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Topiramate-related adverse events
Pattern and signals in the Korea Adverse Event Reporting System, 2010-2017

Junyeong Choi, PharmD, Dongwon Yoon, PharmD, Minhee Park, MS, Kyung-in Joung, PhD,
Ju-Young Shin, PhD* ID

Abstract
Despite safety concerns associated with topiramate use, the pattern of adverse events and signal analysis of antiepileptic drugs remain elusive.

We aimed to determine patient demographics and characteristics of reported AEs of topiramate and to detect the associated signals by comparing those of other antiepileptics.

We used the Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database (KIDS-KD) from 2010 to 2017 to determine patient demographics and characteristics of reported AEs for topiramate and other antiepileptics. The proportional reporting ratio, reporting odds ratio, and information component were used in signal detection. Signals were compared against drug labels in Korea, the UK, the EU, and the US.

A total of 1300 adverse events cases of topiramate were reported, and the number of topiramate-adverse event pairs was 1861. For topiramate, the proportion of women of childbearing age (20-39 years) with adverse events was more than double that for other antiepileptics. A majority of the 36 detected signals were of neuropsychiatric disorders such as cognitive disorders, concentration impaired, amnesia, hypoaesthesia. Patients with topiramate-induced adverse events were likely to be young and female. Also, adverse events related to carbonic anhydrase isoenzyme showed specifically great disproportionalities.

Rigorous clinical management is needed to ensure proper and safe use of topiramate. Special precautions should be taken when prescribing in women of childbearing age.

Abbreviations: AE = adverse event, ATC = Anatomical Therapeutic Chemical, EU = European Union, GABA-A = Gamma-Aminobutyric Acid-A, IC = Information Component, IRB = institutional review board, IT = included term, KIDS-KD = Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database, MFDS = Ministry of Food and Drug Safety, PT = preferred term, PRR = proportional reporting ratio, RCT = randomized-controlled trial, ROR = reporting odds ratio, RR = relative risk., SOC = system organ class, UK = United Kingdom, US = United States, WHO-ART = World Health Organization-Adverse Reaction Terminology.

Keywords: topiramate, signal detection, data mining, Korea Institute of Drug Safety & Risk Management Korea Adverse Event Reporting System database (KIDS-KD)

1. Introduction

Topiramate was approved for use in the treatment of epilepsy and migraine prophylaxis. Although the exact mechanism of action of topiramate is not fully understood, it is known to suppress the excitation of the brain by activating the gamma-aminobutyric acid-A (GABA-A) receptor and inhibiting glutamate receptor.[25] Topiramate is also known to have some adverse events (AEs) associated with the nervous system and cognition like dizziness, paresthesia, somnolence, hypoaesthesia. However, topiramate is being used for obesity, alcoholism, eating disorder, or essential disorder as off-label. Among them, prescriptions, especially for obesity are known to be quite frequent, although varies from country to country. Indeed, some trials demonstrated that topiramate has a weight loss effect.[26] The precise mechanism by which topiramate leads weight loss remains unclear but appears to induce appetite suppression and increased energy expenditure. In the USA, topiramate has been used off-label for obesity patients both as a monotherapy and in combination with other drugs;[19] the combination of phentermine and topiramate (Qsymia) was approved for use in obesity.[4] In contrast, European Medicines Agency refused the marketing authorization for phentermine/topiramate (Qsiva) owing to its AEs.[2] However, there were cases of off-label prescription of topiramate for obesity. It has been commonly prescribed off-label for the same purpose in Korea as well.

Even though the Korea Food & Drug Administration (currently Ministry of Food and Drug Safety, MFDS) issued a "Dear Healthcare Professional" letter owing to the safety concerns about the misuse of topiramate for obesity treatment,[8] it is still being used off-label frequently in Korea. Accordingly, because of the misuse of topiramate, safety concerns about the AEs associated with topiramate have remained.

