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Cognitive effects of topiramate revealed by standardised low-resolution brain electromagnetic tomography (sLORETA) of event-related potentials

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ABSTRACT

Objective: To evaluate the effect of topiramate (TPM) on event-related potentials (ERPs) in patients with epilepsy.
Methods: Neuropsychological tests and ERP study using auditory oddball paradigm were conducted before and after treatment with TPM in drug-naive epilepsy patients. To detect target brain regions in which ERP changed during the cognitive task, cortical current densities of ERP components were analysed using standardised low-resolution electromagnetic tomography (sLORETA).
Results: Neuropsychological tests (n = 18 patients) showed that TPM significantly decreased the score in digit span, Corsi block and Controlled Oral Word Association word fluency. Repeated-measures analysis of variance of ERP data (n = 13 patients) revealed that P2 amplitude was significantly increased at Fz electrode following treatment with TPM. Statistical non-parametric map of sLORETA between pre- and post-TPM ERPs revealed that current density of P200 component was significantly reduced by TPM in bilateral parieto-occipital, temporolimbic and dorsolateral right prefrontal regions.
Conclusions: Our findings suggest that TPM affects selective brain regions which may be related to cognitive side effects.
Significance: Source localisation of ERPs can be helpful in identifying target brain regions for the cognitive side effects of anti-epileptic drugs.

1. Introduction

Anti-epileptic drugs (AEDs) may be a cause of cognitive dysfunction in some patients with epilepsy (Meador, 2006; Park and Kwon, 2008; Trimble and Thompson, 1983). As AEDs are typically taken on a long-term basis, the impact of AED-related cognitive impairment on daily life is an important issue in the treatment of epilepsy. Although topiramate (TPM) is one of the most effective AEDs, it has been reported to have a negative impact on cognition, and patients frequently describe themselves as having slow thoughts, difficulty in calculating and blunted mental reactions. Previous studies reported that the greatest changes were noted in impaired concentration and poor performance on verbal tests, as revealed by various neuropsychological (NP) assessments (Aldenkamp, 2000; Aldenkamp et al., 2000; Blum et al., 2006; Lee et al., 2006; Martin et al., 1999; Meador et al., 2003, 2005; Thompson et al., 2000). Furthermore, withdrawal of TPM causes significant improvement in frontal lobe function-associated measures such as verbal fluency and working memory (Kockelmann et al., 2003). However, NP tests can provide only approximate estimations of the brain regions involved in cognitive dysfunction. Furthermore, temporal information about information processing by the brain cannot be determined by such tests.

The event-related potential (ERP) recorded during an oddball task reflects the brain activities underlying various cognitive functions such as attention and working memory, in which several ongoing cognition-related components such as N100, P200 and P300 are involved. P300, the most studied component, represents aspects of information processing, such as attention allocation and decision-making (Polich and Kok, 1995). P200 is another cognitive ERP component that is usually interpreted as a reflection of evaluating the task relevance of stimulus items, which is achieved by suppressing irrelevant features or enhancing relevant features (Potts, 2004). N100 is an early sensory-perceptual related component that is sensitive to attention. Thus, ERPs provide a

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neurophysiological index of a subject's cognitive function. ERP measurements during task performance may provide a more sensitive avenue for objectively assessing medication-related changes in cognitive function (Chung et al., 2002; Ozmenek et al., 2008).

ERPs have been used to assess pharmacological influences of various drugs (including AEDs, that act on the central nervous system (CNS)) on attention-dependent information processing (Anderer et al., 2004; Anderer et al., 2002a,b, 2008; Barry et al., 2007; Chung et al., 2002; Higuchi et al., 2008; Ohlmeier et al., 2007; Ozmenek et al., 2008; Ruijter et al., 2000; Saletu et al., 2002; Sun et al., 2007). Subtle functional changes in the CNS induced by several old AEDs have been reported. P300 latencies and amplitudes were significantly affected by old AEDs, such as phenobarbital, carbamazepine and valproate (Chen et al., 1996; Enoki et al., 1996). Compared with placebo, an augmentation of the N160 component (corresponding N100 component of the visual ERP occurring between 130 and 180 ms) to match visual stimuli was reduced by phenytoin in healthy young adults (Chung et al., 2002). Valproate may induce impairment of cognitive processing, as revealed by ERP N270 and P300 (Panagopoulos et al., 1997; Sun et al., 2007). N270 is considered as a constant component of ERPs reflecting the cognitive activity in the human brain for processing conflict.

Contrary to old AEDs, only a few studies have reported effects of new AEDs on cognitive ERPs. Smith et al. (2006) reported that in healthy subjects, P300 at Pz electrode was not significantly affected by TPM, while TPM blocked enhancement of positive-going slow wave that followed the P300. Since previous studies had limited ERP measurements from only a few scalp electrodes, the effects of the AEDs could not be evaluated over the whole brain. Thus, target brain regions of AEDs could not be identified.

