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Original article

Influence of propafenone on the anticonvulsant activity of various novel antiepileptic drugs in the mouse maximal electroshock model

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ABSTRACT

Background: The main mechanism of action of propafenone (antiarrhythmic drug) involves the inhibition of the fast inward sodium current during phase 0 of the action potential. Sodium channel-blocking activity is also characteristic for some antiepileptic drugs. Therefore, it could be assumed that propafenone may also affect seizures. In the present study, we evaluated the effect of propafenone on the protective effect of oxcarbazepine, lamotrigine, topiramate and pregabalin against the maximal electroshock-induced seizures in mice.

Methods: Anticonvulsant activity of propafenone was assessed with the maximal electroshock seizure threshold (MEST) test. Influence of propafenone on the anticonvulsant activity of antiepileptic drugs was estimated in the mouse maximal electroshock model (MES). Drug-related adverse effects were determined in the chimney test (motor coordination) and passive-avoidance task (long-term memory). Brain concentrations of antiepileptics were assessed by fluorescence polarization immunoassay.

Results: Propafenone at doses 60–90 mg/kg significantly increased the threshold of seizures, in turn at doses 5–50 mg/kg did not affect this parameter. Administration of propafenone at the subthreshold dose of 50 mg/kg increased antielectroshock activity of oxcarbazepine, topiramate and pregabalin, but not that of lamotrigine. As regards adverse effects, propafenone alone and in combination with antiepileptic drugs did not significantly impair motor coordination or long-term memory in mice. Propafenone (50 mg/kg) significantly increased the brain level of pregabalin. Brain concentrations of topiramate and oxcarbazepine were not affected.

Conclusion: Our findings show that propafenone has own anticonvulsant action and enhances efficacy of oxcarbazepine, topiramate and pregabalin, but not that of lamotrigine, at least in experimental condition.

Introduction

Among patients with epilepsy about 42% also suffer from cardiac arrhythmias, of which the most commonly observed is tachycardia [1]. The basis for co-occurrence of the two disorders may be some similarities in their pathogenesis resulting from their common function – conductivity [2,3]. Abnormal electrical activity of a certain group of brain neurons may lead to epileptic attacks, while hyperactivity of cardiac pacemaker cells results in tachycardia/tachyarrhythmia [4,5]. Cardiac conduction system cells have a structure different from cardiomyocytes and contain membrane ion channels resembling those found in neurons [6]. Although both cardiac and neural action potentials are associated with shifts of Na^+ and K^+ ions, there are some considerable differences between them. One major difference is the duration of the action potentials. In neurons, it lasts around 1 ms, while in cardiac conduction cells it ranges from 200 to 400 ms. Another difference is the role of calcium ions, which are involved in the initial depolarization phase of the action potential in cardiac pacemaker, but not in neurons [2,3].

Interestingly, one of the reasons for both arrhythmias and epilepsy can be a mutation of genes encoding Na^+, K^+ and Ca^{2+} ion channels [7]. Continuing, it was noted that disturbed homeostasis of the central autonomic nervous system, which occurs during seizures, may cause ictal and interictal cardiac disturbances [8]. Serious cardiac arrhythmia co-existing with seizures is considered the most common reason for sudden unexpected death in epilepsy (SUDEP) [9,10]. In addition, epilepsy may slightly increase the risk of cardiac infarction incidence [11]. In patients with long-lasting epilepsy, the interictal cardiac changes were observed, including prolongation of QT, decreased heart rate variability (HRV), subtle

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signs of ischemia (ST-segment depression) and ventricular late potentials [12].

Aforementioned data underlines possibility of interactions between antiarrhythmic and antiepileptic drugs. Firstly, the two groups of medicines may be often used concomitantly. Secondly, such drugs may share some basic mechanisms of action. Phenytoin is considered not only as antiepileptic, but also as antiarrhythmic medication. In our opinion, this is a rationale for examining interactions between antiepileptic and antiarrhythmic drugs in animal models of epilepsy.