Many studies on evaluation of topiramate-induced AEs have been conducted, one of which suggested that the patterns of topiramate-induced AEs differed between epilepsy and migraine patients.[23] Additionally, it was shown that a review of patients with multiple indications for topiramate could provide a more comprehensive understanding of the associated AEs compared with epilepsy trials alone.[16] Although there is a study on the adverse effects of using topiramate in obese patients, it is also randomized-controlled trial (RCT) that does not reflect the real world and is targeted at a very limited number of subjects.[15] Most of the other existing studies on AEs of topiramate were also conducted in strictly controlled conditions, and the results may differ from the status of AEs in actual clinical settings.

Therefore, the purpose of this study was to investigate the AEs associated with the use of topiramate, a drug known as prevalent use in non-approved indications. By using voluntary drug adverse event reports data in Korea, we assessed the latest pattern and signals of the AEs in the real world.

2. Methods

2.1. Data source

This study used data on spontaneous AEs of topiramate and other antiepileptics collected from January 2010 to December 2017 by the Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database (KIDS-KD). KIDS-KD is a system that receives and manages AE reports provided by healthcare providers, pharmaceutical companies, manufacturers, patients, and so on via websites, E-mail, FAX,

mail, and telephone. Input and logical errors of data are filtered out and cleansed in the KIDS-KD. In this database, Anatomical Therapeutic Chemical (ATC) codes and World Health Organization-Adverse Reaction Terminology (WHO-ART) 092 version are used for the drug names and suspected AEs, respectively.[6] The database includes variables such as basic report information, drug information, AE information (WHO-ART preferred term [PT] and included term [IT] level), serious AEs (AEs leading to hospitalization or prolonged hospitalizations, malfunction or permanent disabilities, birth defects, life-threatening illnesses, or death), causality assessment information, and reporter information; according to these variables, the AE data are categorized, and they can be used in various AE analyses.

This study was approved by the Sungkyunkwan University Institutional Review Board (IRB File number: SKKU September 4, 2018).

2.2. Study drug

We analyzed the AE report data of topiramate (ATC code: N03AX11) and 46 other antiepileptics (ATC code: N03A) including barbiturate derivatives, hydantoin derivatives, oxazolidine derivatives, succinimide derivatives, benzodiazepine derivatives, carboxamide derivatives, and fatty acid derivatives.

2.3. Inclusion and exclusion criteria

To detect signals of topiramate using KIDS-KD, we applied the following criteria. If the ATC code or WHO-ART PT code was unknown, the data were excluded. Data were included only when the report type was a spontaneous report or investigation research (including drug review); the data were first reports and reported as a result of using study drugs as suspected drugs or concomitant drugs; and causality assessment was "certain," "probable," or "possible." The causality assessment followed the definitions of "certain," "probable," and "possible" provided by the World Health Organization-Uppsala Monitoring Centre.[10] In demographic analysis, the age was classified into 6 groups: 0–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, and 50 years or older. After filtering according to the conditions mentioned above, data were separated into 2 groups: topiramate group and other antiepileptics group. Finally, the number of reported AEs of topiramate was 1300 and drug- AEs combination of topiramate is 1957, while the number of reported AEs of other antiepileptics was 22,393 and AEs combination was 149,711.

2.4. Data mining indices

We used 3 criteria to detect signals: proportional reporting ratio (PRR), reporting odds ratio (ROR), and information component (IC) given by Bayesian Confidence Propagation Neural Network. We produced a 2×2 contingency table with the row representing topiramate and other antiepileptics and the column representing specific AE and all other AE. The PRR is the ratio of the proportion of a specific AE calculated by dividing the number of reports of a specific AE by the number of all AE reports observed for the drug of interest to the proportion of this AE for all other drugs calculated in the same manner. The ROR is defined as the odds ratio of a specific AE versus all other AEs for the drug of interest to the odds ratios for all other drugs. A signal was considered to be detected by meeting these indices: the number of

Table 1

Comparison of demographics and characteristics of reported adverse events between patients treated with topiramate and those treated with other antiepileptics.

