3. SUMMARY

Epilepsy is one of the most common neurological diseases affecting approximately 50 million people worldwide. Mortality among patients, particularly those aged 40–50, is two- or three fold higher than in the general population. At least one-third of patients suffer from drug-resistant epilepsy, where polytherapy is necessary to control seizures. Unfortunately, despite the introduction of many new antiepileptic drugs, seizures in patients with drug-resistant epilepsy cannot be controlled in a satisfactory manner. Moreover, increasing adverse effects of antiepileptic therapy significantly reduces the patients' quality of life. Thus, new potential antiepileptic drugs should be still searched for among other classes of medications, which may act synergistically with commonly used therapeutics. Experimental seizure animal models and isobolographic analysis are the methods to assess safety and efficacy of tested drug combinations. Isobolographic analysis is considered as the "gold standard" to determine a real type of drug interactions.

The aim of the present study was to determine the characteristic of interactions between mexiletine, an antiarrhythmic drug, and new antiepileptic drugs (oxcarbazepine, lamotrigine, pregbalin, topiramate) in the maximal electroshock test in mice (MES). The drugs were administered in three proportions (1:1, 1:3, 3:1) of ED_{50} doses. Type I of isobolographic analysis was used to assess drug-drug interactions. Acute adverse effects of mexiletine and its combinations with the studied antiepileptic drugs were evaluated in the chimney test (examining the influence of drugs on motor coordination) and step-through passive-avoidance task (assessing the effect of the drug on long-term memory). Brain concentrations of antiepileptic drugs were also measured so as to determine any pharmacokinetic contribution to the observed effects.

Experimental evidence indicates that mexiletine exhibits anticonvulsant activity in the maximal electroshock-induced seizures in mice. Moreover, the isobolographic analysis revealed synergistic interactions between: mexiletine and pregabalin (at the dose ratios of 1:1 and 3:1), mexiletine and topiramat (1:3, 1:1; 3:1). Additivity was found in combinations of mexiletine with oxcarbazepine as well as mexiletine with lamotrigine in all three fixed-dose ratios of 1:3, 1:1, and 3:1. Interaction between mexiletine and pregabalin in the proportion of 1:3 was also additive. In the most tested combinations mexiletine did not change concentration

of antiepileptic drugs in the brain tissue, so the nature of these interactions can be considered as purely pharmacodynamic. The mixture of mexiletine with pregabalin and oxcarbazepine at the fixed-ratio of 1:3 as well as in combination with topiramat at the fixed ratio of 1:1 resulted in reducing the concentration of anticonvulsants in the brain. However, despite revealed pharmacokinetic interactions, the drugs acted additively or synergistically in terms of seizures supression.

Mexiletine alone, or in combinations with oxcarbazepine, lamotrigine and topiramate did not impaired motor coordination or affected long-term memory. However, pregabalin, administered alone or in combinations with mexiletine had significant impact on motor coordination. The 25% reduction of pregabalin dose in fixed ratio of 3:1 seems to reduce percentage of mice with impaired motor coordination caused by pregabalin.

In conclusion, mexiletine may be useful as a adjunctive antiepileptic medication in combination with oxcarbazepine, lamotrigine, pregabalin and topiramate. It should be emphasized that favorable interactions between tested drugs may lead to reduction of adverse effects of applied anticonvulsants without losing their activity. Nevertheless, clinical trials are necessary to assess safety and efficacy of the studied drug combinations.