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ARTICLE ORIGINAL

Laser evoked potentials and carbamazepine in epileptic patients

Potentiels évoqués au laser et carbamazepine chez les patients épileptiques

F. Galeotti, A. Truini, G.D. Iannetti, A. Romaniello, A. Biasiotta, A. Mascia, M. Virtuoso, G. Cruccu *

Department of Neurological Sciences, University "La Sapienza", Viale dell' Università 30, 00185 Rome, Italy

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Abstract
Aims of the study. - Nerve conduction studies have demonstrated that carbamazepine (CBZ), as well as other antiepileptic drugs (AEDs), can affect peripheral nerve conduction; reports on conventional somatosensory evoked potentials and CBZ are controversial. In a previous study, assessing laser-evoked potentials (LEPs) in CBZ-treated patients with idiopathic trigeminal neuralgia, we found that LEPs were dampened even after stimulation of the non-painful side, with a strong correlation between LEP latency and daily CBZ dose. No other study investigated the influence of AEDs on LEPs. In order to clarify the effect of CBZ on LEPs we sought possible LEP changes in epileptic patients taking CBZ.
Materials and methods. - We studied LEPs after trigeminal and hand CO_2-laser stimulation in 20 patients with epilepsy taking CBZ and 20 age-matched controls.
Results. - Although the trigeminal LEP mean latency was slightly longer in epileptic patients ($P = 0.11$), we did not find significant differences between epileptic patients and controls for any LEP data. LEP data did not correlate with the daily CBZ dose, CBZ blood concentration, or duration of therapy ($P > 0.3$).
Conclusion. - The lack of a CBZ-induced dampening of LEPs suggests that small-fibre pathways, compared to large-fibre, might be less susceptible to AED's toxic effect. Although the TN patients in our previous study were older than the epileptic patients in the present study, a possible combined effect induced by drug and age in patients with TN is unlikely because LEP latency is reportedly unaffected by age. The CBZ-induced effect in patients with trigeminal neuralgia is possibly related to pathophysiological changes specific to this disease.

MOTS CLÉS
Potentiels évoqués laser ;

Résumé
Objectifs de l'étude. - La carbamazepine (CBZ) comme les autres médicaments antiépileptiques peut influencer la conduction nerveuse et l'excitabilité centrale. Une étude

* Corresponding author. Tel.: +39 06 4969 4209; fax: +39 06 4991 4758.
E-mail address: cruccu@uniroma1.it (G. Cruccu).

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Carbamazepine ;
Épilepsie

précédente qui a évalué les potentiels évoqués laser (PEL) trigéminaux chez des patients avec névralgie trigéminale idiopathique (NT) soignés par CBZ a montré des PEL trigéminaux déprimés après la stimulation des deux côtés (le non douloureux aussi). Il y avait aussi une corrélation entre la latence des PEL et le dosage quotidien du CBZ. Il n'y a pas d'autres études sur l'effet des autres médicaments antiépileptiques sur les PEL ; pour déterminer celui de la CBZ, nous avons recherché d'éventuelles modifications des PEL chez des patients épileptiques.

Matériaux et méthodes. - Nous avons évalué les PEL-CO_2 trigéminaux et les PEL après la stimulation de la main chez 20 patients épileptiques soignés avec CBZ comparés avec 20 sujets sains.

Résultats. - On n'a pas trouvé de différence statistiquement significative entre patients épileptiques et sujets sains pour les résultats des PEL et il n'y a pas de corrélation entre ces derniers et le dosage quotidien du CBZ, la concentration hématique et la durée de la thérapie ($P > 0.3$).

Conclusions. - L'absence d'atténuation des PEL produite avec CBZ a suggéré que les petites fibres nerveuses sont moins sensibles que les grandes fibres à l'action toxique des antiépileptiques. L'atténuation donc des PEL par CBZ chez les patients avec NT peut être corrélée avec des modifications pathophysiologiques spécifiques de cette maladie.

Introduction

Chronic treatment with antiepileptic drugs (AEDs) may affect nervous function even without clinical signs of intoxication and with plasma concentrations within therapeutic range. Motor and sensory nerve conduction velocity is generally slowed after long-term treatment with AEDs [7,8,14]. Most AEDs also decrease central nervous system (CNS) excitability [16]. Many studies investigated the possible influence of antiepileptic therapy on evoked potentials, with contradictory results [1,2,9,11,13].

Concerning the effects of carbamazepine (CBZ), a slowing of conduction velocity in the distal portion of long limb nerves [7,8,14], as well as an increased latency of auditory and visual evoked potentials have been reported [10,11,13,15,17,18]. In contrast, reports on somatosensory evoked potentials and carbamazepine are controversial. Some investigators found a slowed central conduction [11,14], whereas others found it normal [1,2].

