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Verapamil enhances the anticonvulsant effect of oxcarbazepine in the maximal electroshock-induced seizure model in mice

Werapamil nasila przeciwdrgawkowe działanie okskarbazepiny w modelu maksymalnego wstrząsu elektrycznego u myszy

Calcium ions (Ca^{2+}) play a fundamental role in the pathophysiology of epilepsy because changes in both extracellular and intracellular calcium concentrations are usually observed prior to the onset of seizure activity [7, 15, 21]. Experimental evidence indicates that some calcium channel antagonists reduce the incidence of seizures and possess anticonvulsant properties in various seizure models in rodents [10, 11, 17, 18, 21]. For instance, it was found that some calcium channel blockers were effective in the maximal electroshock seizure (MES), pentylenetetrazole, picrotoxin, N-methyl-D-aspartic acid, pilocarpine, amygdala-kindling, and sound-induced seizure models in rodents [12, 19, 33, 36, 37, 44, 48].

Experimental evidence indicates that verapamil (an L-type calcium channel antagonist) potentiated the anticonvulsant action of oxcarbazepine (a second-generation antiepileptic drug) in the pilocarpine-induced seizure model in rats [9]. In contrast, verapamil did not alter the anticonvulsant action of various antiepileptic drugs (e.g., carbamazepine, phenytoin, phenobarbital, valproate, topiramate and lamotrigine) in the mouse MES model [10, 29, 30]. Since verapamil potentiated the anticonvulsant action of oxcarbazepine in the pilocarpine-induced seizure model, it was of pivotal importance to determine whether the calcium channel antagonist also enhances the protective action of oxcarbazepine in the mouse MES model.

It is noteworthy that oxcarbazepine has been licensed as an add-on treatment for adults with refractory epilepsy and as monotherapy in newly diagnosed epilepsy (especially, in patients with generalized tonic-clonic seizures and partial convulsions with or without secondary generalization) [4]. It is widely accepted that the MES test is considered to be an experimental animal model, allowing to select drugs that are effective in the suppression of generalized tonic-clonic seizures and, to a certain extent, of partial seizures with or without secondary generalization [24]. Thus, it was appropriate to examine the anticonvulsant effects of oxcarbazepine administered alone and in combination with verapamil in the MES test in mice. Additionally, the acute adverse-effect potentials of oxcarbazepine in combination with verapamil were determined in the chimney test (motor performance), step-

through passive avoidance task (long-term memory) and a grip-strength test (muscular strength) in mice. To confirm or exclude pharmacokinetic characteristics of interactions between oxcarbazepine and verapamil, total brain oxcarbazepine concentrations were measured with high-pressure liquid chromatography (HPLC).

MATERIAL AND METHODS

Animals and experimental conditions. Adult male Swiss mice (weighing 22–26 g) that were kept in colony cages with free access to food and tap water, under standardized housing conditions (natural light-dark cycle, temperature of 23±1°C, relative humidity of 55 ± 5%), were used. After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to experimental groups each comprising 8 mice. Each mouse was used only once and all tests were performed between 08.00 a.m. and 03.00 p.m. Procedures involving animals and their care were conducted in accordance with current European Community and Polish legislation on animal experimentation. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data. The experimental protocols and procedures described in this manuscript were approved by the First Local Ethics Committee in Lublin (License no.: 516/2005/550/2005) and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Guide to the Care and Use of Experimental Animals.

Drugs. The following drugs were used in this study: oxcarbazepine (Novartis Pharma AG, Basel, Switzerland), and verapamil (Abbott GmbH & Co. KG, Ludwigshafen, Germany). The drugs were suspended in a 1% aqueous solution of Tween 80 (Sigma, St. Louis, MO, USA) and administered intraperitoneally (i.p.), in a volume of 5 ml/kg body weight. Fresh drug solutions were prepared on each day of experimentation and administered 30 min. before electroconvulsions, motor coordination, muscular strength and long-term memory evaluation, as well as before brain sampling for the measurement of oxcarbazepine concentrations. These pretreatment times were based upon information about their biological activity from the literature and our previous studies [10, 17, 18, 26–30]. The time to the peak of maximum anticonvulsant effects for oxcarbazepine was used as the reference time in all behavioral tests and pharmacokinetic estimation of brain oxcarbazepine concentrations. In this study, oxcarbazepine was administered at doses ranging from 6 to 14 mg/kg.

