145.

Epilepsy & Behavior **2**, 579–584 (2001)
doi:10.1006/ebeh.2001.0285, *available online at http://www.idealibrary.com on* IDEAL®

Language Disturbances as Side Effects of Topiramate and Zonisamide Therapy[1]

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Received May 25, 2001; revised September 4, 2001; accepted for publication October 1, 2001

Reversible side effects of two sulfa-containing antiepileptic drugs (AEDs), topiramate (TPM) and zonisamide (ZNS), are reported. These effects differ from those of other AEDs in that language impairment was the predominant cognitive complaint. Information was available for 42 patients exposed to TPM. Twenty-two (52%) complained of adverse effects; 12, specifically of deficits in language-related functions. Brief neuropsychological testing in four patients on TPM confirmed verbal deficits. These deficits could appear shortly after initiating TPM and disappear variably after drug withdrawal. Similar complaints were seen in a pilot study of ZNS monotherapy, administered in supratherapeutic doses, confirmed by neuropsychological testing. TPM and ZNS both contain a sulfa moiety, suggesting that verbal processing is especially sensitive to these sulfa-containing AEDs. © 2001 Elsevier Science

Key Words: **anomia; aphasia; language; epilepsy; antiepileptic drug toxicity; topiramate; zonisamide; sulfa.**

INTRODUCTION

Studies of the cognitive side effects of antiepileptic drugs (AEDs) have most commonly demonstrated effects in the areas of psychomotor speed, visual–spatial performance, concentration, and memory (1–6). Missing from this list is language, which has typically not been associated with AED effects. However, seemingly focal deficits related to language were unexpectedly spontaneously reported by our patients during the course of topiramate (TPM) therapy in the University of Washington Regional Epilepsy Center Clinic. It was of the same nature as the spontaneously reported language problems of two patients during the pilot study of zonisamide (ZNS) (7).

Initial reports of anomia alone in our patients were followed by complaints of difficulty in formulating language. This prompted a review of our experience with these AEDs.

METHODS

Topiramate Experience

The report of experience with topiramate is a *retrospective study*. The information was collected in 1998 from data entered into the patients' charts by experienced epileptologists in the University of Washington Regional Epilepsy Center in 1997 and 1998. Patients exposed to TPM were identified through the University of Washington Regional Epilepsy Center at Har-

[1] This study was presented in abstract form at the 1999 Annual Meeting of the American Epilepsy Society (8).

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1525-5050/01 $35.00

borview Medical Center hospital pharmacy database. Since some patients receive their medications from other pharmacies, not all patients for whom topiramate was prescribed are included. Any bias due to selection of patients using this pharmacy would be negated since all categories of patients are represented. Those who are language toxic, non-language toxic, and nontoxic patients are represented here.

Fifty-one patients were identified. Information was available for 42 patients. Their charts were reviewed and those who complained of toxicity were identified. Characteristics of those 12 patients with language toxicity were compared with those of 10 patients with nonlanguage side effects and with those of a control (nontoxic) group of 20 patients for whom there were no reports of adverse effects.

Four of the twelve patients complaining of language problems while on TPM were available for brief neuropsychological batteries both while they were and while they were not taking TPM. In two cases, the first testing was while they were on TPM and the second testing was when they were off TPM. In the other two cases, the order was reversed. The average TPM dose in these four patients was 200 mg/day at the time of testing.

The tests that were administered included the Controlled Oral Word Association Test (9), a measure of verbal fluency in giving words beginning with the letters F, A, and S and in naming as many animals as possible; the Stroop Test (10), a measure of reading speed and interference; and the Trail Making Test (11), a measure of attention and problem solving. A total of six variables resulted from these tests.

Zonisamide Study

The ZNS data are taken directly from the previous pilot study (7).

