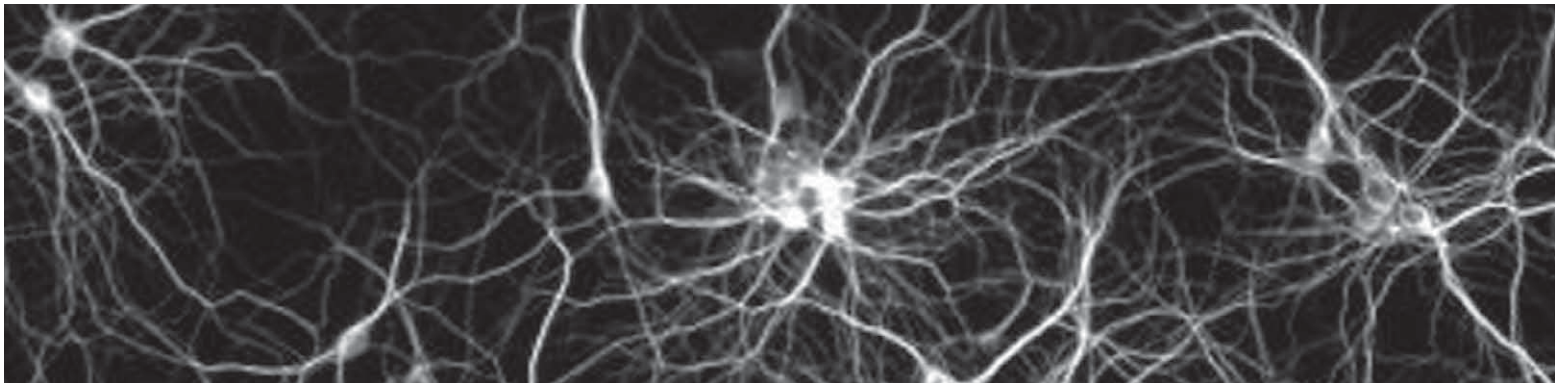

Efficacy of carbamazepine and oxcarbazepine co-administration in the treatment of epilepsy

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ABSTRACT – *Objectives:* Carbamazepine (CBZ) and oxcarbazepine (OXC) are first-line antiepileptic drugs (AEDs) for partial and generalized seizures with focal onset. However, from the pharmacodynamic and pharmacokinetic point of view, CBZ and OXC are not identical medications. As CBZ and OXC nonetheless differ, their co-administration should be considered in pharmacoresistant patients. *Methods:* We performed a retrospective study with the aim to determine the efficacy of concurrent administration of CBZ and OXC in the treatment of pharmacoresistant patients with partial epilepsy. The study included 24 patients in whom former a combination of other first- and second-line AEDs for partial seizures had been ineffective. The mean follow up time was 23.50±8.81 months. The majority (72.9%) of patients had symptomatic epilepsy and the mean disease duration was 22.29±15.30 years. The efficacy was estimated 6 months after therapy introduction. *Results:* The number of seizures before combined CBZ + OXC therapy introduction was higher (8.47±8.52) compared to the number of seizures after therapy introduction (4.49±5.44) and the difference was statistically significant (p=0.015). The combination of OXC and CBZ yielded improvement. Reduction of seizures (25%-99%) was recorded in 50% of patients. Clinically significant seizure reduction by ≥50% was observed in 29.17% of patients. The most common side effects were drowsiness, vertigo and hyponatremia, which was not clinically significant. *Conclusions:* Our study demonstrated the efficacy of combined CBZ and OXC therapy, notably in pharmacoresistant partial epilepsy, with recommendation of using lower doses, which leads to better tolerance and avoidance of adverse effects.