The method of source localisation may provide information for identifying the generators of particular EEG activities (Michel et al., 2004). Low-resolution electromagnetic tomography (LORETA) provides three-dimensional images of brain electrical activity, consequently giving information for brain regions that are involved in neurocognitive processes and are the targets of therapeutic drug action (Pascual-Marqui et al., 1994). Thus, electrophysiological neuroimaging using LORETA may reveal those parts of the structural network that make major contributions to the scalp-recorded ERP component affected by AEDs. We hypothesised that information processing might be changed by treatment with TPM. Subsequently ERP analysis by LORETA (ERP–LORETA) could reveal brain regions that may be related to ERP changes.

The purpose of the present study is to evaluate the effects of TPM on cognitive ERPs in drug-naive patients with epilepsy, focussing particularly on temporal relationships and the target brain region where TPM results in qualitative alterations in neuronal activity related to cognitive tasks. Based on the literature, we hypothesised that sLORETA should reveal changes in cerebral source activity in certain brain regions, particularly prefrontal and temporo-parietal areas, in relation to the cognitive effects of TPM. To detect target brain regions in which ERPs change during a cognitive task, depending on the temporal processing of cognitive function, cortical current densities of ERP components were analysed using sLORETA (Pascual-Marqui, 2002).

2. Methods

2.1. Subjects and TPM schedule

Twenty-four consecutive drug-naive patients with partial epilepsy were enrolled from an outpatient epilepsy clinic. Exclusion criteria included not being right-handed, a diagnosis of mental retardation, use of other CNS-acting drugs, brain lesions other than hippocampal sclerosis or having a progressive neurological or psychiatric disease.

Each patient received TPM monotherapy for 12–16 weeks. Before the TPM treatment, all subjects underwent a physical examination, routine blood tests, magnetic resonance imaging (MRI) of the brain, electroencephalogram (EEG), NP tests and an initial ERP study. TPM was given at 50 mg/day for the first 2 weeks and at 100 mg/day for the next 2 weeks. From the fifth week, TPM was gradually increased, up to a maximum of 400 mg/day, as needed, to control seizures and was maintained at a fixed dose for at least 2 weeks before the second ERP study was conducted. However, if a patient complained of intolerable adverse events because of TPM administration, the dosage was decreased by 25 mg/day each week until the symptoms subsided. Blood testing for haematology and liver function was performed twice, before medication administration and at the end of the study period. The frequency of seizures was checked by a self-recorded seizure diary when the patient visited the outpatient clinic.

All patients were informed of the procedure and informed consent was obtained from all subjects in accordance with the guidelines of the institutional review board at Samsung Medical Center.

2.2. NP tests

A battery of NP tests, standardised for the Korean population, was administered. The first NP test (NP1) was given within 1 week of the ERP1 study and the second NP test (NP2) was conducted at least 6 months after NP1. The following NP tests were performed.

(1) The Korean version of the mini-mental state examination (K-MMSE) (Kang et al., 1997) and the short form of the Korean Wechsler Intelligence Scale (KWIS) to evaluate general cognitive function (Lim et al., 2000).
(2) Digit span forward and backward and Corsi block forward and backward, which test attention and working memory.
(3) Digit symbol tests to assess psychomotor performance, sustained attention and visuo-motor coordination.
(4) The trail-making test (TMT, A and B types) to test attention, visuo-motor tracking abilities and mental flexibility.
(5) The Wisconsin Card Sorting Test (WCST) to test executive functions such as conceptual formation and cognitive set-shifting.
(6) The Stroop test of inhibitory control ability, mental vitality and flexibility.
(7) Controlled Oral Word Association test (COWA) (Kang and Na, 2003) to measure phonemic word fluency (generating words beginning with the Korean characters , ㅇ, ㅅ and semantic word fluency (generating names of animals and supermarket goods).
(8) The Korean version of the Boston Naming Test (K-BNT) (Kim and Na, 1997) for language function.
(9) Raven's Coloured Progressive Matrices (RCPM) for non-verbal reasoning ability.
(10) The Korean version of the California Verbal Learning Test (K-CVLT) (Kim and Kang, 1997) for verbal memory and the Rey complex figure test of visual memory (Meyers and Meyers, 1995).

All NP tests were performed by a single examiner (CKM).

2.3. ERP study

Two ERP studies were carried out; the first (ERP1) was performed just before giving the first dose of TPM and the second (ERP2) was conducted at 12–16 weeks after TPM administration was started. EEGs were recorded with a SynAmps 32-channels amplifier (Neuroscan, Herndon, VA, USA) with 30 Quick-cap electrodes. The reference electrode was set to linked mastoid elec-