Epilepsy Research (2008) **78**, 140—146

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

Relative influences of adjunctive topiramate and adjunctive lamotrigine on scanning and the effective field of view

Kenneth C. Mills[a,*], **Joseph F. Drazkowski**[b], **Anne E. Hammer**[c], **Paul T. Caldwell**[c], **Robert P. Kustra**[c], **David E. Blum**[c]

[a] *Profile Associates, Chapel Hill, NC, United States*
[b] *Mayo Clinic, Phoenix, AZ, United States*
[c] *Neurosciences, GlaxoSmithKline, Research Triangle Park, NC, United States*

Received 21 June 2007; received in revised form 8 October 2007; accepted 28 October 2007
Available online 21 December 2007

KEYWORDS
Lamotrigine;
Topiramate;
Epilepsy;
Driving skills;
Effective field of view

Summary A subsample of 67 adult patients with partial seizures participating in a randomized, double-blind study comparing the cognitive effects of adjunctive lamotrigine (LTG) and adjunctive topiramate (TPM) was administered Performance On-Line (POL) in addition to a battery of neuropsychological tests at baseline, week 8 and week 16 of treatment. The POL is a self-administered computer task that measures scanning, divided-attention, and the effective field of view. Although the POL does not measure driving performance, POL scores are correlated with driving performance. The results show that adjunctive TPM, but not adjunctive LTG, negatively impacted cognition. Both simple target identification and divided-attention performance on POL were compromised in the TPM group but not in the LTG group. The relative POL impairment associated with chronic TPM treatment was similar to that observed with the acute effects of alcohol with a breath level of .045% or a low dose of alprazolam (0.5 mg). Thus, driving-related visual and cognitive skills were compromised by adjunctive TPM treatment. Therapeutic doses of adjunctive TPM pose a potential risk of impaired scanning and divided-attention skills.

Introduction

People with epilepsy (PWE) often take antiepileptic drugs (AEDs) to control seizures so they can legally drive a motor vehicle (Yale et al., 2003). When patients with moderately severe epilepsy were asked to list concerns of living with recurrent seizures, driving was cited over all others (Gilliam et al., 1997). However, evidence suggests that drivers with

* Corresponding author at: 111 Cloister Court, Suite 212, Chapel Hill, NC 27514, United States. Tel.: +1 919 967 9400.
E-mail address: profiler@intrex.net (K.C. Mills).
URL: http://www.scientificdriverassessments.com (K.C. Mills).

0920-1211/$ — see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2007.10.013

epilepsy who are seizure free and compliant with local driving restrictions pose little to no increased risk of motor vehicle accidents, especially when compared with other chronic diseases (van der Lugt, 1975; Hansotia and Broste, 1991; Drazkowski et al., 2003).

All AEDs have undesirable side effects. Dose-dependent cognitive effects often associated with AEDs include impaired attention, vigilance, and psychomotor speed, all of which are relevant to the driving task (Meador, 2002). Although the magnitude of cognitive side effects is modest with most AEDs, these effects may compromise driving safety.

Cognitive impairment generally appears to be more common with older AEDS than newer AEDs, but few systematic comparisons of newer agents have been undertaken. Among the newer AEDs, lamotrigine (LTG) and topiramate (TPM) have been most thoroughly studied with respect to cognitive effects. LTG is reported to have a favorable cognitive profile in both healthy volunteers and patients with epilepsy (Meador, 2002; Meador et al., 2005). TPM, in contrast, has been associated with cognitive impairment—particularly on attention/vigilance tasks, tests of cognitive/motor speed, memory, language, grapho-motor coding, and reading/naming speed (Meador et al., 2005). Data from a recent study of driving accident death investigations suggest the presence of psychomotor impairment in some drivers with blood TPM concentrations in the normal therapeutic range (Gordon and Logan, 2006). This study reviewed all topiramate-positive cases in the Washington State Toxicology Laboratory between 1998 and 2004 ($n = 132$ including 63 death investigations, 68 suspected impaired drivers, and 1 sexual assault case). The majority of cases (94%) were positive for at least one drug in addition to topiramate. Concentrations of topiramate in blood ranged from 1 to 180 mg/L. Deaths attributed to topiramate alone occurred at topiramate concentrations as low as 50 mg/L. Considered in aggregate, the data suggest that TPM may adversely affect the ability to process information, respond to stimuli, and multitask.

