ORIGINAL ARTICLE

Treatment of posttraumatic epilepsy with new generation antiepileptic drugs (AEDs) – our experience

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ABSTRACT

Aim To investigate influence of therapy with new generation antiepileptic drugs (AEDs) in fastening of posttraumatic epilepsy (PTE) remission comparing to therapy with standard AEDs, as well as the time to remission in the presence of psychiatric comorbidities.

Methods The study was conducted during the 1988-2008 period and included 113 patients (47 females and 67 males) with PTE and 113 patients (93 females and 20 males) suffering from complex partial seizures (CPS) of temporal lobe origin. In both patient groups, epileptic seizure phenotype, brain magnetic resonance imaging (1.5 T and 3.0 T) and electroencephalogram were analyzed within 24 hours of epileptic seizure and after 5 years of treatment. Psychological testing was administered prior to therapy initiation.

Results The patients treated with standard AEDs achieved remission in 82 (73%) cases as compared with 87 (77%) patients administered with a new generation AEDs; in the latter group, remission was achieved faster (1.85 *vs*. 1.6 months). In both patient groups, psychiatric comorbidity prolonged time to remission by 3.4 months.

Conclusion Therapy with new generation AEDs enables achieving faster and complete remission in PTE patients.

Key words: classification, epidemiology, surgery, therapy, traumatic brain injury

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INTRODUCTION

Cerebral cortex with the epileptic focus contains a large number of pathologically altered nerve cells (neurons), so called deafferented neurons, mostly lacking synapses (1-3). In the so called ‘’silent period’’ following brain injury, the process of epileptogenesis, including structural, biochemical and cellular alterations, takes place in the brain (4-12). Brain injury results in focal or diffuse brain hemorrhage and hemolysis during which ions are released from the hem iron, promoting neuronal lipid peroxidation, free radical release and their excitotoxic action, thus causing damage to the deoxyribonucleic acid (DNA) and causing epileptic seizures (7-12). According to posttraumatic timing of epileptic seizure onset, they are categorized as immediate, early and late seizures (8,12).

Previously, the treatment included prophylactic use of antiepileptic drugs but they did not prevent the development of the disease (13-15). Today, a lot of attention adds applying remedies that will allow patient quality of life, intellectual activity and avoiding psychological changes caused by drugs (14,15).

Previous observation showed that patients with posttraumatic epilepsy respond better to treatment with new antiepileptics than patients with other types of epilepsy (10-15).

The lack of similar studies in our environment, as well as the observation that people with posttraumatic epilepsy better respond to new than standard antiepileptics drugs (16-21) were reasons for conducting this study.

The aim of this study was to investigate influence of therapy with new generation antiepileptic drugs (AEDs) in fastening of posttraumatic epilepsy (PTE) remission comparing to therapy with standard AEDs, as well as the time to remission in the presence of psychiatric comorbidities

PATIENTS AND METHODS

Patients

The study included 113 PTE patients (46 females and 67 males) and 113 patients (93 females and 20 males) suffering from complex partial seizures of temporal lobe origin (control group) treated during the 1988-2008 period.

Data were collected retrospectively during 1988-2000 and prospectively during 2000-2008 periods. The end of the follow up was 2013. The data collected retrospectively were: history, initial electroencephalogram (EEG), brain magnetic resonance imaging (MRI) at one month of brain injury and after 5 years of treatment, and neuropsychological testing. The data collected prospectively were: follow up EEG and brain MRI after 5-year AED therapy, with continuous patient follow up at Epilepsy Clinic.

Phenotypes of analyzed epileptic attacks were included: elementary partial seizures (EPS) complex partial seizures (CPS), generalized tonic- clonic seizures (GTCS), elementary partial seizures with generalization (EPS+GS), complex partial seizures with generalization (CPA+GS) and mixed (different types of attacks: EPS,CPS,GTCS).