Category	Subcategory	Topiramate (Total: 1300) n (%)	Other antiepileptics (Total: 22,393) n (%)	P value
Sex	Male	440 (33.8)	8585 (38.3)	<.0001
	Female	784 (60.3)	13,529 (60.4)	
	Unknown	76 (5.8)	279 (1.2)	
Age (years)	0–9	58 (4.5)	791 (3.5)	<.0001
	10–19	103 (7.9)	773 (3.5)	
	20–29	130 (10.0)	1188 (5.3)	
	30–39	184 (14.2)	1710 (7.6)	
	40–49	157 (12.1)	2598 (11.6)	
	50≤	299 (23.0)	13,811 (61.7)	
	Unknown	369 (28.4)	1522 (6.8)	
Serious AE	Hospitalization	31 (2.4)	807 (3.6)	.491
	Disabilities	0 (0.0)	16 (0.1)	
	Birth defects	0 (0.0)	1 (0.0)	
	Life-Threatening illnesses	1 (0.1)	33 (0.1)	
	Deaths	0 (0.0)	18 (0.1)	
	Other	17 (1.3)	345 (1.5)	
Report type	Spontaneous report	830 (63.8)	20,090 (89.7)	<.0001
	Research	470 (36.2)	2303 (10.3)	
Reporting groups by professions	Doctor	456 (36.2)	5842 (26.1)	<.0001
	Nurse	383 (29.5)	6634 (29.6)	
	Pharmacist	114 (8.8)	7620 (34.0)	
	Consumer	39 (3.0)	678 (3.0)	
	Etc.	61 (4.7)	805 (3.6)	
	Unknown	247 (19.0)	814 (3.6)	
Reporting groups by affiliation	Regional pharmacovigilance center	774 (59.5)	19,465 (86.9)	<.0001
	Manufacturer	493 (37.9)	2370 (10.6)	
	Medical institution	21 (1.6)	364 (1.6)	
	Pharmacy	12 (0.9)	185 (0.8)	
	Consumer	0 (0.0)	2 (0.0)	
	Etc. (Public health center, etc.)	0 (0.0)	6 (0.0)	
	Unknown	0 (0.0)	1 (0.0)	

AE = adverse event.

cases ≥3, the PRR and ROR≥2, Chi-Squared values ≥4.[27] The IC is a logarithmic value that can be calculated by dividing the probability of drug use and a specific AE occurrence [P (AE, Drug)] by the product of the individual probabilities of drug use and a specific AE occurrence [P(AE)P (Drug)], if the drug use and the specific AE occurrence are independent. This can be expressed as the following formula: IC=$\log_2$P (AE, Drug)/P (AE)P (Drug).[21] We also applied an IC criterion, that is, the lower limit of the 95% confidence interval was 0 or larger when detecting signals.[18]

In summary, we detected a signal when a specific AE satisfied all 3 criteria (PRR, ROR, and IC); if PRR and ROR could not be calculated as there was no report associated with the AE in the control group (other antiepileptics), only the IC criterion was used. Although these criteria were satisfied, an AE was excluded from a signal when it was caused by factors other than drugs, such as an incorrect technique in the drug usage process, ineffective drug, and medication error. After this step, we compared the signals with drug label information in Korea, the UK, the EU, and the US to determine which AEs were included in the evaluated drug labels.[1,3,5,9]

2.5. Statistical analysis

To assess the demographics and characteristics of the reported AEs for topiramate and other antiepileptics, we analyzed the frequency and percentage (%) for each categorical variable and conducted a Chi-Squared test. Subgroup analysis was conducted by age and sex excluding patients for whom sex data were missing. Using the drug-AE pairs, we assessed the frequencies and proportions of AEs based on the WHO-ART PT code and system-organ class (SOC) code. P value <.05 was defined as statistically significant. All statistical analyses were performed by SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

Table 1 shows that the cases of serious AE were more often in other antiepileptics (5.4%) than topiramate (3.8%). Statistically significant differences were found between the 2 groups in demographic data. In both groups, the number of AEs in females was more than 1.5 times higher than that in males. In the group that was treated with other antiepileptics, 61.7% AEs were reported in patients aged above 50 years. In contrast, in the group treated with topiramate, 23% AEs were reported in patients aged above 50 years, but the number of AE reports did not present any trend with respect to age.

Table 2 shows subgroup analysis of sex and age with AEs induced by topiramate and other antiepileptics. It was found that females aged 20 to 49 years who were treated with topiramate accounted for a much larger proportion than those of the same age range but exposed to other antiepileptics.