So far there are no studies specifically dealing with the influence of AEDs on laser-evoked potentials (LEPs), except for one study in patients with trigeminal neuralgia treated with CBZ [3].

In this previous study we evaluated trigeminal CO_2-LEPs in patients with idiopathic or symptomatic trigeminal neuralgia (TN). All patients with symptomatic and 51% of those with idiopathic TN had frankly abnormal LEPs on the painful side. The mean latency was significantly higher and mean amplitude lower on the painful than the non-painful side. However, even on the non-painful side, LEPs were dampened (longer latency and smaller amplitude in TN patients than in controls). When we analyzed the data for the patients with idiopathic TN separately (because patients with multiple sclerosis or tumors might have bilateral dysfunction), the latency on the normal side was almost 20 ms longer in patients than in controls ($P < 0.001$) and correlated with the daily CBZ dose ($P < 0.0001$). Conversely, in patients with TN receiving no medication, the contralateral latency almost matched that of healthy subjects.

To investigate the influence of CBZ on LEPs, and ascertain whether the reported effects are specific to trigeminal neuralgia, we sought possible LEP changes in epileptic patients taking CBZ in monotherapy.

Material and methods

We studied 20 epileptic patients, aged 18–74 years (mean age 37 years), treated with CBZ in monotherapy as their only medication for at least 1 year (mean dose 660 mg, range 400–1200 mg; mean duration of therapy 6 years, range 1–25 years; mean plasma drug concentration 7.3 μg/ml, range 4.6–12.3). Twenty healthy volunteers, matched for age (18–76 years, mean age 40 years), served as controls.

Patients were enrolled consecutively as they referred to the outpatient department. Patients with overt polyneuropathy, diabetes mellitus or other known toxic-metabolic conditions that may induce subclinical polyneuropathy, and patients reporting facial hypoesthesia were excluded; those participating in the study had simple or complex, partial epilepsy, with or without secondary generalization, as defined using a reference gold standard [6]. Brain MRI scans were normal except for two patients with hippocampus sclerosis.

Patients and controls gave their informed consent and the study was approved by the local Ethics Committee.

Neurophysiological technique

Using a CO_2-laser stimulator (Neurolas, Electronic Engineering, Florence, Italy), we studied LEPs after stimulation of the perioral region (V2 and V3) and after stimulation of the dorsum of the hand. Details of stimulation and evoked-potential recording are described elsewhere [4,5,12]. In brief, laser stimuli (1.5–15 W; duration 10–15 ms, beam diameter 2.5 mm; irradiated area 5 mm^2; stimulus intensity set at twice the perceptive threshold) were delivered at 10–20 s interstimulus intervals. In the two patients with hippocampus sclerosis we stimulated the side ipsilateral to the cerebral lesion.

Signals (bandpass 0.5–50 Hz) were recorded with disc electrodes from the vertex referenced to linked earlobes. Simultaneous electroculography monitored ocular movements or eye-blinks. Two series of 10 artifact-free trials were collected and averaged off-line. We measured the peak latency of the main negative (N) vertex component and the peak-to-peak amplitude between the N and the following positive (P) components (Fig. 1). The examiners who recorded and measured the variables knew the subject's group but had no information about the patient's therapy.

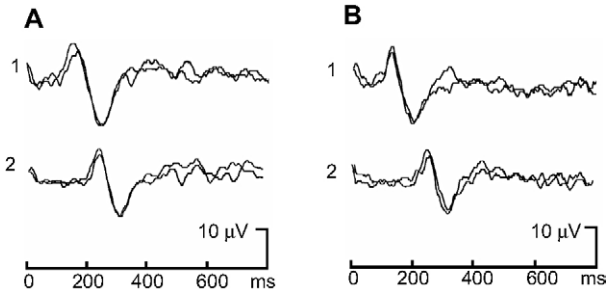

Figure 1 LEPs in a control subject and in a representative epileptic patient.
Trigeminal (1) and hand (2) LEPs in an age-matched control (A) and in a representative patient with epilepsy taking CBZ (B). Note the absence of significative differences. Stimulation of the perioral region (V2–V3) and of the dorsum of the hand. Two series of 10 artifact-free trials were collected and averaged off-line. Recordings from the vertex referenced to linked earlobes.

Statistics

Differences between normally distributed LEP data in patients and controls were evaluated with the unpaired *t*-test or analysis of variance (ANOVA). Correlations between LEP data and CBZ dose, CBZ plasma concentration, duration of treatment, or age were evaluated with the Spearman *R* correlation index for non-parametric data. Results are given as mean ± S.D.