Eight patients with partial or partial with secondarily generalized seizures participated in this pilot study of the efficacy and safety of ZNS as monotherapy. An extensive battery of neuropsychological tests were administered after 12 weeks on patients on high-dose ZNS monotherapy and the results were compared with those of their neuropsychological testing while on carbamazepine (CBZ) monotherapy.

Four patients taking ZNS dropped out of the original study because of toxicity prior to its completion. The neuropsychological data represent the four patients who completed the study.

TABLE 1
Patient Characteristics

	Language toxic	Non-language toxic	Non toxic
Number	12	10	20
Age (years)			
Range	22–48	20–50	12–52
Average	34	38	36
Gender, F/M	8/4	8/2	13/7
Seizure type			
Primary generalized	6	3	3
Partial	3	0	5
Partial/GTC	3	7	12

RESULTS

Topiramate Experience

Of 51 patients identified as having been exposed to TPM, information concerning presence or absence of side effects was available in 42 cases. Of these, 22 complained of adverse effects, 12 specifically of language deficits (anomia and/or impairment of verbal expression). Of these 12 patients with deficits related to language, 3 also complained of decreased ability to concentrate, and 1 of transient paresthesias. The remaining 10 patients with adverse effects other than language experienced increased seizure severity or frequency (4), insomnia (3), depression (1), worsening of depression (2), worsening of behavior problem (1), transient paresthesias (1), and weight loss (2). Two patients experiencing toxicity reported better seizure control.

The characteristics of the patients grouped by presence or absence and type of toxicity are described in Table 1. There were more women than men in all groups; age was similar in all groups. A primary generalized seizure disorder was more frequently associated with the language toxic group. There were generalized epileptiform discharges in the EEGs of the six patients with primary generalized seizures in this language toxic group. In the six patients with partial seizures with or without secondary generalization, EEG abnormalities (slow waves) were seen in the left, language-dominant hemisphere in one patient. Epileptiform discharges were bilaterally independent in two patients and right-sided in three patients (they were not tested for language dominance). Higher doses of TPM, higher dose at initiation of therapy, and faster rate of escalation of dose were associated with both toxic groups. There were differences in titration

TABLE 2
TPM Dosing Information

	Language toxic	Non-language toxic	Non toxic
TPM dose at time of toxicity (or max dose), mg/day			
Average	294	262	255
Range	50–600	50–600	25–600
Initial dose, mg/day (No. of patients)	25 (0)	25 (3)	25 (5)
	50 (8)	50 (5)	50 (5)
	100 (1)	100 (1)	100 (1)
	NA[a] (3)	NA (1)	NA (9)
Rate of escalation, mg/week or month		25/2W (1)	25/2W (1)
		25/W (1)	25/W (3)
	50/W (6)	50/W (5)	50/2W (1)
		50/M (1)	50/W (4)
	100/W (1)		
	200/2d (1)		
	NA (4)	NA (2)	NA (11)

[a] NA, not available.

rates between the groups; TPM dose was escalated more rapidly in the language-toxic group than the others (Table 2).

Comedications are indicated in Table 3. LTG comedication was more frequent in the language toxic group. LTG was the comedication in 5 of the 12 patients this group.

On the neuropsychological test battery, each of the four patients tested on and off TPM performed more poorly on topiramate than off this drug on both measures of word fluency (generation of words beginning with F, A, and S in successive 1-minute periods; giving as many names as possible of animals in a 1-minute period). On these measures, the typical patient generated 47% fewer words overall on topiramate (average of 25 words over four 1-minute trials) than off it (average of 48 words). Likewise, on both measures of speed on the Trail Making Test (Trails A, Trails B), each patient was slower on TPM than off it with an average change of 17% for Trails A (29 seconds on topiramate, 24 seconds off TPM) and an average change of 55% for Trails B (119 seconds on TPM, 53 seconds off TPM). On the Stroop Test, reading speed was about 11% slower with TPM (average of 98 seconds) than without it (average of 88 seconds). The interference portion of the Stroop Test resulted in scores that on average were 26% slower on TPM (average of 273 seconds) than off it (average of 216 seconds). Overall, these performances on this select group of language-toxic patients clearly confirmed the cognitive and especially the verbal complaints that they reported.