Propafenone, investigated in this study, belongs to class 1C antiarrhythmic drugs and is used in the treatment of supraventricular arrhythmias. The drug stabilizes cardiac cell membranes presenting some features of local anaesthetics. However, the main mechanism of action involves the inhibition of the fast inward sodium current during phase 0 of the action potential. Moreover, propafenone weakly blocks β-adrenoceptors, its activity in humans corresponds to about 1/50 of the activity of propranolol [13]. Regarding influence on sodium transport, propafenone blocks *sodium channel protein type 5 subunit alpha.* Some antiepileptic drugs as phenytoin and carbamazepine also block sodium channels, however, in a subtly different manner [14–16]. Sodium channel-blocking activity is characteristic for some antiepileptic and antiarrhythmic drugs [17,18]. Therefore, it could be assumed that propafenone may also affect seizures.

In our previous study, we demonstrated that propafenone at its subthreshold doses enhanced the antielectroshock activity of classical antiepileptic drugs, i.e. valproate, carbamazepine, phenytoin and phenobarbital [19]. This encouraged us to extend experiments to some new generation antiepileptics. In the present study, we evaluated the effect of propafenone on the protective effect of oxcarbazepine, lamotrigine, topiramate, and pregabalin against the maximal electroshock-induced seizures in mice. This animal model corresponds well to the tonic-clonic convulsions in humans and is used as a screening test for potential anticonvulsant substances [20].

Materials and methods

Animals and experimental conditions

Inbred female Swiss mice of body weight 20–25 g were used for this study. The animals were kept in a room with controlled temperature (22 °C ± 1 °C) and a natural dark-light cycle. Animals had free access to food and water. After 7 days of adapting to laboratory conditions, the animals were chosen randomly and assigned to experimental groups consisting of 8–10 mice. Each mouse was used only once. All experiments in this study were carried out between 9 a.m. and 3 p.m. Furthermore, all efforts were made to reduce animal suffering and the number of animals (by using the minimum number of the mice, which is necessary to obtain reliable scientific data). All the procedures performed in this study were approved by the local ethics committee for animal experiments (license No 29/2014 and 40/2017) and they comply with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Drugs

In the study we used the following substances: an antiarrhythmic drug – propafenone (Polfenon®, Polpharma SA, Starogard Gdański, Poland) and four antiepileptic drugs: oxcarbazepine (Trileptal®, Novartis Pharma GmbH, Nürnberg, Germany); lamotrigine (Lamitrin®, GlaxoSmithKline, Brentford, Middlesex, Great Britain); topiramate (Topamax®, Janssen-Cilag, Beerse, Belgium); pregabalin (Lyrica®, Pfizer Limited, Sandwich, Kent, UK). Tween 80 (Sigma, St. Louis, USA) served as excipient. Before administration all drugs were suspended in 1% solution of Tween 80 in vehicle. All compounds were prepared freshly before administration. All drugs and vehicle (in control groups) were given intraperitoneally (*ip*) in a volume of 10 ml/kg of body weight and at following time schedules: oxcarbazepine – 30 min, propafenone, lamotrigine and topiramate – 60 min and pregabalin – 120 min before all tests. The pretreatment time, as the time to peak of maximum anticonvulsant activity of each drug, was based on our previous experiments and source data [19,21].

Maximal electroshock seizure threshold (MEST) test

Effects of the propafenone on the threshold for electroconvulsions were first assessed in the MEST test. Experimental procedures were previously described [22]. The electroconvulsive threshold was calculated according to a log-probit method by Litchfield and Wilcoxon [23] and was expressed as the median current strength value (CS_{50}). The value of CS_{50} is the current strength (expressed in mA), which caused convulsions in 50% of the animals tested.

Maximal electroshock seizure (MES) test

MES is recognized as a standard preclinical animal model that reflects tonic-clonic seizures in humans and is a measure of anticonvulsant activity of the tested substances. All procedures were previously described [22]. The antiepileptic drugs administered alone (in proportionally increasing doses) and their combination with propafenone (at constant dosage for every combination) were tested for their ability to increase the number of animals not responding with tonus (i.e., protected from tonic hind limb extension) after stimulation. The antielectroshock properties were shown as a protective median effective doses (ED_{50}) which were calculated according to a log-probit method by Litchfield and Wilcoxon [23] for antiepileptics and their combinations.