Results

Although trigeminal-LEPs had a slightly longer latency in epileptic patients than in age-matched controls (173 ± 22 vs. 162 ± 14 ms), the difference failed to reach statistical significance ($P = 0.11$). There was no difference in amplitude between the two groups (27 ± 11 vs. 25 ± 11 μv, $P > 0.50$).

Hand-LEPs had a similar latency (N 242 ± 23 vs. 248 ± 22 ms) and amplitude (17 ± 9 vs. 19 ± 10 μv) in epileptic patients and controls ($P > 0.50$). However, we were unable to however, to identify hand-LEPs in three patients; these three patients were similar to the others with respect to CBZ dosages (600, 400, and 600 mg), CBZ plasma concentration (6, 8, and 6 μg/ml), age (29, 48, and 22 years), and background disease; none had clinical symptoms suggestive of a possible peripheral neuropathy.

In the epileptic patients, neither latency nor amplitude of trigeminal- or hand-LEPs correlated with the CBZ plasma concentration, daily CBZ dose (Fig. 2), or treatment duration ($P > 0.3$).

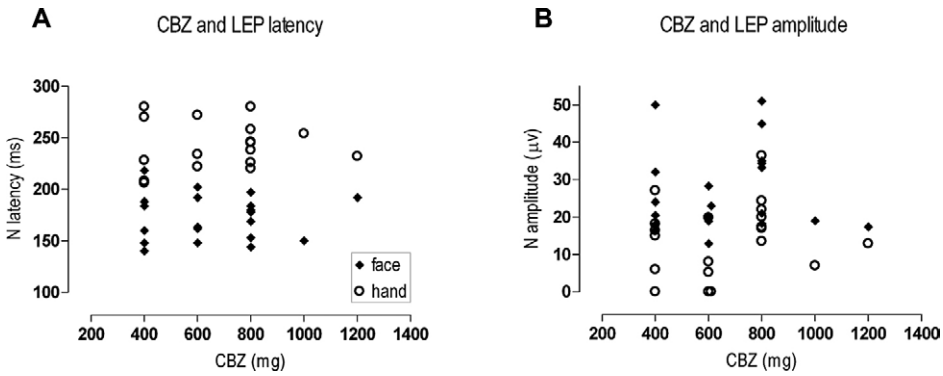

Figure 2 CBZ–LEP data correlations in patients with epilepsy.
Correlation between CBZ daily dose (CBZ, X-axis) and N latency (A) and amplitude (B) (Y-axis) of trigeminal and hand-LEPs in patients with epilepsy. Spearman R correlation index detected no correlation between latency or amplitude and CBZ dose ($P > 0.3$).

Discussion

Except for the lack of recordable hand-LEPs (for which we have no explanation) in three patients, we found no significant differences in trigeminal and hand-LEPs between epileptic patients and age-matched controls. More importantly, we found no correlation between LEP latency or amplitude and daily CBZ dose, CBZ plasma concentration, or treatment duration.

All patients had received CBZ in monotherapy for at least 1 year, at common therapeutic dosages, similar to those reported in the studies that found peripheral and central slowing of conduction [7,11]. All the previous studies, however, assessed large-fibre pathways. This is the first neurophysiological study investigating a possible effect of an AED on nervous conduction in pain pathways. The Aδ primary neurons might be more resistant to toxic effects because their proximal axon, ending in the spinal dorsal horn, is shorter than that of Aβ primary neurons, ending in the medulla; the longer the axon the greater the burden for the cell body and thus the neuron susceptibility to toxic perturbations.

In an earlier study [3], however, we found that CBZ indeed dampened trigeminal-LEPs in patients with trigeminal neuralgia, even the LEPs after stimulation of the non-painful side (the correlation between latency and CBZ dosage reached a $P < 0.0001$ level of significance).

Because the patients with TN in our previous study were older than the epileptic patients in this study, we cannot altogether exclude a possible effect induced by drug and age combined. Whereas the LEP amplitude is influenced by age [5], the absence of correlation between age and LEP latency stands against this hypothesis [3,5,12].

The lack of any correlation between LEP data and CBZ therapy in epileptic patients would suggest that the LEP attenuation seen in patients with trigeminal neuralgia, rather than being a toxic effect on nerve conduction or an unspecific lowering of central excitability, might be specific for some characteristic of trigeminal pathophysiology.

Further studies, investigating the early, lateralized LEP component (N1), may help to understand the CBZ effects.

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