Maximal electroshock-induced seizures. Electroconvulsions were produced by a current (fixed current intensity of 25 mA, 0.2 s stimulus duration) delivered via ear-clip electrodes by a Rodent Shocker generator (constant-current stimulator Type 221, Hugo Sachs Elektronik, Freiburg, Germany). The criterion for the occurrence of seizure activity was the tonic hind limb extension (i.e., the hind limbs of animals outstretched 180° to the plane of the body axis). The protective activity of oxcarbazepine was determined as its median effective dose (ED_{50} value in mg/kg) against MES-induced seizures. The animals were administered different drug doses so as to obtain a variable percentage of protection against MES, allowing the construction of a dose-response relationship curve for oxcarbazepine administered alone, according to Litchfield and Wilcoxon [23]. The ED_{50} value represents the dose of a drug required to protect half of the animals tested against MES. Similarly, the anticonvulsant activity of mixtures of oxcarbazepine with verapamil was evaluated and expressed as ED_{50}, corresponding to the dose of oxcarbazepine necessary to protect 50% of mice against tonic hindlimb extension in the MES test. This experimental procedure was described in detail in our earlier studies [26–30].

Chimney test. The chimney test of Boissier et al. [2] was used to quantify the adverse-effect potential of oxcarbazepine administered alone and in combination with verapamil on motor performance in mice. In this test, the animals had to climb backwards up a plastic tube (3 cm inner diameter, 25 cm length), and motor performance impairment was indicated by the inability of the mice to climb backward up the transparent tube within 60 s. The adverse-effect potentials of oxcarbazepine co-administered with verapamil were determined for drugs administered at doses corresponding to their ED_{50} values from the MES test. This experimental procedure was described in detail in our earlier studies [26–31].

Grip-strength test. The effects of oxcarbazepine, verapamil and their combination (at doses from the MES test) on skeletal muscular strength in mice were quantified by the grip-strength test. The time before the commencement of the grip-strength test (after drug administration) was identical to that for the MES test. The grip-strength apparatus (BioSeb, Chaville, France) comprised a wire grid (8 × 8 cm) connected to an isometric force transducer (dynamometer). The mice were lifted by the tails so that their forepaws could grasp the grid. The mice were then gently pulled backward by the tail until the grid was released. The maximal force exerted by the mouse before losing grip was recorded. The muscular strength in mice was expressed in N (newtons) as means ± SEM of 8 animals per group. This experimental procedure was described in detail in our earlier studies [29, 30].

Step-through passive avoidance task. Each animal was administered oxcarbazepine with verapamil at doses corresponding to their ED_{50} values from the MES test on the first day before training. The time before the commencement of the training session (after drug administration) was identical to that for the MES test. Subsequently, animals were placed in an illuminated box (10 × 13 × 15 cm) connected to a larger dark box (25 × 20 × 15 cm) equipped with an electric grid floor. Entrance of animals to the dark box was punished by an adequate electric footshock (0.6 mA for 2 s). The animals that did not enter the dark compartment were excluded from subsequent experimentation. On the following day (24 h later), the pre-trained animals did not receive any treatment and were placed again into the illuminated box and observed up to 180 s. Mice that avoided the dark compartment for 180 s were considered to remember the task. The time that the mice took to enter the dark box, was noted and the median latencies (retention times) with 25^{th} and 75^{th} percentiles were calculated. The step-through passive avoidance task gives information about the ability to acquire the task (learning) and to recall the task (retrieval). Therefore, it may be regarded as a measure of long-term memory [45]. This experimental procedure was described in detail in our earlier study [31].