Table 2

Age- and sex-based subgroup analyses for reported adverse events in patients treated with topiramate and other antiepileptics.

Age (years)	Topiramate AE			Other antiepileptics AE		
	Male (Total: 440) n (%)	Female (Total: 784) n (%)	Female / Male	Male (Total: 8585) n (%)	Female (Total: 13,529) n (%)	Female / Male
0–9	35 (8.0)	22 (2.8)	0.63	442 (5.1)	338 (2.5)	0.76
10–19	55 (12.5)	47 (6.0)	0.85	412 (4.8)	354 (2.6)	0.86
20–29	32 (7.3)	95 (12.1)	2.97	519 (6.0)	660 (4.9)	1.27
30–39	40 (9.1)	138 (17.6)	3.45	699 (8.1)	1005 (7.4)	1.44
40– 49	27 (6.1)	129 (16.5)	4.78	964 (11.2)	1623 (12.0)	1.68
50≤	98 (22.3)	196 (25.0)	2.00	5,011 (58.4)	8678 (64.1)	1.73
Unknown	153 (34.8)	157 (20.0)	1.03	538 (6.3)	871 (6.4)	1.62

AE = adverse event.

We investigated the frequency and proportion of AEs due to the administration of topiramate and other antiepileptics according to WHO-ART PT classification (Supplementary Table 1, http://links.lww.com/MD/E994). Among the 1861 cases of AEs reported after taking topiramate, the most common events were dizziness in 157 cases (8.4%), followed by 124 cases (6.7%) of paraesthesia and 89 cases (4.8%) of rash. Among the 137,745 cases of AEs reported after taking other antiepileptics, the most common events were dizziness in 13,450 cases (9.8%), followed by 10,716 cases (7.8%) of nausea and 7743 cases (5.6%) of somnolence. We also calculated the frequency and proportion between drug and AEs for WHO-ART SOC classification (Supplementary Table 2, http://links.lww.com/MD/E995). Among the cases of AEs due to the administration of topiramate, the most common events were those involving the central and peripheral nervous system (29.6%), followed by psychiatric disorders (20.4%).

The signals of topiramate detected in this study are shown in Table 3. Among the 231 cases of AEs reported for patients taking topiramate, 36 AEs (15.6%) satisfied all 3 signal analysis indices or only IC when PRR and ROR could not be calculated due to lack of relevant AE reports for patients treated with other antiepileptics. The top 3 AEs ranked with the strongest signals were sweating decreased (PRR: 277.56, ORR: 279.81), renal calculus (PRR: 123.36, ROR: 123.69) and hypercalciuria (PRR: 98.69, ORR: 9890). Nervous, psychiatric, and gastrointestinal AEs accounted for a large part of the detected signals. The detected signals were compared against drug labels in 4 countries, Korea, the UK, the EU, and the US. Steatorrhoea was not included in the label of each country, but all other detected signals were labeled in Korea.

4. Discussion

As safety concerns regarding the increasing off-label usage of topiramate have been raised globally, this study focused on the recent patterns of AE reports for topiramate. By using voluntary drug adverse event reports in Korea, we found that topiramate had a high proportion of young women who reported AEs comparing to the other antiepileptic drugs. Sweating decreased, renal calculus, hypercalciuria, and cognitive disorders were among various AEs associated with topiramate usage, ranking the highest disproportionalities. Steatorrhoea was detected as a new signal.

Although some studies have been conducted on the safety and tolerability of topiramate, no real-world AE reporting data at actual clinical sites are available. In a randomized trial on

topiramate use for migraine prevention, paraesthesia and fatigue were noticeably frequent AEs with other neuropsychiatric AEs including anorexia, hypoaesthesia, and difficulty with memory also occurring.[14] Similar AEs were also demonstrated in another controlled trial on topiramate use for migraine prevention.[11] When topiramate was used for treating epilepsy, neuropsychiatric AEs such as paraesthesia, headache, somnolence, and dizziness were frequently reported.[12,28] The pattern of AEs for topiramate in our study shows a tendency similar to that demonstrated in previous clinical trials.