Several case histories further illustrate the language toxicity with TPM.

Case 1. A 36-year-old man with Lennox–Gastaut syndrome and severe retardation with a vocabulary of 15–20 single words was seen several years after callosal section. He continued to experience atonic/tonic and myoclonic seizures daily as well as myoclonic status epilepticus occurring ~10 times monthly. His seizures were refractory to all AEDs currently available. TPM was added to LTG and started at 50 mg/day. One week later it was increased to 100 mg daily. His seizures were markedly reduced in severity and he had no further episodes of status epilepticus. He returned for a routine clinic visit. His mother reported that he had never been better. He was no longer lethargic, was alert, and was helping with chores; especially enjoying gardening. But she reported that he no longer spoke!

TPM was slowly withdrawn. They returned to the clinic reporting that his seizures worsened, but his vocabulary improved. Mother felt the quality of life with better seizure control and increased alertness and psychomotor activity far outweighed the verbal impairment and TPM was reinstituted. One month later, mother called to report the patient was much improved and that they were moving out of state. No further information was obtained with regard to any change in his language function.

Case 2. A 39-year-old woman with onset of generalized seizure disorder at age 16 years was having

TABLE 3
Concomitant AEDs

Language toxic	Non-language toxic	Nontoxic
None (2)	None (3)	None (3)
LTG (3)	CBZ (1)	CBZ (5)
LTG/CZP (1)	CBZ/PHT (1)	CBZ/GBP (2)
LTG/CBZ (1)	CBZ/GBP (1)	CLZ/DZP (1)
VPA (2)	VPA/ESM (1)	PHT (3)
PHT (1)	VPA/PHT (2)	PHT/VPA (1)
PHT/ESM (1)	VPA/CBZ (1)	PHT/CBZ (1)
CBZ/TGB (1)		CBZ/LTG (1)
		LTG (1)
		PRM (1)
		FBM/CLZ (1)

Note. CBZ, carbamazepine; CZP, clonazepam; CLZ, clorazepate; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; LTG, lamotrigine; PHT, phenytoin; PRM, primidone; TGB, tiagabine; VPA, valproic acid.

TABLE 4
Effect of TPM on Naming and Memory in Case 3: Observations Made during 8 Days of Monitoring with Intracranial Grid

Day	AED	Naming errors[a]	Memory errors[a]
1	All AEDs stopped		
3	None	0/17	15/29 (52%)
6			
AM	None	0/36	28/56 (50%)
PM	None	0/22	23/33 (70%)
7	TPM 325 mg CBZ 1100 mg VPA 2000 mg	17/60 (28%)	7/12 (58%)
8	No TPM CBZ 1100 mg VPA 2000 mg	1/27 (4%)	12/16 (75%)

[a] Nonstimulation trials.

myoclonic seizures occurring singly or in clusters almost daily. Her generalized tonic–clonic seizures were fairly well controlled (one or two yearly). TPM 50 mg daily was added to VPA 1000 mg daily. One hour after the first dose of TPM she noted difficulty with language, described as an inability to express herself due to an inability to form a phrase or use words in a sentence. After 1 week, she stopped topiramate and was seen 1 week after her last dose. At that time her language abilities improved; she said she felt "fifty percent toxic."

Neuropsychologic testing performed at that time revealed language-related deficits (TPM level at that time was 0.7 μg/ml, and VPA level was 53 μg/ml while still on VPA 1000 mg/day). When tested 1 month later while taking still taking VPA alone, her scores had improved.

