Seizure 29 (2015) 86–89

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Topiramate may not increase risk of urolithiasis: A nationwide population-based cohort study

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ARTICLE INFO

Article history:
Received 27 December 2014
Received in revised form 4 February 2015
Accepted 16 March 2015

Keywords:
Urolithiasis
Renal stone
Topiramate
Health insurance database

ABSTRACT

Purpose: Topiramate is an effective anti-epileptic drug and can be associated with increased risk for urolithiasis because of its effects on acid–base profile. Evidences that supported an association of topiramate and urolithiasis were limited to case reports or series. We investigated the association of topiramate and urolithiasis in a nationwide population-based cohort study.
Methods: We analyzed 1377 patients receiving topiramate and 1377 age- and gender-matched control patients (not receiving topiramate) between 1997 and 2008. The risk of urolithiasis was analyzed using Kaplan–Meier analysis, followed by Cox proportional hazard regression.
Results: Of the 2754 patients, 79 (2.9%) patients developed urolithiasis in two (interquartile range: 1.2–4.2) years. The proportion of patients who developed urolithiasis in the patients receiving topiramate was not different from that of the control patients ($p = 0.138$, χ^2 test). The urolithiasis free survival was not different between the patients receiving topiramate and the control patients ($p = 0.168$) in Cox proportional hazard regression. The duration and total dosage of topiramate were not associated with risk of urolithiasis in patients receiving topiramate ($p = 0.482$ and $p = 0.751$).
Conclusion: Topiramate may not increase the risk of urolithiasis. The duration and the total dosage of topiramate were not associated with urolithiasis risks.

1. Introduction

Topiramate is an effective antiepileptic drug for seizure [1] and migraine [2]. As other antiepileptic drug, topiramate posed the adverse effect of central nervous system, such as drowsiness and mental suppression. However, topiramate has two unusual non-neurological side effects: urolithiasis [3–5] and body weight loss [6,7]. Topiramate can cause metabolic acidosis through the inhibition of carbonic anhydrase. The risk of urolithiasis may be increased through the increased urinary pH, urinary bicarbonate excretion in patients receiving topiramate [8].

Studies for urolithiasis in patients receiving topiramate were limited to case reports, case series [3–5,9], and biochemical characteristics that favor stone formation [8,10,11]. So far, there was no observational cohort study that compares the risk of urolithiasis in patients receiving and not receiving topiramate. The aim of the study was to investigate topiramate associated urolithiasis using a nationwide population-based cohort.

2. Methods

2.1. Database

We extracted data from a sampling longitudinal subset of National Health Insurance Research Dataset (NHIRD). The NHIRD contains all claim data that covered over 99% of the total population in Taiwan (approximately 23.72 million individuals). The sampling longitudinal subset, published by National Health Research Institute of Taiwan, contained the ambulatory service and hospitalization records of 1,000,000 individuals. The subset was randomly sampled from the NHIRD and was divided into 25 equal groups. There is no significant difference in distribution of

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http://dx.doi.org/10.1016/j.seizure.2015.03.009
1059-1311/

age and gender between the patients in the subset and the original NHIRD. All the personal identifiers were encrypted before published. The confidentiality was assured by the data regulations of the Bureau of National Health Insurance.

2.2. Study sample

We analyzed all patients who took topiramate (ATC code N03AX11) between January 1, 1997 and December 31, 2008 in the NHIRD subset ($n = 1880$). Patients treated with topiramate less than 30 days ($n = 503$) were excluded. The analyzed cohort consisted 1377 patients receiving topiramate and 1377 control patients. Most of the patients took topiramate for seizure or migraine. The control patients were selected from patients who were not receiving topiramate and were matched for their age, gender, and year of enrollment.

2.3. Study design

The earliest date of topiramate prescribed was recorded as an index date. In control patients, the index date was defined as the date of first visit. Each patient was individually tracked from the index date to the last ambulatory service visit. Urolithiasis events were defined using ICD-9-CM code 592.x for kidney or ureter stone, 594.x for bladder and urethra stone, and 602.0 for prostate stone. A history of urolithiasis was defined as patients with urolithiasis diagnosed before the index date. The end of observation was defined as the date of urolithiasis diagnosed or the last ambulatory service visit if no urolithiasis identified. The time from index date to the end of observation was recorded for urolithiasis free survival analysis. Gouty arthritis was defined as ICD-9-CM code 274.x. In patients who took topiramate, duration and total dosage of topiramate were calculated.