Chimney test

The chimney test, according to Boissier et al. [24], was used to assess possible motor deficits after administration of propafenone, antiepileptic drugs and combinations of propafenone with antiepileptics. The test was thoroughly described elsewhere [22]. Chimney test was carried for combinations of antiepileptic drugs and propafenone (50 mg/kg), which protected 50% of mice against the MES test. The control animals were administered with antiepileptic drugs alone at their ED_{50}s or propafenone at the dose of 50 mg/kg.

Passive-avoidance task

To determine the effect of propafenone, antiepileptic drugs, and their combinations on the long-term memory, the passive avoidance task was used. This test is associated with the natural aversion of rodents to bright compartments. Detailed methodology was described previously [22]. Like in the chimney test, passive avoidance task was carried for combinations of antiepileptic drugs and propafenone (50 mg/kg), which protected 50% of mice against the MES test. Mice administered with antiepileptic drugs alone at their ED_{50}s or propafenone at the dose of 50 mg/kg served as control groups.

Measurement of total brain antiepileptic drug concentrations

Total brain concentrations of antiepileptic drugs was measured for combinations with propafenone, which were beneficial in the

MES test. Control groups were administered either an antiepileptic drug or propafenone (50 mg/kg). Detailed methodology was described previously [22]. Brain concentrations were measured by fluorescence polarization immunoassay by using an ARCHITECT PLUS C 4000 immunoassay analyzer (Abbott Laboratories, Warszawa, Poland) and Abbott or ARK Diagnostics reagents.

Statistical analysis

Statistical analysis of the results obtained in the MES test, the ED_{50} values of AEDs with their 95% confidence limits were calculated by computer log-probit analysis according to Litchfield and Wilcoxon [23]. The basis for calculation of SEM values were confidence limits, number of mice and slope function obtained from log-probit analysis. The calculated ED_{50}s were compared in ANOVA followed by a *post hoc* Bonferroni's test. The Fisher's exact probability test was used to compare the results obtained in the chimney test. In turn, to compare the results from the step-through passive avoidance task Kruskal–Wallis nonparametric ANOVA was used followed by a *post hoc* Dunn's test. Total brain AEDs concentrations were compared by the use of the unpaired Student's *t*-test. In all tests, $p < 0.05$ indicated statistically significant differences between compared groups.

Results

MEST test

In the electroconvulsive threshold test, the effects of propafenone administered at doses 5–90 mg/kg were assessed. The antiarrhythmic drug at doses 60, 70, 90 mg/kg significantly increased the threshold seizure from 5.9 ± 0.39 mA to 7.8 ± 0.52, 7.3 ± 0.48 and 8.2 ± 0.54 mA, respectively. Propafenone at doses 5–50 mg/kg did not affect this parameter (Table 1).

MES test

Propafenone (50 mg/kg) administered with pregabalin and topiramate significantly decreased their ED_{50} values: from 161.4 ± 13.08 to 104.2 ± 13.51 for pregabalin and from 95.0 ± 10.76 to 64.8 ± 7.97 for topiramate. The antiarrhythmic drug applied at lower dose range of 5–40 mg/kg did not affect the action of pregabalin and topiramate (Figs. 1 and 2). With regards to oxcarbazepine, the effect of this drug was enhanced by propafenone administered at doses of 40 and 50 mg/kg, decreasing its ED_{50} value from 13.3 ± 0.73 to 8.5 ± 0.95 and 8.4 ± 0.86, respectively. Lower doses of propafenone (2.5–30 mg/kg) did not change significantly ED_{50} value of the tested drug (Fig. 3). Finally, propafenone in the dose range of 5–70 mg/kg had no significant effect on the antielectroshock action offered by lamotrigine (Fig. 4).

Table 1
Effects of propafenone administration on the electroconvulsive threshold in mice.

Treatment (mg/kg)	CS_{50} (mA)
Vehicle	5.9 ± 0.39
PROP (5)	5.8 ± 0.39
PROP (10)	6.8 ± 0.45
PROP (20)	6.5 ± 0.43
PROP (30)	6.7 ± 0.44
PROP (40)	6.9 ± 0.46
PROP (50)	6.6 ± 0.44
PROP (60)	7.8 ± 0.52**
PROP (70)	7.3 ± 0.48**
PROP (90)	8.2 ± 0.54**

Results are expressed as a current strength inducing tonic-clonic convulsions in 50% of tested mice (CS_{50}) ± SEM. PROP, propafenone.
** $p < 0.01$ *vs.* vehicle-treated animals.