As topiramate-induced AEs have been frequently reported in women of childbearing age, caution is required regarding topiramate use in these women. A cohort study assessing the risk of oral cleft in infants whose mothers took topiramate during pregnancy revealed that the adjusted relative risk (RR) for oral clefts related to topiramate exposure during the first trimester was 2.90 (95% CI 1.56–5.40) in comparison to non-use.[20] The MFDS issued the "Dear Healthcare Professional" letter for the increasing risk of cleft lips and palate in infants born to women who are exposed to topiramate in pregnancy and informed healthcare professionals of the associated precautions and indications for intervention.[7] Combined with this information, the results of this study, which indicate that women of childbearing age may be more susceptible to topiramate-induced AEs, suggest that precautions are necessary to prevent imprudent use of topiramate by these women.

Notably, in our study, AEs related with carbonic anhydrase isoenzyme such as sweating decreases (PRR: 277.56, ORR: 279.81), renal calculus (PRR: 123.36, ROR: 123.69) and hypercalciuria (PRR: 98.69, ORR: 9890) showed great disproportionalities. Topiramate is known to inhibit carbonic anhydrase type II and type IV expressed in proximal and distal renal tubular cells, causing increased urinary bicarbonate excretion, and subsequent urinary calcium phosphate supersaturation significantly.[29,30] Consequently, higher calcium ion concentration in the body may induce renal calculus and hypercalciuria. In case of sweating decreases, although the mechanism is not fully understood, several studies have suggested that inhibition of carbonic anhydrase may cause sweat decreases which can be clinically significant during heat stress and exercise challenge.[24] The results address that these AEs with strong signals, although rarely happens, should be taken into account by healthcare providers when prescribing topiramate especially for high-risk groups for these AEs.

Our study has several strengths. It is the first study that evaluated the characteristics of AE reports for topiramate by using KIDS-KD. Our database is a nationwide spontaneous

Signals detected for topiramate that fulfill the criteria of PRR, ROR, and IC compared against drug labels in 4 countries (Korea, UK, EU, and US) classified by WHO-ART PT code.

Adverse event	PRR	ROR	IC	Label			
				KOR	UK	EU	US
Sweating decreased	277.56	279.81	5.97	Y	Y	Y	Y
Renal calculus	123.36	123.69	5.69	Y	Y	Y	Y
Hypercalcinuria	98.69	98.90	5.60	Y	Y	Y	Y
Cognitive disorders	45.55	45.94	4.99	Y	Y	Y	Y
Weight decrease	30.23	31.51	4.57	Y	Y	Y	Y
Steatorrhoea	27.76	27.80	4.82	N	N	N	N
Acidosis	21.77	21.83	4.60	Y	Y	Y	Y
Concentration impaired	17.08	17.21	4.34	Y	Y	Y	Y
Cramps legs	17.08	17.11	4.19	Y	Y	Y	Y
Menstrual disorder	15.86	15.96	3.94	Y	Y	Y	Y
Amnesia	15.49	15.78	3.84	Y	Y	Y	Y
Hypoaesthesia	12.94	13.27	3.63	Y	Y	Y	Y
Emotional lability	11.75	11.81	3.40	Y	Y	Y	Y
Ptosis	9.81	9.86	3.25	Y	N	N	N
Skin tightness	9.25	9.27	3.47	Y	N	N	N
Paraesthesia	9.10	9.67	3.06	Y	Y	Y	Y
Aggressive reaction	7.34	7.37	3.01	Y	Y	Y	Y
Torticollis	5.69	5.70	2.38	Y	Y	Y	Y
Muscle contractions involuntary	5.69	5.70	2.42	Y	Y	Y	Y
Aphasia	5.21	5.22	2.33	Y	Y	Y	Y
Agitation	4.84	4.86	2.35	Y	Y	Y	Y
Thinking abnormal	4.58	4.59	2.11	Y	Y	Y	Y
Paralysis	4.41	4.42	2.39	Y	N	N	N
Speech disorder	4.15	4.18	2.30	Y	Y	Y	Y
Depression	3.87	3.90	2.05	Y	Y	Y	Y
Haematuria	3.17	3.18	1.76	Y	Y	Y	N
Palpitation	2.98	3.00	1.65	Y	Y	Y	Y
Nervousness	2.86	2.87	1.97	Y	Y	Y	Y
Anorexia	2.73	2.82	1.34	Y	Y	Y	Y
Hallucination	2.66	2.66	1.32	Y	Y	Y	Y
Tremor	2.51	2.54	1.55	Y	Y	Y	Y
Hepatic enzymes increased	2.38	2.40	1.29	Y	Y	N	Y
Insomnia	2.28	2.32	1.32	Y	Y	Y	Y
Vision abnormal	2.27	2.28	1.36	Y	Y	Y	Y
Psychomotor development impaired[*]	-	-	1.18	Y	Y	Y	Y
Menorrhagia[*]	-	-	1.16	Y	Y	Y	Y