The frequency of seizures was compared before and after the introduction of AEDs. Each patient group was divided into two subgroups: treated with a standard AED (carbamazepine) and with administered new generation AED (lamotrigine), according to age and profession of the patients. For younger intellectually active patients lamotrigine was administered. For older intellectually not active patients carbamazepine was administered. According to the frequency of epileptic seizures before and after 5-years therapy, patients were divided into four categories: complete remission, one seizure per year, 2-5 seizures per year, and 6-10 seizures per year. According to the time of onset, seizures were divided into three categories, i.e. immediate onset seizures occurring within 24 hours of brain injury, early 24 h to 7 days after trauma and late onset seizures occurring after 24 hours of brain injury.

Prior to entering the study, all patients underwent neuropsychological testing by clinical psychologist using MMPI (Minnesota Multiphasic Personality Inventory) (2, 7-10, 13).

Medium dose of antiepileptics was carbamazepine 600 mg, lamotrigine 150 mg.

Before switching on the research, patients signed informed consents.

The survey was last approved the Ethics Committee of General Hospital “Dr.Josip Benčević”.

Methods

Brain injury was defined as mild (without loss of consciousness), moderate (with loss of consciou-

sness lasting for up to 30 min) or severe (with loss of consciousness lasting for more than 30 min and anterograde or retrograde amnesia) (3,14).

We analyzed the severity of craniocerebral trauma, neuroimaging MRI (normal, atrophy, gliosis), type of seizures for each group of patients and frequency of seizures, the type and dose of drugs that are administered, and EEG changes immediately after the trauma and after 5 years of therapy.

Study patients underwent native EEG (Nihon, Koden, Japan) and EEG with provocation tests (photic stimulation and hyperventilation) within 24 hours of the first seizure and after 5 years of AED therapy. EEG findings were classified into five categories: normal, diffusely dysrhythmic, focally altered, diffusely dysrhythmic with focus, and diffusely paroxysmal dysrhythmic with focus. Changes in EEG were analyzed before and after 5-year therapy.

In PTE patients, brain MRI was done at a clinical hospital at one month and 5 years of brain injury on 1.5 T and 3 T device (Magnetom, Siemens, Germany) and analyzed by neuroradiologist. In patients with complex partial seizures of temporal lobe origin, initial brain MRI was also performed on 1.5 T device and follow up brain MRI on 3 T device.

Statistical analysis

The methods of parametric statistics (for variables with normal distribution and quantitative data) and nonparametric statistics (for variables of non-normal distribution and qualitative data) were used. Mann-Whitney U test was used for differences between groups. The level of statistical significance was set at $p<0.05$.

RESULTS

A total of 226 patients were included in the study, i.e. 113 PTE patients (46 females and 67 males, mean age 43 years) and 113 patients with complex partial seizures of temporal lobe origin as control group (93 females and 20 males, mean age 30 years). According to severity brain injuries were determined as mild in 58 (51%) patients, moderate in six (5%) and severe in 49 (43%). According to the time of epileptic seizure onset, early seizures were found in 28 (25%) and late seizures in 85 (75%) patients.

Brain MRI findings were normal in 31 (27%) cases, while gliosis was found in 64 (57%), brain atrophy in 12 (11%), and both gliosis and brain atrophy in six (6%) cases. In the PTE group, the following types of seizures were recorded: elementary partial seizures (EPS) and complex partial seizures in nine (8%) cases each, generalized tonic-clonic seizures in 44 (GTCS) (38%), elementary partial seizures with secondary generalization (EPS+GS) in 11 (10%), complex partial seizures with secondary generalization in 38 (CPA+GS) (34%) and mixed (different types of attacks: EPS,CPS,GTCS) in two (2%) patients. In the group of patients with complex partial seizures of temporal lobe origin, the following types of seizures were recorded: EPS was detected in two (2%), CPS in four (4%), GTCS in 32 (28%), EPS+GS in nine (8%), CPS+GS in 57 (50%) and mixed in nine (8%) patients (Figure 1).