Chimney test

Propafenone (50 mg/kg) and oxcarbazepine, lamotrigine and topiramate, administered in doses corresponding to their ED_{50} values in the MES test, did not affect motor performance. Similarly, propafenone co-administered with the abovementioned antiepileptic drugs did not affect this parameter. With regards to pregabalin, administered either alone (at the dose corresponding to its ED_{50} value) or in combination with the antiarrhythmic drug, it significantly impaired motor coordination (Table 2).

Passive-avoidance task

Oxcarbazepine, lamotrigine, topiramate and pregabalin, administered at doses corresponding to their ED_{50}s, did not significantly affect long-term memory in mice in the passive-avoidance task. Similarly, propafenone (50 mg/kg), administered either alone or in combinations with antiepilepics, did not cause any significant memory deficits (Table 2).

Brain concentrations of propafenone

Propafenone (50 mg/kg) significantly increased the brain level of pregabalin. Brain concentrations of topiramate and oxcarbazepine were not affected (Table 3).

Discussion

The purpose of this study was to determine the effect of propafenone on the electroconvulsive threshold and protective action of four new antiepileptic drugs: oxcarbazepine, lamotrigine, topiramate and pregabalin, in the mouse maximal electroshock model. Our results indicate that single administration of propafenone increased the electroconvulsive threshold and antielectroshock activity of oxcarbazepine, topiramate and pregabalin, but not that of lamotrigine. The effect on pregabalin may be partially due to pharmacokinetic interactions, since propafenone increased the brain concentration of this antiepileptic.

Propafenone, the IC class antiarrhythmic, is a relatively old drug still willingly used in cardiology because of its undeniable advantages. Propafenone is quite effective and safe medication, and presents some properties of beta-blockers. According to many reports, blockade of cardiac β 1-receptors is recommended in patients treated with antiarrhythmic drugs. Thanks to such beneficial properties propafenone is one of the most commonly used drugs in paroxysmal atrial fibrillation and flutter without structural heart disease and in patients with severe ventricular arrhythmias. Furthermore, in patients with organic cardiac disease, mainly after myocardial infarction, propafenone did not enhance mortality [13,25–32].

Studies on tissue distribution of propafenone in rats have shown that the drug reaches significant concentration in the brain, with the brain/plasma ratio above 1 [33]. Good blood-brain permeability is a prerequisite for the impact on seizure phenomena. Indeed, we confirmed the influence of propafenone on the electroconvulsive threshold in one of previous studies [19]. There is also another study available in literature, where propafenone, but not its metabolite 5-hydroxypropafenone, reduced convulsions induced by MES in rats. Nevertheless, this effect was characterized as a much weaker than that offered by lidocaine and flecainide [34]. Among other antiarrhythmics, mexiletine, a class IB drug, also showed anticonvulsants activity in some experimental models in mice: the MES test, pentylenetetrazole-induced convulsions and sound-induced seizures in DBA/2 mice [35,36].

It is worth remembering that propafenone exhibits properties of β-blockers, particularly in the aspect of its anticonvulsive effects