Key words: carbamazepine, oxcarbazepine, epilepsy, pharmacoresistance

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INTRODUCTION

Carbamazepine (CBZ) and oxcarbazepine (OXC) are first-line antiepileptic drugs (AEDs) for partial and generalized seizures with focal onset. However, from the pharmacodynamic and pharmacokinetic point of view, CBZ and OXC are not identical medications. Carbamazepine (CBZ) is an iminodibenzyl derivative (10,11-dihydro 5H-dibenzo(b,f) azepine). The mechanism of action of CBZ is based on binding to voltage-dependent sodium channels, both pre- and post-synaptic, causing channel blocking and blockage of high-frequency discharges and excitatory transmission. The main metabolic pathway is first epoxidation in carbamazepine 10,11-epoxide, then hydrolysis in carbamazepine 10,11-trans-dihydrodiol, followed by glucuronidation and sulfuration. The main path of epoxidation is *via* cytochrome P450 CYP3A4. During treatment, some adverse effects can occur in 30%-50% of patients treated with CBZ, however, these are mostly mild, not requiring therapy interruption. However, about 5% of patients must cease therapy due to severe adverse effects. Most frequent adverse effects are drowsiness, general fatigue, dizziness, ataxia, diplopia, sedation, insomnia, tremor, impotence, leucopenia, hyponatremia, rash and other skin reactions (including Stevens-Johnson and Lyell syndromes) (1,2).

Oxcarbazepine is a 10-keto derivative of carbamazepine (10,11-dihydro-10-oxo-5H-dibenz(b,f)azepine-5-carboxamide). Pharmacological activity of OXC is exclusively through the main action metabolite 10-monohydroxy derivative (MHD). The main action mechanism is, as in CBZ, blockage of voltage-dependent sodium channels, which results in stabilization of neural membrane, inhibition of repeated neural discharges and prevention of discharge spreading. In contrast to CBZ, MHD amplifies potassium conductivity and modulates high voltage types of calcium channels. It acts similarly to CBZ upon NMDA receptors, but without greater impact upon serotonergic, GABA and acetylcholine receptors. In contrast to CBZ, OXC has no auto induction. OXC has actually emerged as the result of aimed search for structured variation of CBZ, all with the goal of eliminating epoxide CBZ metabolites responsible for the occurrence of most adverse effects. The elimination half-life is 8-10 hours (1-4). The main adverse effects of OXC are basically similar to those of CBZ. However, OXC is better tolerated when compared to standard CBZ formula, and in comparison with CR preparation did not show substantial differences. Discontinuation rate was still significantly lower for OXC compared to CBZ (14%-26%). Regarding its role in add-on therapy in clinical studies, a higher frequency of cessation was found in higher doses of the drug, at percentages of 12%, 36% and 67% for the doses of 600, 1200 and 2400 mg, respectively (5). The main adverse affects are headache, dizziness, nausea, ataxia, diplopia and hyponatremia, and of the severe ones skin rash occurs in approximately 5% of cases, in comparison with 10%-15% for CBZ.

PATIENTS AND METHODS

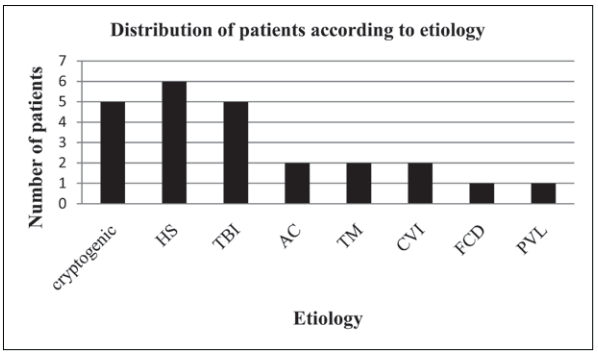
At the Referral Centre for Epilepsy of the Ministry of Health of the Republic of Croatia at the Department of Neurology, Zagreb University Hospital Centre, we performed a retrospective study with the aim of determining the efficacy, optimum doses and tolerability of co-administration of CBZ and OXC in the treatment of pharmacoresistant patients with partial epilepsy with or without secondary generalization. Twenty-four patients in whom former administration of a combination of other first- and second-line AEDs for partial seizures had been ineffective were included in the study conducted during the 2009-2013 period. The follow up period was 6 to 37 months. The efficacy was estimated 6 months after therapy introduction. In the cases where the doses of drugs in the mentioned period were increased, additional follow up period was 3 months after dose correction. Statistical analysis was done by using the IBM SPSS Statistics 20 statistical package. Quantitative variables were expressed as arithmetic mean and standard deviation (SD). Qualitative variables were expressed as prevalence and percentage (%). Student's t-test was used for comparison among subunits for quantitative variables. The relation of individual variables that were partly qualitative and partly quantitative was evaluated by Spearman correlation coefficient (r_s). The probability value of p=0.05 was considered statistically significant.