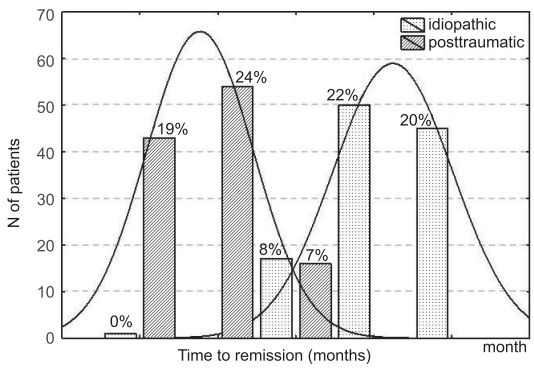

Figure 1. Time to remission in posttraumatic epilepsy versus idiopathic complex partial epilepsy patients

In the PTE group, 68 (60.2%) and 45 (39.8%) patients were on therapy with conventional AED and new generation AED, respectively. Remission was achieved in 82 (73%) patients administered with conventional AED and 87 (77%) of those administered with new generation AED. According to the time to remission, it was achieved at a mean of 1.6 months in PTE patients *versus* 1.85 months in patients with complex partial seizures of temporal lobe origin ($p<0.05$) (Figures 2,3)

Electroencephalography findingsm which were analyzed before and after 5-year AED therapy, did not yield any statistically significant difference between patient groups on conventional and new generation AEDs before and after therapy introduction, but did point to a reduced severity of EEG changes.

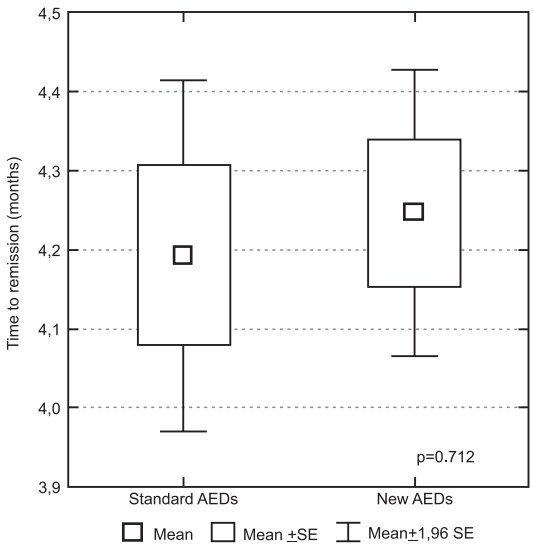

Figure 2. Time to remission in idiopathic complex partial epilepsy patients with standard AEDs (antiepileptic drugs) versus new generation AEDs
SE, standard error

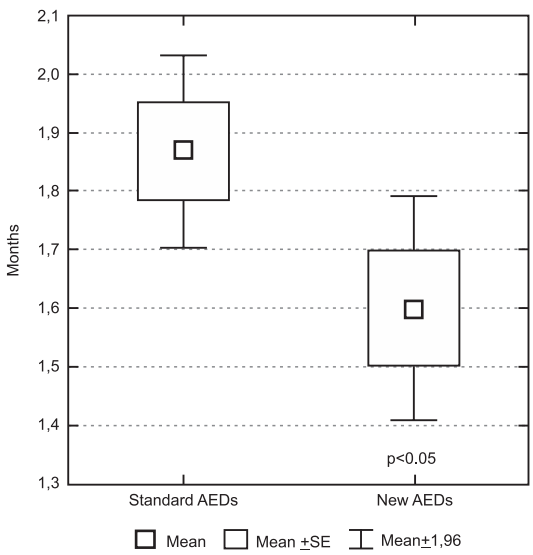

Figure 3. Time to remission in posttraumatic epilepsy patients with standard AEDs (antiepileptic drugs) versus new generation AEDs

The time to remission of 3.4 months was found significantly prolonged in patients diagnosed with psychiatric comorbidities comparing to patients with posttraumatic epilepsy on standard AEDs (p 0.712 vs 0.05). In patients on standard AEDs time to remission was longer than in patients on new AEDs (Figure 1).

