorption and H^+ secretion in PT cells and α-type intercalated cells of the collecting ducts, respectively. Cytosolic type II CA is distributed in both cell types. Note that PT cells also express type IV CA in the apical brush border and basolateral membrane. (**B**) Comparative structure of topiramate and acetazolamide. Both molecules present a sulfonamide group responsible for the inhibition of CA activity.

proximal and distal tubules, leading to a mixed form of RTA. By extension, it may also affect bone resorption, leading to bone pain [4].

The main adverse effects of topiramate include ataxia, impaired concentration, confusion, dizziness, fatigue and weight loss. An increased incidence of nephrolithiasis has been reported, in relation with defective urinary acidification and hypocitraturia [5]. Although non-anion gap metabolic acidosis was initially considered as a rare complication of topiramate, it may actually be more frequent than expected, particularly in children [5,6]. The plasma HCO_3^- levels return to normal when the drug is discontinued [5]. Since the use of topiramate has recently been extended to the treatment of migraine, clinicians should be aware of its potential effect on renal tubular functions and monitor plasma HCO_3^- and K^+ concentrations as long as the drug is administered.

Conflict of interest statement. None declared.

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Blood pressure in hypertensives—what is the real value?

Sir,

To date there is still great uncertainity as to the best way to measure blood pressure (BP). Actually the debate is focused on the reliability of three techniques: self-made (SM), nurse-made (NM) and physician-made (PM) BP readings [1,2].

Recently, we analysed the relationships between SM, NM and PM readings in a cohort of hypertensives consecutively referred to our brand new out-patient clinic from 1 January 2005 to 30 June 2005. Essential hypertensives on wash-out, without comorbidities, owning a sphygmomanometer, have been considered. Our policy in this clinical setting foresees the following steps: At the first visit, serum levels of creatinine, uric acid and glucose are assessed. Moreover, after a detailed training on SM reading followed by the calibration of the sphygmomanometer the patients are invited to record the reading at home just before the following visit, scheduled 1 week later. At the second visit, the patients are approached by the nurse (V.N.) who, after a 5 min sitting rest, takes the NM reading, (average of three determinations within 3 min). Then the physician (L.V.) measures the PM reading in a blinded fashion.

Table 1. Values of blood pressure components found with the 3 different techniques

	SBP (mmHg)	DBP (mmHg)	MBP (mmHg)
SM	131.3 (14.7)	76.3 (11.8)	94.6 (10.9)
NM	131.6 (14.2)	77.4 (10.2)	95.4 (10.2)
PM	135.5 (20.1)	79.7 (11.4)	98.3 (12.9)

During the observation period we screened 182 patients among whom 20 (eight males) met the inclusion criteria. Average (SD) values of age (years) and serum lab parameters (mg/dl) were: age 58.2 (9.4), creatinine 0.96 (0.19) mg/dl, uric acid 4.5 (1.4) mg/dl and glucose 99.1 (13.7) mg/dl. Table 1 reports the systolic, diastolic and mean BP (SBP, DBP and MBP, respectively) values found during the study.

For all the components of BP, PM values were significantly higher than the SM and NM values (one-way analysis of variance and Tukey's *post-hoc* test: $P < 0.05$). After stratifying the analysis according to median values of the lab parameters, the differences between PM, NM and SM values remained significant only in those patients with serum levels of uric acid >4.2 mg/dl and creatinine >0.97 mg/dl. In the entire cohort of patients, a significant relationship between the MBPs measured by means of PM reading, and the serum uric acid levels ($R = 0.54$; $P = 0.01$) was demonstrated.

According to our findings, we suggest that SM and NM readings provide more reliable BP values while PM may suffer from emotional reactions driven by sympathetic activation. The latter is mostly represented in hypertensives with higher serum levels of uric acid and creatinine, confirming, somehow, the suggested close relationship between the clues of renal damage and the sympathetic drive in determining hypertension status and target organ damage [3]. Moreover, our experience underlines the need to take caution and to evaluate the techniques of BP measurement, in evaluating or planning clinical trials focused on hypertension.

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