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The effect of topiramate plasma concentration on linguistic behavior, verbal recall and working memory

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ABSTRACT

This is the first study of the effect of topiramate on linguistic behavior and verbal recall using a computational linguistics system for automated language and speech analysis to detect and quantify drug-induced changes in speech recorded during discourse-level tasks. Healthy volunteers were administered a single, 100-mg oral dose of topiramate in two double-blind, randomized, placebo-controlled, crossover studies. Subjects' topiramate plasma levels ranged from 0.23 to 2.81 μg/mL. We found a significant association between topiramate levels and impairment on measures of verbal fluency elicited during a picture description task, correct number of words recalled on a paragraph recall test, and reaction time recorded during a working memory task. Using the tools of clinical pharmacology and computational linguistics, we elucidated the relationship between the determinants of a drug's disposition as reflected in plasma concentrations and their impact on cognitive functioning as reflected in spoken language discourse.

1. Introduction

Topiramate, a second-generation antiepileptic drug (AED) with formal indications for partial and generalized seizures and migraine prophylaxis, is being increasingly prescribed for a variety of other conditions including obesity, pain, bipolar disorder, and alcoholism. Despite its widespread use, topiramate is associated with adverse effects on attention and memory [1–3]. Topiramate is also associated with a unique cognitive signature affecting language use in a subset of patients [3,4] who often describe their impairment as "a word finding difficulty" [3,4].

Topiramate's broad spectrum of applications is likely a consequence of its multiple mechanisms of action that include modification of Na^{+}- or Ca^{2+}-dependent action potentials, enhancement of GABA-mediated receptors, and inhibition of kainate-mediated conductance at glutamate receptors of the AMPA/kainate type as well as carbonic anhydrase (CA II and IV) [5,6]. Yet, the mechanisms by which topiramate's effect on the brain impact an individual's cognition are poorly understood.

Moreover, not all individuals complain of topiramate-induced cognitive impairment, and the percent of those who are affected varies with the study and population under consideration [7]. For example, between 11 and 20% of patients with refractory epilepsy treated with topiramate report some type of cognitive adverse event [8,9]. There is strong evidence that the number and magnitude of both subjective and objective accounts of topiramate-induced cognitive deficits can be partially attributed to the effects of polytherapy, titration rate, and maintenance dose in both patients and healthy adults [10,11], yet these factors do not fully capture the majority of the inter-individual variability in the cognitive response to topiramate.

It has been postulated that the topiramate-induced language impairment is secondary to changes in frontal lobe or executive function rather than exerting direct effects on linguistic processing [2,12]. This hypothesis is supported by topiramate-induced decreases in neuropsychological measures of generative (phonemic) verbal fluency, working memory, and attention [1–3,13–19] that persist through the titration period [2,20,21] and improve after topiramate is discontinued [2,12]. Topiramate's effect on verbal fluency may actually reflect a widespread disruption of language-specific networks that

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include regions within the frontal and parietal cortices [22] and the cerebellum [23,24].

Current investigations into topiramate's effect on language and cognition are limited by the use of laboratory-based neuropsychological assessment tools that do not capture the interplay of cognitive processes that underlie complex behaviors such as spontaneous speech. For example, standard neuropsychological measures have been criticized due to their poor ecological predictive validity outside the context of a controlled assessment setting [25]. Therefore, it is not surprising that traditional neuropsychological tests such as confrontation naming or generative verbal fluency correlate poorly with subjective patient reports of word-finding difficulties [26,27].

Automatic computerized classification of spontaneous speech into predefined categories based on its prosodic characteristics (e.g., duration and frequency of hesitations, intonation, rhythm) has been the subject of much study in computational linguistics [28–30]. Multiple investigators, including our group, have successfully applied automated speech and language analysis tools to the assessment of individuals with mild cognitive impairment [31], aphasia in children [32], and frontotemporal lobar degeneration [33]. However, these tools have not yet been applied to characterize effects of medications on cognition.

Our primary objective was to demonstrate the relationship between topiramate and non-laboratory-based measures of linguistic behavior (e.g., spontaneous speech fluency) and verbal recall. We applied an innovative System for Automated Language and Speech Analysis (SALSA), coupled with standard neuropsychological tests, to studies of healthy volunteers who received a single, 100-mg oral dose of topiramate in a randomized, double-blind, crossover, placebo-controlled design. Our central hypotheses were: a) topiramate adversely affects individual performance on measures of linguistic behavior and verbal recall compared to a no-drug baseline and b) the magnitude of topiramate's effect is proportional to its plasma concentration.