DISCUSSION

In the present study, we assessed justifiability of prophylactic administration of conventional AEDs for prevention of PTE. Many studies with new generation AEDs (topiramate, gabapentin and levetiracetam) point to their neuroprotective effect and suggest their prophylactic use to be relatively justifiable (7-11). Randomized clinical trials investigating justifiability of using conventional AEDs (phenytoin, phenobarbital and carbamazepine) in comparison to control groups administered with placebo found the prophylactic use of AEDs to be justified for prevention of early epileptic seizures, whereas decision on chronic AED therapy (conventional or new generation AEDs) should be made upon making the diagnosis of PTE and depending on the risk factors for the disease development (15-28).

Studies comparing conventional and new generation AEDs administered after brain injury report on the beneficial effects of new generation AEDs on faster remission by preventing formation of the so called 'epileptic neuron' and good drug tolerance (1, 8-11, 22,25,27,28).

Our study results were consistent with these reports. In PTE patients, remission was achieved faster with the use of a new generation AED as compared with a conventional AED, i.e. in 1.4-1.8 months *versus* 1.7-2.0 months.

Analysis of EEG changes before and after 5-year therapy yielded significant difference in the severity of EEG changes in both patient groups administered with standard and new generation AEDs in terms of reduced grade of EEG changes with the improvement and in the application of standard and new drugs. There was no difference in the EEG changes depending on the type of drugs used.

The world incidence of epilepsy in the general population is 1% (17-20). The town of Slavonski Brod and surroundings has 75,000 population, so 750 patients with epilepsy would be expected. According to current literature, PTE patients account for 5% of all epilepsy patients (21-24). During the 1988-2008 period, 1000 epilepsy patients were recorded at the Epilepsy Clinic of our General Hospital. The number of epilepsy patients was greater than expected, and the proportion of PTE patients (11.3%) also exceeded literature data (25-30).

In conclusion, this study confirms previous investigations that PTE patients treated with a new

generation AED achieved remission considerably earlier than those administered with a conventional AED, with the time to remission being prolonged by the presence of psychiatric comorbidities. The application of new antiepileptic drugs, especially in presence of psychiatric comorbidity is recommended.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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Liječenje posttraumatske epilepsijeantiepilepticima nove generacije – naša iskustva

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SAŽETAK

Uvod Istražiti utjecaj antiepileptika nove generacije u postizanju remisije posttraumatske epilepsije (PTE) u usporedbi sa standardnim antiepilepticima, kao i utjecaj izraženih psihijatrijskih poremećaja na postizanje remisije bolesti.

Metode U istraživanje, provedeno u razdoblju od 1988. do 2008. godine, bilo je uključeno 113 pacijenata (47 ženskih i 67 muških) s PTE-om i 113 bolesnika (93 ženskih i 20 muških) s kompleksnim parcijalnim napadajima temporalnog ishodišta. U obje skupine bolesnika analiziran je fenotip epileptičnih napadaja magnetskom rezonancom (1.5 T i 3,0 T) i elektroencefalogramom 24 sata od epileptičkog napadaja i nakon 5 godina liječenja. Psihološko testiranje je primijenjeno prije početka terapije.

Rezultati Pacijenti oboljeli od PTE-a, liječeni standardnim antiepilepticima, postigli su remisiju u 82 (73%) u usporedbi s 87 (77%) bolesnika koji su primili antiepileptike nove generacije; u potonjem, remisija je postignuta brže (1,85 *vs*. 1,6 mjeseci). U obje skupine bolesnika psihijatrijski komorbiditet produžio je vrijeme postizanja remisije za 3,4 mjeseca.

Zaključak Terapija antiepilepticima nove generacije omogućuje postizanje brže i potpune remisije u pacijenata s PTE-om.

Ključne riječi: klasifikacija, epidemiologija, kirurgija, terapija, traumatska ozljeda mozga