The randomized, double-blind study reported herein was conducted to compare the effects of LTG with those of TPM as adjunctive therapy in adult patients with partial seizures. Participants were given a dynamically paced computerized test, Performance On-Line (POL), in addition to a battery of neuropsychological tests. The POL test continuously monitors scanning, divided-attention, and the effective field of view. This test has been shown to be sensitive to the time-series effects of low and moderate doses of alcohol, a low dose of alprazolam, and the stimulant effects of a low dose of dextroamphetamine (Mills et al., 1996, 2001). The POL test was validated with police cadets, and significant positive correlations were found between peripheral divided-attention scores and trainer ratings of cadet on-the-track driving performance (Mills et al., 1999; Mills and Hubal, 2001).

Like other computerized tests, POL assesses an individual's ability to detect and respond continuously to targets (or hazards) in both the central and peripheral landscape—the effective field of view (Chapman and Underwood, 1998; Underwood et al., 2002). When an individual's field of view is restricted it is sometimes referred to as tunnel vision (Easterbrook, 1959; Dirkin, 1983; Christianson, 1992). A restriction in the useful field of view (UFOV) has also been observed in older drivers and is a predictor of accidents (Ball et al., 1988; Ball and Owsley, 1991, 1993; Owsley et al., 1998). Restrictions in the field of view can also affect steering performance in healthy young drivers (Brooks et al., 2005).

Restrictions in the field of view can be pharmacologically induced (Mills et al., 1996). A recent study replicated POL stimulant-induced tunneling and used a driving simulator to link effects from 0.42 mg of dexamphetamine to driving behaviors such as ''failing to stop at a traffic light'' and ''slow reaction times'' to traffic events (Silber et al., 2005). Pharmacologically induced tunneling thus increases the risk for errors in driving performance.

The POL test was administered in selected centers as a subsample of a larger study (Blum et al., 2006) that examined the cognitive effects of LTG and TPM as well as seizure frequency, adverse events, and drug serum concentrations in patients with epilepsy. The neuropsychological results of the full sample were previously reported (Blum et al., 2006). In the current manuscript, we report in detail the results of the POL and compare the results of the other neuropsychological measures in this subsample.

Methods

Patients

Males and females $\geq$18 years of age were eligible for the study if they had a confident diagnosis of partial epilepsy for at least 6 months; had experienced $\geq$1 complex partial or secondarily generalized tonic-clonic seizure in the last 3 months but $\leq$8 per month; were currently receiving carbamazepine or phenytoin as monotherapy or combined with 1 additional AED that did not change the enzyme-inducing status of carbamazepine or phenytoin; and had no change of AED dose >10% for at least 1 month before enrollment. Sixteen of the 45 investigators from the double-blind study were randomly selected to conduct the POL substudy at their centers. All patients provided written, informed consent.

Procedures

The protocol for this randomized, double-blind, parallel-group study (GlaxoSmithKline protocol LAM40112) was approved by an institutional review board for each of the study sites (Blum et al., 2006). The study was conducted in the United States and Canada. The study comprised a screening phase of up to 2 weeks during which eligibility was determined; an 8-week dose-escalation phase during which study medication was introduced and titrated as previously described (Blum et al., 2006) to target doses of 500 mg/day for LTG and 300 mg/day for TPM; and an 8-week, double-blind maintenance phase during which dosages of study medication and concomitant AEDs were maintained.

The titration schedule followed the labeled dosing recommendations for LTG as adjunctive treatment with an enzyme-inducing AED but followed a slower schedule than that in the labeled dosing recommendations for TPM in epilepsy. It has been suggested that slower titration of TPM may cause less cognitive impairment than a more rapid titration schedule (Aldenkamp et al., 2000). The maintenance dose of LTG (500 mg/day) was at the high end of its labeled dose range (300—500 mg/day); the maintenance dose of TPM (300 mg/day) was in the middle of its labeled dose range (200—400 mg/day).