An informed consent was obtained from all patients included in the study.

RESULTS

Twenty-four patients (15 male and 9 female) with pharmacoresistant partial epilepsy were included in the study, seven of them without and 17 with secondary generalized seizures. The majority (n= 19; 72.9%) had symptomatic epilepsy. Considering seizure etiology, most of the patients had hippo-

campal sclerosis (n=6), followed by traumatic brain injury (n=5), arachnoidal cysts (n=2), tumors (n=2), stroke (n=2), focal cortical dysplasia (n=1) and perinatal vascular lesions (n=1) (Fig. 1). Some of the patients with positive brain magnetic resonance imaging (MRI) results were operated on after the follow up period. The results regarding clinical outcome following epilepsy surgery are beyond the scope of this article. The mean patient age was 40.96±14.99 years, mean duration of disease 22.29±15.30 years, and mean follow up period 23.50±8.81 months. The majority of patients (50%) had one additional AED besides the mentioned combination, 33.3% had another two AEDs, and 12.5% had three additional AEDs. Only one patient was administered exclusively the combination of CBZ and OXC. Additional AED mostly was lamotrigine (LTG) (n=15), followed by valproate (VPA) (n=10) and methylphenobarbitone (MPB) (n=6). The mean CBZ dose was 750.00±284.37 mg, with the mean CBZ serum concentration of 26.55±10.65 μmol/L (therapeutic concentration 17-50 μmol/L). CBZ was in therapeutic range in 79.2% of patients (n=19), 12.5% of patients (n=3) had CBZ below therapeutic range, whereas 4.2% of patients (n=1) had CBZ slightly above therapeutic range. The mean dose of OXC was 1012.50±403.58 mg with the mean OXC serum concentration of 42.43±19.42 μmol/L (therapeutic concentration 24-140 μmol/L). In the majority of patients (79.2%; n=19), OXC was in therapeutic range, whereas in 20.8% (n=5) OXC was below therapeutic range.



HS – hippocampal sclerosis; TBI – traumatic brain injury; AC – arachnoidal cyst; TM – tumor; CVI – cerebrovascular insult; FCD – focal cortical dysplasia; PVL – perinatal vascular lesions

Fig. 1. *Patient distribution according to etiology.*

The mean number of epileptic seizures *per* month before the introduction of combined CBZ + OXC therapy was 8.47±8.52 and the number of seizures *per* month after the introduction of the mentioned therapy was lower, 4.49±5.44 (Fig. 2). The difference was statistically significant (p=0.015). Comparison of the mean number of seizures before and after the introduction of dual therapy (OXC + CBZ) showed improvement. Significant reduction in the number of seizures was observed in 50% of patients (n=12); 20.83% (n=5) of them had minimal improvement, i.e. 25%-49% seizure reduction. In 16.67% of patients (n=4), there was 50%-74% seizure reduction, whereas 12.50% of patients (n=3) had ≥75% seizure reduction (Fig. 3). Clinically significant ≥50% seizure reduction was observed in 29.17% of patients (n=7). There was no aggravation of seizures in any patient. The median of improvement was 22.50%.