2.4. Statistical analysis

Data are reported as mean ± SD for normally distributed variables, median and interquartile range for not normally distributed continuous variables, or percent frequency for categorical variables. Pearson χ^2 tests were used to determine the differences in categorical variables. The risk of urolithiasis was analyzed using Kaplan–Meier analysis with log-rank test. Variables that may be associated with urolithiasis were analyzed using Cox proportional hazard regression and hazard ratios (HRs) and 95% confidence interval (CI) were calculated. A p value lower than 0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical package, version 9.1 (SAS, Inc., NC, USA).

3. Results

Patients' age and the proportion of male gender were not different in patients receiving topiramate and the control patients (Table 1). Of the patients receiving topiramate, 46 (3.3%) patients developed urolithiasis in 2.3 (1.3–4.3) years. The percentage of patients who developed urolithiasis was not different to that (2.4%) of the control patients ($p = 0.138$). The duration of follow-up, the proportion of patients with a history of urolithiasis, and the proportion of patients with gouty arthritis in patients who took topiramate were not different from that of control patients. The urolithiasis free survival (Fig. 1) was not different in patients receiving topiramate and the control patients ($p = 0.166$, log-rank test). In multivariable Cox regression for possible risk factors of urolithiasis (Table 2), the use of topiramate was not associated with a higher risk of urolithiasis ($p = 0.13$). A history of urolithiasis was the most important risk factors for the development of urolithiasis with a HR of 17.78 (95% CI: 11.12–28.43, $p < 0.01$). Patients' age was significantly associated with the risk of urolithiasis and the HR was 1.13 (95% CI: 1.00–1.28, $p = 0.04$) for every 10 additional years. Male gender and a history of gout arthritis were not associated with the risk of urolithiasis.

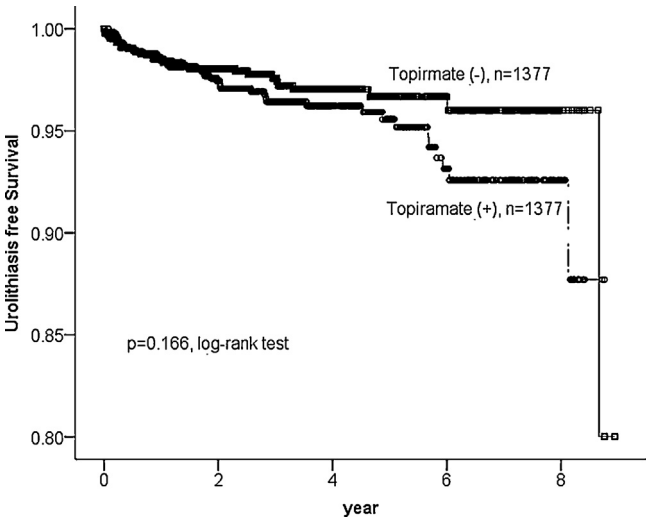

Fig. 1. Urolithiasis-free survival of patients receiving topiramate and control patients.

In patients receiving topiramate (Table 3), patients with urolithiasis were older ($p = 0.009$), more likely to be male ($p = 0.049$), and more likely to have a history of urolithiasis ($p < 0.001$). The duration and the total dosage of topiramate were not different in patients with and without urolithiasis. In patients receiving topiramate, a history of urolithiasis was associated with the risk of urolithiasis (Table 4) with an aHR of 10.45 (95% CI: 5.17–21.22, $p < 0.001$). Male patients were associated with a higher risk of urolithiasis ($p = 0.049$) with an aHR of 1.87 (95% CI: 1.00–3.49). The duration of topiramate had no effect on the risk of urolithiasis ($p = 0.482$) and the total dosage of topiramate was not associated with increased risk for urolithiasis ($p = 0.751$).

4. Discussion

This is the first observational cohort study in investigating the risk of urolithiasis in patients receiving topiramate. We found that

Table 1
Demographics of patients who took topiramate and patients who did not took topiramate (control) in 1997–2008.

Variable	Topiramate $n = 1377$		Control $n = 1377$		p
Age (year)	38.2	±20.5	38.3	±20.5	1.000
Follow-up (year)	2.3	1.3–4.3	2.8	±2.1	0.200
Male	613	44.5	613	44.5	1.000
Urolithiasis	46	3.3	33	2.4	0.138
History of urolithiasis	67	4.9	84	6.1	0.158
Gouty arthritis	121	8.8	142	10.3	0.173

Data was expressed as mean ± standard deviation (SD) or n percentage as appropriate.

Table 2
Multivariable Cox regression of possible risk for urolithiasis in patients receiving and not receiving topiramate ($n = 2754$).

Variable	HR	95% CI	p
Topiramate	1.64	0.91–2.58	0.13
History of urolithiasis	17.78	11.12–28.43	<0.01
Age (every 10 additional years)	1.13	1.00–1.28	0.04
Male	1.54	0.97–2.44	0.07
Gouty arthritis	1.29	0.97–2.44	0.41