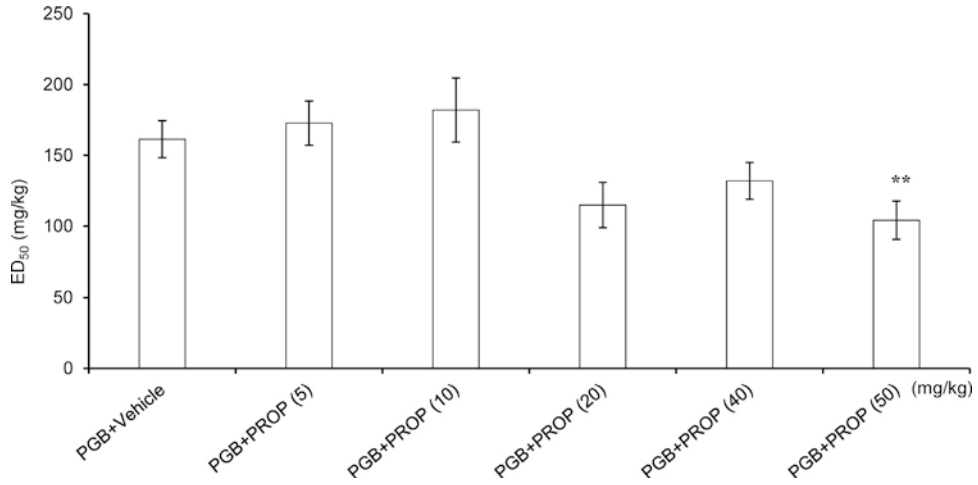

Fig. 1. Effect of propafenone (PROP) on the anticonvulsant action of pregabalin (PGB) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} dose with SEM values), at which PGB alone and in combinations with PROP protected 50% of animals against seizures. $^{**}p < 0.01$ *vs.* control (animals treated with PGB plus vehicle).

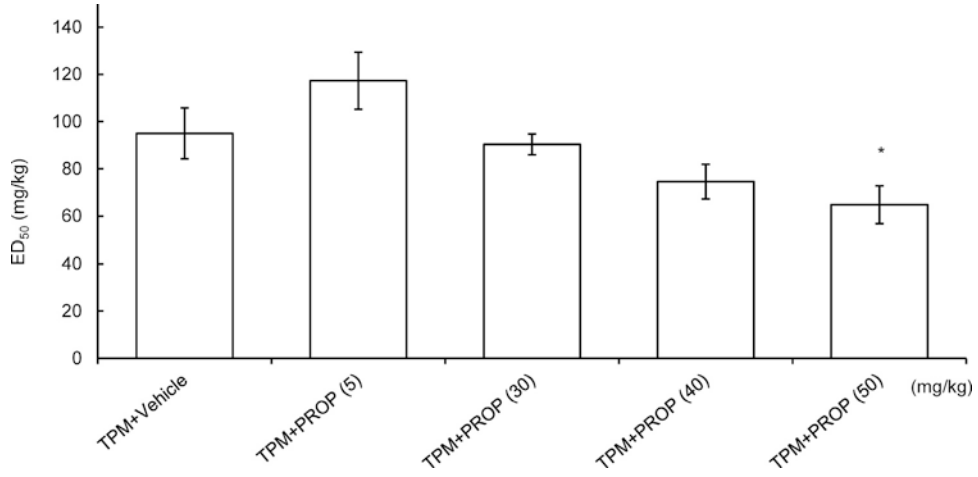

Fig. 2. Effect of propafenone (PROP) on the anticonvulsant action of topiramate (TPM) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} dose with SEM values), at which TPM alone and in combinations with PROP protected 50% of animals against seizures. $^{*}p < 0.05$ *vs.* control (animals treated with TPM plus vehicle).

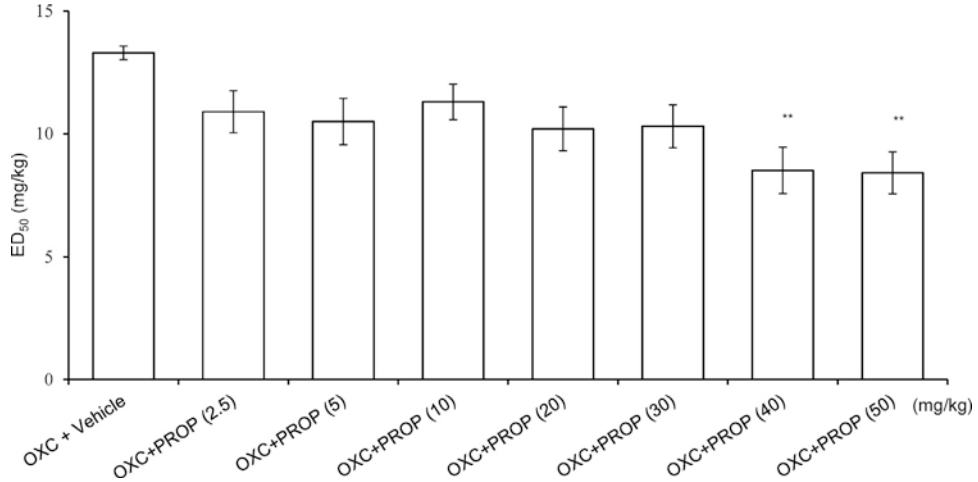

Fig. 3. Effect of propafenone (PROP) on the anticonvulsant action of oxcarbazepine (OXC) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} dose with SEM values), at which OXC alone and in combinations with PROP protected 50% of animals against seizures. $^{**}p < 0.01$ *vs.* control (animals treated with OXC plus vehicle).