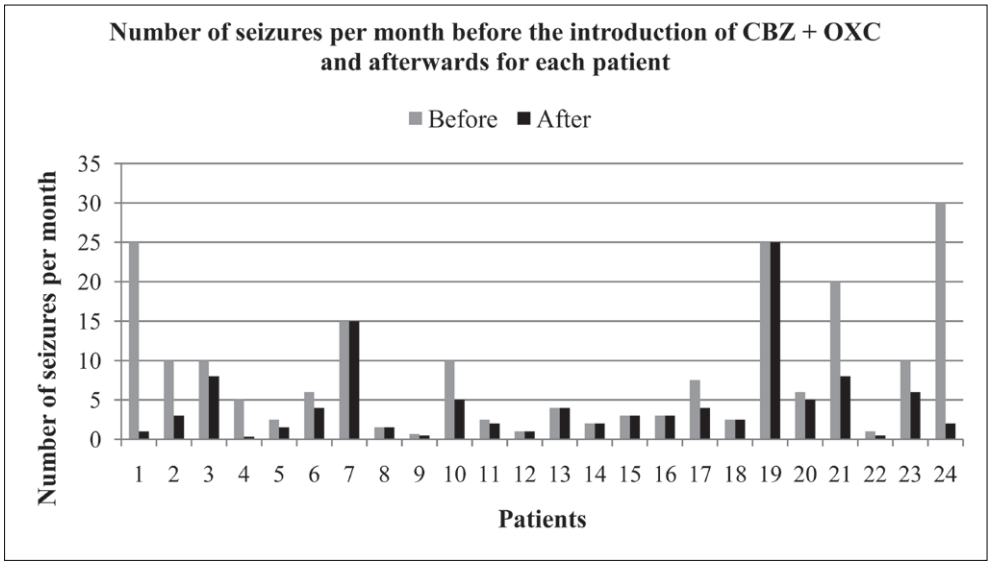


Fig. 2. *The number of seizures per month (0-30) before the introduction of CBZ + OXC therapy was higher compared to the number of seizures after therapy introduction; the difference was statistically significant (p=0.015).*

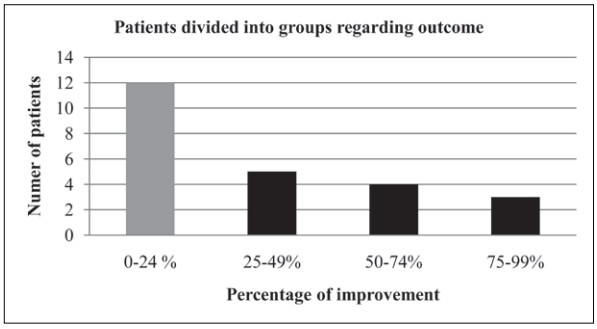


Fig. 3. *Patients divided into groups according to outcome; total reduction in the number of seizures by 25%-99% was observed in 50% (n=12) of patients.*

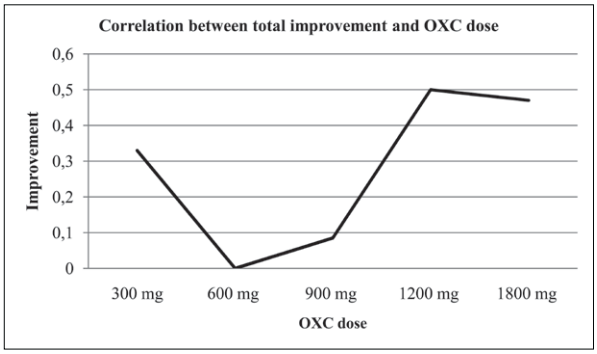


Fig. 4. *Statistically significant correlation between total improvement (%) and OXC dose (mg) (r_s=0.546; p=0.006).*

The following adverse effects were recorded: drowsiness (n=4), vertigo (n=3), hyponatremia (n=3), with a note that the lowest Na value was 121 mmol/L, then diplopia (n=2), vision disturbances (n=1), nausea and vomiting (n=1). In three patients, adverse effects disappeared upon decreasing the dose of one of the drugs. Therapy was ceased in 41.70% of patients (n=10), in 29.2% (n=7) of them due to inefficacy, in 8.3% (n=2) due to adverse effects, whereas in 4.2% (n=1) there was no clear cause (non-compliance); 58.3% of patients (n=14) continued to take combined CBZ + OXC therapy.