In the first study, a single, 2-mg oral dose of lorazepam was chosen as an active comparator to 100-mg topiramate. Unlike topiramate, lorazepam produces its cognitive effects via a mild generalized sedation, which will be characterized by more generalized effects on verbal fluency and recall. In the second study, we examined the effects of 100-mg oral topiramate on the reaction times (RTs) recorded during performance of a working memory task [34]. Here, we postulated that when compared to a no-drug baseline, topiramate induces cognitive changes via effects on frontal lobe function that are reflected in the subject's behavioral performance (i.e., RTs). In both studies, we measured the drug concentration at the time of the task performance. Plasma concentration is a more direct indicator of drug exposure than dose due to differences in pharmacokinetic processes such as absorption, distribution, elimination, and metabolism. Since patients with epilepsy are, by the very nature of their disorder, prone to cognitive impairments [35], including those affecting language, any untoward cognitive effects of pharmacological seizure control may prove to be particularly debilitating. The characterization and quantification of linguistic behavior, including speech, memory, and executive functions, and their relationships to topiramate exposure in healthy adults are necessary to lay the groundwork for determining the mechanisms leading to individual intolerability and discontinuation of drug therapy in patients with epilepsy.

2. Methods

2.1. Subjects

Twenty-five native English-speaking, healthy volunteers (8 women, 17 men) between 18 and 50 years of age were recruited from two sites, the University of Minnesota (N = 14; 6 women, 8 men) and the University of Florida (N = 11; 2 women, 9 men). Exclusion criteria included histories of significant cardiovascular, endocrine, hematopoietic, hepatic, neurologic, psychiatric, or renal disease; current or a history of drug or alcohol abuse within the past 5 years; the use of concomitant medications known to affect topiramate or lorazepam, or that alter cognitive function including antidepressants, anxiolytics, psychostimulants such as Ritalin, prescribed analgesics, and antipsychotics; prior hypersensitivity to topiramate, lorazepam or related compounds; a positive pregnancy test (administered to all women before the start of each test session); use of any investigational drug within the previous thirty days; non-native speakers of English; diagnosed with a speech and/or language impairment/disability; uncorrectable low vision; a dominant left hand (to control for brain lateralization of language).

2.2. Study design

The University of Minnesota and University of Florida served as study sites. In a randomized, double-blind, crossover design, Minnesota subjects received 100-mg oral topiramate, 2-mg oral lorazepam, and an inactive placebo (three-period crossover), whereas Florida subjects received topiramate and placebo (two-period crossover). One baseline (no treatment) period was pre-pended, and another was appended, to each crossover design. Traditional neuropsychological tests were administered in each period. In addition, we employed SALSA to precisely and objectively quantify various measures of language on discourse-level tests of verbal recall and spontaneous speech. The Institutional Review Boards at each site approved the respective protocols. The study design for each site is presented in Fig. 1.

Session 1. The subjects signed an IRB-approved consent form, after which they supplied a brief demographic, medical, and medication history. A neuropsychological test battery (Baseline 1) lasting approximately 1 h was administered, after which the subjects were randomly assigned to a study treatment sequence (at Minnesota: topiramate, lorazepam, placebo in random order; at Florida: topiramate, placebo in random order).

Sessions 2–4. The subjects were administered their randomized drug, with neuropsychological testing performed between 1 and 1.5 h after drug ingestion. Vital signs were recorded, and a blood sample was drawn immediately after testing to establish plasma drug levels. Florida subjects did not undergo any testing during Session 4.

Session 5. The subjects returned for a second neuropsychological baseline (Baseline 2).

All language-based tests were audio-recorded using an array microphone at a 16-kHz sampling rate for subsequent computerized analysis. All tests were administered by a single, trained examiner at each site.

2.3. Neuropsychological measures

The neuropsychological test battery included:

Word-level language/verbal tests:

Controlled oral word association (COWA) test [36]: a measure of generative phonemic word fluency that requires the subjects to generate words (no proper nouns) beginning with specific letters in three 60-second trials.

Category (or semantic) fluency [37]: the subjects name as many items from a particular category, e.g., animals, as they can within a 60-second time period. *Switching* is a variation of category fluency requiring alternate retrieval of items from two different categories, e.g., furniture/musical instruments.

Discourse-level language/verbal tests:

MCG paragraph memory [38]: a test of verbal recall; after being read a short story, the subject is asked to recall the story exactly as