Case 3. An 18-year-old woman with medically refractory seizures of left frontal origin was evaluated with left frontal grid electrodes, including seizure recording and electrical stimulation mapping of language (measured by naming) and recent verbal memory, using previously described techniques (12). AEDs at the time of grid placement were: TPM 325 mg/day, CBZ 1100 mg/day, and VPA 2000 mg/day. The grid was placed on Day 0. Her AEDs were discontinued on Day 1 and restarted on Day 7 when an adequate number of seizures had been recorded. Table 4 describes her course.

The addition of TPM with her other AEDs was associated with the appearance of a documented naming deficit that disappeared immediately on the withdrawal of TPM but continuation of her other AEDs. Performance on the more demanding recent memory measure changed little when topiramate and her other AEDs were restarted and, if anything, was worse when TPM was stopped (and the naming deficit improved) but the other AEDs continued, suggesting that the naming deficit with topiramate was not related to a general cognitive deficit.

Zonisamide Study

During the ZNS monotherapy pilot study (7), prior to knowledge of the extent of drug interaction of CBZ with ZNS (ZNS half-life is 60 hours in monotherapy and half that when added to CBZ) levels of ZNS were much higher than projected when calculating therapeutic doses of ZNS. The withdrawal of CBZ during the crossover to ZNS monotherapy resulted in high serum levels of ZNS. These levels were in a supratherapeutic range, greater than 30 μg/ml. One patient spontaneously complained of severe anomia without any other problems related to language nor of any impairment of cognitive function. Another patient complained of dysphasia and mental slowing. The remaining six complained of impairment of cognitive function. Adverse side effects seemed to be dose related. Toxicity cleared with lowering the dose of ZNS. Results of an extensive battery of neuropsychological tests administered after 12 weeks on either CBZ or ZNS monotherapy revealed lower verbal performance compared with nonverbal performance while on high-dose ZNS monotherapy, when compared with the neuropsychological test results of these same patients while on CBZ monotherapy (Table 5). With ZNS administration, verbal intelligence as evaluated by the WAIS was specifically diminished an average of 5 points. Neuropsychological functioning did not change overall, however, and there were no systematic alterations in adjustment as shown on either the MMPI or the WPSI.

DISCUSSION

Our observations of impairment of language-related function in patients taking TPM and ZNS are different from those seen with other AEDs (1–6). Use of these two compounds is associated with impaired higher mental function, but most interesting, sometimes specifically *only* with impairment in language-related tasks. Several patients complained of only anomia. Formal testing showed adverse effects in language-related functions, consistent with the subjective com-

TABLE 5
Comparison of Carbamazepine and Zonisamide on Summary Measures of Performance

	Carbamazepine		Zonisamide		
Test variable	Mean	SD	Mean	SD	Significance
WAIS Verbal IQ	98.50	21.24	93.00	19.88	$P < 0.005$
WAIS Performance IQ	103.25	21.61	99.25	25.00	NS
WAIS Full Scale IQ	100.00	22.76	95.75	22.77	$P < 0.001$
Halstead Impairment	0.38	0.21	0.60	0.42	NS
MMPI average profile elevation	60.83	10.91	59.56	10.15	NS
WPSI	17.00	15.47	19.75	14.66	NS

Note. WAIS, Wechsler Adult Intelligence Scales; MMPI, Minnesota Multiphasic Personality Inventory; WPSI, Washington Psychosocial Seizure Inventory.

plaints of patients of expressive language deficits. As illustrated in case 3, these can be quite specific to naming. However, in other patients, the anomia worsened with time, and by the time the neuropsychological examinations were performed more difficulties with language formulation were evident along with deficits in attention and speed of response. In several patients, i.e., cases 2 and 3, the language changes appeared rapidly after initiating TPM therapy and, as illustrated in case 3, could disappear rapidly, after TPM was stopped even though the concomitant AEDs were continued. Yet, in another patient (case 2) it took weeks for language toxicity to clear. There is some evidence in our TPM study that language deficits are more likely to be seen when TPM is administered in rapid titration, with LTG and in the presence of a generalized seizure disorder.