On comparing the two groups of patients regarding seizure types, i.e. the group with partial seizures with secondary generalization and the group with partial seizures without secondary generalization, there was no statistically significant difference in the treatment outcome. There was no statistically significant difference in the outcome regarding seizure etiology, i.e. whether it was cryptogenic or symptomatic epilepsy, either. When compared whether there was more significant improvement if LTG was added to the mentioned CBZ + OXC combination (n=15), no statistically significant difference was found. However, a correlation was found between overall outcome and OXC dose, i.e. the higher the OXC dose, the better was seizure reduction (r_s=0.546; p=0.006) (Fig. 4). There was no statistically significant correlation between overall outcome and CBZ dose (r_s=-0.215; p=0.312).

DISCUSSION AND CONCLUSION

From the pharmacodynamic point of view, CBZ and OXC are not identical medications (6). CBZ binds doubly to plasma proteins than the active OXC metabolite MHD, so OXC is a more effective drug. In contrast to CBZ that oxidizes *via* cytochrome P-450 system, OXC yields to reduction metabolism of MHD that is glucuronidated and extracted through urine. The influence of liver cytochrome P-450 upon OXC metabolism is minimal. This explains why the combination with other AEDs, e.g., VPA, could be more efficacious, i.e. why the combined administration of OXC and CBZ should be effective. CBZ has a shorter elimination half-life, particularly when combined with other enzyme inducing AEDs, which can cause significant fluctuation of CBZ serum concentration and the occurrence of adverse effects. Daily fluctuation of MHD concentration is relatively low, lower than expected regarding the half-life of MHD elimination, with the note that relatively large fluctuations can be seen in some patients. The OXC concentration is much less affected by some other conventional AEDs such as VPA, phenobarbitone (PB) and phenytoin (PHT). Therefore, the oscillation in concentrations of OXC and its metabolite MHD is much less expressed than in CBZ (7). Thus, instead of increasing the CBZ dose, it would be justified to add lower OXC doses.

Oxcarbazepine is used in monotherapy for all types of partial seizures with or without secondary generalizations, as well as in add-on therapy. Also, OXC proved to be the optimal therapeutic choice in patients with refractory partial epilepsy, where seizure reduction by 27%-29% was achieved at the minimal OXC dose of 1200 mg (5,8). Add-on therapy with OXC in pharmacoresistant epilepsies brought to seizure reduction, by more than 50% in 20%-50% of patients, and was dose dependent. At the dose of 600 mg, the seizure reduction by 27% was achieved, at the dose of 1200 mg it was 41%, and at the dose of 2400 mg it was 50%. Adverse effects were also dose dependent, so that the percentage of adverse effects ranged from 91% to 72% at the dose of 2400 mg, 90% to 76% at the dose of 1200 mg, and without substantial difference in adverse effects at the drug dose of 600 mg. This indi-

cates that drug adverse effects are more pronounced at higher doses (5).

As it has been undoubtedly proven that the adverse effects of CBZ and OXC administration are dose dependent and more pronounced in higher doses of both AEDs, and there are evident differences in the action mechanisms of both drugs, it seems reasonable to consider co-administration of both drugs at somewhat lower individual doses.

As CBZ is extensively metabolized through the liver, it could be hepatotoxic. These adverse effects could be diminished and avoided by lowering the CBZ dose and adding OXC that is not hepatotoxic. This is particularly important in elderly patients with reduced liver function who also take some potentially hepatotoxic medications (statins, non-steroidal antirheumatics).