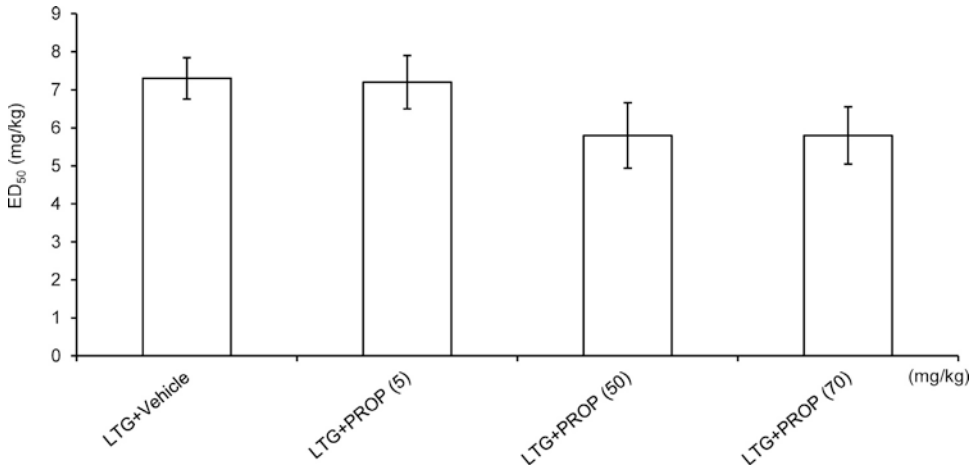

Fig. 4. Effect of propafenone (PROP) on the anticonvulsant action of lamotrigine (LTG) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} dose with SEM values), at which LTG alone and in combinations with PROP protected 50% of animals against seizures.

Table 2
Effect of propafenone, lamotrigine, topiramate, oxcarbazepine, pregabalin and combinations of propafenone with antiepileptic drugs on motor performance and long-term memory in mice.

Drug administered (mg/kg)	Mice impaired (%)	Median (25, 75 percentiles)
Vehicle	0	180 (180;180)
PROP (50.0)	10	180 (180;180)
LTG (7.2)	10	180 (180;180)
LTG (5.8) + PROP (50.0)	10	180 (180;180)
TPM (95.0)	0	180 (180;180)
TPM (64.8) + PROP (50.0)	0	180 (180;180)
OXC (13.3)	0	180 (180;180)
OXC (8.4) + PROP (50.0)	30	180 (158;180)
PGB (161.4)	70**	180 (180;180)
PGB (104.2) + PROP (50.0)	100***	180 (180;180)

Results are expressed as percentage of animals that failed to perform the chimney test, and as median retention time (with 25th and 75th percentiles) during which the animals avoided the dark compartment in the step-through passive avoidance task. PROP, propafenone; LTG, lamotrigine; TPM, topiramate; OXC, oxcarbazepine; PGB, pregabalin.
** $p < 0.01$.
*** $p < 0.001$ *vs.* control (animals treated saline).

Table 3
Brain concentrations of antiepileptic drugs applied alone and in combinations with propafenone.

Treatment (mg/kg)	Brain concentration (μg/ml)
TPM (64.8) + vehicle	11.88 ± 1.16
TPM (64.8) + PROP (50.0)	11.72 ± 1.70
PGB (104.2) + vehicle	1023.34 ± 127.13
PGB (104.2) + PROP (50.0)	1224.64 ± 219.14*
OXC (8.4) + vehicle	0.045 ± 0.01
OXC (8.4) + PROP (50.0)	0.050 ± 0.01

Results are presented as means ± SD of at least eight determinations. Statistical analysis of the brain concentrations of antiepileptic drugs was performed using the unpaired Student's *t* test. PROP, propafenone; LTG, lamotrigine; TPM, topiramate; OXC, oxcarbazepine; PGB, pregabalin.
* $p < 0.05$, *vs.* an antiepileptic applied with vehicle.