[*] As these adverse events were not reported for the control group, PRR and ROR cannot be assessed, and only the IC criterion was satisfied.

EU = European Union, IC = information component, KOR = Korea, PRR = proportional reporting ratio, ROR = reporting odds ratio, UK = United Kingdom, US = United States, WHO-ART PT = World Health Organization-Adverse Reactions Terminology Preferred Terms.

adverse event reporting system based on 27 local centers in Korea, and it also includes new drug review data. It is the second-largest AE report database in the world and has the largest number of AE reports per million population. Moreover, unlike insurance claims data, as AE reports are accumulated regardless of drug insurance coverage in KIDS-KD, it is an appropriate database to evaluate the AEs of a drug like topiramate, which is frequently prescribed off-label. As we used a large amount of data reported between January 2010 and December 2017 in Korea, it is appropriate to represent the pattern of topiramate AE reports in Korea in recent years. Our study presented well-organized demographics and characteristics of AE reports, and it facilitated the identification of a group susceptible to AEs of topiramate.

However, some limitations of this study should be considered. First, there are some inherent limitations of a spontaneous reporting database. As AEs are generally underreported in a spontaneous reporting system like KIDS-KD, we were unable to detect the total number of patients exposed to a particular drug.

Thus, the results of our study are not associated with the incidence rates of AEs. Although there can be various determinants of underreporting, the knowledge and attitude of health professionals is an important factor.[22] In a patient-targeted survey, 87% of patients spoke to their physician about a possible connection between the drug and their symptoms, but physicians were more likely to deny than affirm the possibility of a connection.[17] To overcome this limitation, we used a large amount of data collected within recent years to obtain significant results, and the pattern of AEs was similar to that of controlled trials as mentioned above. Second, data mining methods in pharmacovigilance practices provide information on signals rather than evidence of safety problems.[13] Lastly, lack of exact and obvious findings regarding the mechanisms of action of topiramate made it difficult to interpret the correlation between new signals and AEs known to be associated with topiramate use.

In conclusion, we ascertained that the majority of AEs of topiramate was associated with neuropsychiatric disorders.

Current results are consistent with those of existing controlled trials. Especially, the results of our age- and sex-based analysis indicate that women of childbearing age should exercise caution regarding the use of topiramate. Further, our study shows that disproportionalities of AEs related to carbonic anhydrase isoenzymes in topiramate are very high compared to other antiepileptics suggesting that clinical attention is needed for these AEs.

Author contributions

Conceptualization: Junyeong Choi, Dongwon Yoon, Minhee Park, Ju-Young Shin.
Data curation: Minhee Park, Kyung-in Joung.
Formal analysis: Junyeong Choi, Dongwon Yoon, Kyung-in Joung.
Funding acquisition: Minhee Park, Kyung-in Joung.
Investigation: Junyeong Choi, Dongwon Yoon.
Methodology: Junyeong Choi, Dongwon Yoon.
Project administration: Junyeong Choi, Dongwon Yoon, Minhee Park.
Resources: Junyeong Choi, Dongwon Yoon, Minhee Park.
Supervision: Junyeong Choi, Dongwon Yoon, Minhee Park, Ju-Young Shin.
Validation: Junyeong Choi, Dongwon Yoon.
Visualization: Junyeong Choi, Dongwon Yoon.
Writing – original draft: Junyeong Choi, Ju-Young Shin.
Writing – review & editing: Dongwon Yoon, Ju-Young Shin.

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