A relatively frequent adverse effect of OXC (but less common in CBZ) is hyponatremia. A study including 75 patients with normal sodium levels at the onset of OXC therapy showed that 26% of patients had mild decrease in sodium levels. A more pronounced decrease under 125 mmol/L was recorded in 2.6% of patients, whereas 1.3% had symptomatic lowering (9). The mechanism of hyponatremia occurrence is possibly a sequel of inappropriate antidiuretic hormone secretion (10). Some investigations suggest that it may be a direct impact of OXC on renal tubules, with the occurrence of reduced excretion of free water leading to relative drop of sodium concentration (11). In younger patients, no clear correlation of hyponatremia, age, concomitant use of other drugs, serum concentration of active substance and OXC dose was found (10,11). In adults and elderly persons, hyponatremia is related to dose, possibly due to weakened renal function that can cause more expressed hyponatremia at a higher drug level, particularly if the patient concomitantly takes medications such as diuretics, antidepressants or non-steroidal antirheumatics (12). Thus, in case of hyponatremia, the OXC dose should be lowered along with the addition of a lower CBZ dose with the aim of achieving satisfactory therapeutic effect.

Carbamazapine and OXC have shown poorer efficacy in the treatment of older people, taking into account seizure reduction and drug withdrawal during the study due to adverse effects and inefficacy. In elderly, the half-life of drug elimination is longer. CBZ clearance is lower, so smaller doses are required. Sedative effect of a drug can diminish its tolerability, thus therapy should be commenced with a very low dose (100 mg/day) and titrated up to the total of 400 mg/day, divided into two daily doses (13). As OXC does not lead to the occurrence of epoxide metabolites responsible for the majority of CBZ adverse effects, it has been proven safe for use in elderly patients. Also, it is recommended to start with a low dose with gradual increase to 600 mg/day divided in two daily doses, which can be raised in case of clinical indication. Among adverse effects in elderly people, a higher risk of hyponatremia has been observed with the concurrent use of diuretics, followed by skin rash, nausea, vertigo and vomiting. CBZ as the cell membrane stabilizer increases the risk of cardiac arrhythmia, and its anticholinergic effect can precipitate urinary retention. It is possible that the OXC and CBZ combination could also give better results in this indication with lower individual doses of both AEDs causing fewer adverse effects.

Along with the impact on voltage dependent sodium channels, CBZ and OXC can block neuronal nicotine receptors. Due to this capacity, they can be used in the treatment of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). ADNFLE is an autosomal dominant disorder for which two genes have been identified, CHRNA4 and CHRNB2 that code neuronal nicotine acetylcholine receptor α4 and β2 subunits. CBZ inhibits α4β2, α2β2 and α2β4 receptors and thus achieves good effect upon neuronal nicotine receptors, but has various effects on particular subunits. OXC mostly affects α4β2, if in therapeutic concentrations, and somewhat less α2β4 subunit. As CBZ is the drug of first choice in the treatment of ADNFLE but proved ineffective in 30% of cases, probably because of different impact on individual subunits of nicotine acetylcholine receptors, as well as their variable expression in particular ADNFLE cases, co-administration of OXC and CBZ would make sense regarding specific blockage of individual subunits (14,15). By using the usual OXC doses, the appropriate concentration of MHD in cerebrospinal fluid for the inhibition of nicotine receptors is achieved. It could not be reached with CBZ without adverse effects related to higher drug doses.

Taking in account all the differences between CBZ and OXC, their mechanisms of actions and indications mentioned above, the question arises whether this combination would be more effective than the administration of each of these two AEDs alone, particularly in the treatment of pharmacoresistant epilepsies (16-21).

On review of the available literature, we found no studies that measured the efficacy of combined CBZ and OXC administration in reducing epilep-

tic seizures. Our study showed the mentioned combination to be justified, particularly in pharmacoresistant partial epilepsies with or without secondary generalization.