[13]. Some β-blockers were previously tested in different seizure models. Most of the data refers to propranolol, which limited seizures induced by lidocaine, strychnine and electrical threshold currents in mice, as well as by sound in DBA/2 mice and amygdala-kindling in rats. Data on the effect of propranolol on pentylenetetrazole-induced convulsions are inconsistent (no effect or seizure reduction) [37–41]. In turn, timolol and nebivolol clearly increased the seizure threshold in the pentylenetetrazole model. Additionally, nebivolol showed attenuated seizures in the increasing current electroshock model. Pindolol proved its protective effect against the electroconvulsive threshold, while metoprolol against sound-induced seizures in DBA/2 mice [38,40,42,43]. Finally, verapamil and diltiazem, calcium channel antagonists belonging to class IV of antiarrhythmics, inhibited seizures in many various animal models [44–49]. It seems that antiseizure properties may be characteristic for different classes antiarrhythmics, and is not connected with one specific mechanism of action. In human studies, lidocaine and propranolol were effective in patients with chronically unstable generalized epilepsy [50,51], mexiletine decreased seizures in partial epilepsy and Lennox-Gastaut syndrome [52–54], in turn verapamil limited convulsions in recurrent status epilepticus [55–57].

Common elements of the pathogenesis of epilepsy and arrhythmia, and also frequent co-occurrence of these diseases increases possibility of polytherapy with antiepileptic and antiarrhythmic drugs [6]. The most important principle of polytherapy is its safety. The choice of optimal drugs should be preceded by numerous studies on drug interactions. In the available literature there is a little data on the interactions between antiepileptic and antiarrhythmic drugs.

Based on our findings, propafenone applied at subthreshold doses increases the protective effect of oxcarbazepine, topiramate and pregabalin, but not that of lamotrigine in the MES test. Previous studies showed that the same effect was observed in relation to classical antiepileptics: carbamazepine, phenytoin, phenobarbital and valproate [19]. It seems that propafenone enhances the action of antiepileptics regardless their mechanism of action. Another I class antiarrhythmic, mexiletine, also potentiated antielectroshock activity of conventional antiepileptics. Isobolographic analysis showed an additive interaction between mexiletine and carbamazepine, phenytoin or phenobarbital in proportions 1:3; 1:1; 3:1 and with valproate in proportion 1:3. In turn, antagonistic interaction was found between mexiletine and valproate in proportion 1:1 and 3:1. However, the authors attribute the observed antagonism to pharmacokinetic phenomena – decreased brain concentration of valproate co-administered with mexiletine [35].

Literature data mentions also some interactions between antiepileptics and β-blockers or calcium channel antagonists. The action of lamotrigine was potentiated (in contrast to combinations with propafenone) by propranolol and metoprolol against sound-induced convulsions in DBA/2 mice and by nebivolol in the increasing current electroshock seizure test. Additionally, propranolol and metoprolol enhanced protective action of

diazepam, phenobarbital and valproate in DBA/2 mice, and, in the case of diazepam and valproate, also in the MES test [38,58,59]. Among calcium channel antagonists, verapamil enhanced anti-electroshock activity of topiramate, but not that of lamotrigine. In the same test, diltiazem did not affect the action of either lamotrigine or topiramate [22,60,61].

It is not without meaning that behavioral tests performed in this study indicated that propafenone alone and in combinations with antiepileptics did not impair motor coordination or long-term memory in mice. Actually, these results are consistent with data provided by available literature [19]. Although we observed a significant impairment of motor coordination after administration of pregabalin alone and its combination with propafenone, this effect can be attributed only to the action of pregabalin, not propafenone.

Conclusion

The results presented herein indicate that propafenone has its own anticonvulsant effect, potentiates the action of oxcarbazepine, topiramate and pregabalin, and remains without effect on the action of lamotrigine. On the other hand, propafenone did not enhance adverse effects caused by antiepileptic drugs alone. This and advantageous profile of adverse effects suggests that propafenone may be safely used in patients with epilepsy. However, to state that, our results should be confirmed in chronic seizure models and clinical conditions.

Conflict of interest

Authors do not have any conflict of interest to declare.

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