Martin *et al.* (6) reported that impairment of language-related function in patients taking TPM is different from what is seen with two other new AEDs, GBP and LTG. Healthy young adults were randomized to one of the three drugs. Tests of attention, psychomotor speed, language, memory, and mood were administered. Compared with baseline, the TPM group had selective, statistically significant declines on measures of attention and word fluency at acute doses, whereas the GBP and LTG groups did not.

In a retrospective study by Thompson *et al.* of patients taking TPM (13), findings similar to those identified by us were noted. Patients were treated with a median dose of 300 mg TPM (comedication was not mentioned in the report). Neuropsychological test scores of these patients indicated impairment in verbal IQ, verbal fluency, and verbal learning. Improvement in scores with these tasks and in digit span was noted when TPM was withdrawn or reduced.

A patient taking TPM and CBZ during a presurgical evaluation had scores so low on neuropsychological testing and a WADA test as to exclude him for consideration for surgical therapy, according to the authors (14). His scores improved when TPM was discontinued and he was maintained on LTG and CBZ.

In a pilot study of ZNS monotherapy (15) Berent *et al.* described findings similar to those in our earlier study (7). On neuropsychological examination of patients on ZNS monotherapy with serum concentrations greater than 30 μg/ml, impairment was noted in verbal learning while visual–perceptual learning was unimpaired.

What ZNS and TPM have in common is a sulfa moiety; TPM a sulfamate, ZNS a sulfonamide. There is some evidence of specific language toxicity with other drugs containing a sulfa moiety. Dodrill (16) reported impairment in verbal but not in perceptual learning with another sulfa-containing drug, sulthiame. A report of "difficulty with speech" was found in an old textbook (17) in a discussion of the sulfa drug Sulfonal (sulfonmethanone). Among other mechanisms of action, to different extents these drugs have in common the property of carbonic acid inhibition. Other drugs containing sulfa moieties that have aphasia as a reported side effect include sulfasalazine (18), ritinavir (Prod Info Norvir, 1999), and risperidone (Prod Info Risperdal® 2000). However some non-sulfa-containing drugs have also been associated with language disturbance, for example, mirtazepine (Prod Info Remeron, 2000) and lamotrigine (Prod Info Lamictal 2000), though the association of aphasia with these drugs was either rare or infrequent.

Toxicity of other AEDs shows specificity to particular neural systems. Toxicity with PHT most frequently involves the cerebellar vestibular system,

while that with CBZ, the oculomotor system (19). This suggests the neurocircuitry subserving these systems has specific neurochemical constituents. Thus there may be a specific neurochemistry (perhaps related to sensitivity to sulfa-containing compounds) responsible for the formulation of language.

Naming is often the most fragile language function. It is the only language function disrupted in all aphasic syndromes. This may explain why a few patients felt that naming was disturbed before there was difficulty putting sentences and thoughts together. All this appeared to occur prior to generalized impairment in cognition. Sequencing deficits were also noted with TPM. Sequencing of tasks has been related to brain mechanisms involved in language (20); thus those deficits with TPM therapy may also be related to an effect on language circuits.

In addition to the well-known functional and structural asymmetry of the human brain, there is also evidence of asymmetry of neurotransmitters in the human brain. Amaducci *et al.* (21) demonstrated, in humans, greater concentrations of choline acetyltransferase (ChAT) in the left than the right superior temporal gyrus. Glick *et al.* (22) reported lateralization in the human cerebral hemispheres of gamma γ-aminobutyric acid (GABA), glutamic decarboxylase (GAD), dopamine (DA), and ChAT. There was also interpatient variability of the distribution of these compounds. These chemical asymmetries could provide the basis for the language-specific toxicity we observed with supratherapeutic levels of ZNS and with TPM; the variability of the concentrations of these compounds within individuals may account, in part, for the selective vulnerability of patients who experience language-related toxicity.

ACKNOWLEDGMENT

This work was supported, in part, by the Drueding Foundation.

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