In our study, the combination of OXC and CBZ yielded improvement in 50% of patients (n=12), i.e. reduction of seizures by 25%-99%. Clinically significant seizure reduction by ≥50% was observed in 29.17% of patients. There was no aggravation of seizures in any patient. It should be mentioned that these were mainly the cases of pharmacoresistant partial epilepsies with the average disease duration of 22 years, in whom former administration of a combination of other first- and second-line AEDs for partial seizures had been ineffective. Considering seizure etiology, most of the patients had hippocampal sclerosis (25%). There is the possibility that in non-pharmacoresistant patients even better efficacy could be achieved. The most common adverse effects were drowsiness, vertigo and hyponatremia that was not clinically significant. In 21.4% of patients side effects disappeared upon decreasing the dose of one of the drugs, whereas in only 8.3% of patients therapy was discontinued due to adverse effects. A statistically significant correlation was observed between the OXC dose and reduction of seizure number, i.e. the higher the OXC dose, the better efficacy was recorded. The average dose was 1012 mg. A somewhat higher dose would probably display even better efficacy, thus the recommendation may be to use the total OXC dose of 1200 mg (possibly up to 1500 mg), and in older groups 600-900 mg *per* day. The average CBZ dose was 750 mg, and the recommend total CBZ daily dose would be 600-800 mg, and 400 mg in the elderly. The introduction of drugs should be gradual, and in reaching the recommended doses monitoring serum concentration of both medications is advised.

As it is undoubtedly the issue of two AEDs with different action mechanism, their co-administration proved justified, particularly in some types of epilepsy. Our study also demonstrated the efficacy of combined CBZ and OXC therapy, notably in pharmacoresistant partial epilepsy, with the recommendation of using lower doses, which leads to better tolerability of both drugs.

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Učinkovitost istodobne primjene karbamazepina i okskarbazepina u liječenju epilepsije

SAŽETAK – *Cilj*: Karbamazepin (CBZ) i okskarbazepin (OXC) su antiepileptici prvog izbora za parcijalne (žarišne) i generalizirane epileptične napadaje. Međutim, s farmakodinamskog i farmakokinetskog stajališta CBZ i OXC nisu jednaki lijekovi. S obzirom na to da se CBZ i OXC ipak razlikuju, njihovu istodobnu primjenu treba razmotriti u slučaju farmakorezistentnih bolesnika. *Metode*: Proveli smo ovo retrospektivno istraživanje kako bismo utvrdili učinkovitost istodobne primjene CBZ i OXC u liječenju farmakorezistentnih bolesnika s parcijalnom epilepsijom. Istraživanje je obuhvatilo 24 bolesnika kod kojih se prethodna kombinacija antiepileptika prvog i drugog izbora za parcijalne epileptične napadaje pokazala neučinkovitom. Srednje vrijeme praćenja bilo je 23,50±8,81 mjeseci. Većina bolesnika (72,9 %) imala je simptomatičnu epilepsiju, a srednje trajanje bolesti bilo je 22,29±15,30 godina. Učinkovitost liječenja procijenjena je 6 mjeseci od uvođenja terapije. *Rezultati*: Broj napadaja prije uvođenja kombinirane terapije lijekovima CBZ i OXC bio je viši (8,47±8,52) u usporedbi s njihovim brojem nakon uvođenja ove terapije (4,49±5,44), a razlika je bila statistički značajna (p=0,0159). Kombinacija lijekova OXC i CBZ rezultirala je poboljšanjem. Smanjenje napadaja (25%-99 %) zabilježeno je u 50 % bolesnika. Klinički značajno smanjenje napadaja za ≥50 % utvrđeno je u 29,17 % bolesnika. Najčešće nuspojave bile su pospanost, vrtoglavica i hiponatremija, ali nisu bile klinički značajne. *Zaključak*: Naše istraživanje je pokazalo učinkovitost kombinirane terapije lijekovima CBZ i OXC, osobito kod farmakorezistentne parcijalne epilepsije, uz preporuku davanja nižih doza koje se bolje podnose, a ujedno se izbjegavaju nuspojave.

Ključne riječi: karbamazepin, okskarbazepin, epilepsija, farmakorezistencija