Measurement of total brain oxcarbazepine concentration. The measurement of total brain concentrations of oxcarbazepine was undertaken at the drug dose which corresponded to its ED_{50} value from the MES test for the combination of oxcarbazepine with verapamil. Mice were killed by decapitation at times chosen to coincide with that scheduled for the MES test and the whole brains of mice were removed from skulls, weighed, harvested and homogenized using Abbott buffer (1:2 w/v) in an Ultra-Turrax T8 homogenizer (IKA-Werke, Staufen, Germany). The homogenates were centrifuged at 10,000 *g* for 10 min. The supernatant samples (400 µl) were analyzed for oxcarbazepine content by HPLC according to the method described earlier [27]. The total brain concentrations of oxcarbazepine were expressed in µg/ml of brain supernatant as means ± SD of at least 8 determinations (8 separate brain preparations).

Statistical analysis. The ED_{50} values for oxcarbazepine with their 95% confidence limits were calculated by computer log-probit analysis according to Litchfield and Wilcoxon [23]. Subsequently, the respective 95% confidence limits were transformed to SEM, as described previously [26]. Statistical analysis of data from the MES test was performed with one-way analysis of variance (ANOVA) followed by the post-hoc Tukey-Kramer test for multiple comparisons. Qualitative

variables from the chimney test were compared useing the Fisher's exact probability test, whereas the results obtained in the passive avoidance task were statistically evaluated using Kruskal-Wallis nonparametric ANOVA. The results from the grip-strength test were verified with one-way ANOVA. Total brain oxcarbazepine concentrations were statistically compared using the unpaired Student's *t*-test. Differences among values were considered statistically significant if $P<0.05$. All statistical tests were performed using GraphPad Prism version 4.0 for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

EFFECTS OF VERAPAMIL ON THE PROTECTIVE ACTION OF OXCARBAZEPINE IN THE MOUSE MAXIMAL ELECTROSHOCK-INDUCED SEIZURE MODEL

Oxcarbazepine administered alone (i.p.) produced a clear-cut anticonvulsant effect against MES-induced seizures in mice and its ED_{50} value is presented in Table 1. Verapamil at a dose of 20 mg/kg considerably enhanced the protective action of oxcarbazepine in the MES test in mice by reducing the ED_{50} value of the latter drug from 12.24 to 7.48 mg/kg (by 39%; $P<0.01$; Table 1). In contrast, verapamil at doses of 5 and 10 mg/kg had no significant impact on the protective action of oxcarbazepine in the MES test in mice, although the drug slightly diminished the ED_{50} of oxcarbazepine (Table 1).

Table 1. Influence of verapamil on the anticonvulsant activity of oxcarbazepine in the mouse maximal electroshock seizure (MES) model

Treatment (mg/kg)	ED_{50} (mg/kg)	n
Oxcarbazepine + vehicle	12.24 ± 0.793	16
Oxcarbazepine + verapamil (5)	11.89 ± 0.857	24
Oxcarbazepine + verapamil (10)	9.87 ± 0.862	24
Oxcarbazepine + verapamil (20)	7.48 ± 0.752 **	16
F (3;76) = 5.751; P = 0.0013		

Results are presented as median effective doses (ED_{50} ± SEM in mg/kg) required to protect 50% of animals tested against MES-induced seizures. The ED_{50} values were calculated by the use of log-probit method [23, 26]. Verapamil and oxcarbazepine were suspended in 1% aqueous solution of Tween 80 and administered systemically (i.p.) at 30 min. before electroconvulsions. Statistical analysis of data was performed with one-way ANOVA followed by the post-hoc Tukey-Kramer test for multiple comparisons. n – number of animals at those doses, whose anticonvulsant effects ranged between 16% and 84% (4 and 6 probits). **$P<0.01$ vs. the respective control group (Oxcarbazepine + vehicle-treated animals)

EFFECTS OF OXCARBAZEPINE IN COMBINATION WITH VERAPAMIL ON MOTOR PERFORMANCE, LONG-TERM MEMORY, AND MUSCULAR STRENGTH OF ANIMALS IN THE CHIMNEY, STEP-THROUGH PASSIVE AVOIDANCE AND GRIP-STRENGTH TESTS

When oxcarbazepine was administered in combination with verapamil at doses corresponding to its ED_{50} from the MES test, motor performance as assessed by the chimney test was unaffected (Table 2). Furthermore, the combination of oxcarbazepine with verapamil did not impair long-term memory as determined in the passive avoidance test, the median retention times being approximately 180 s (Table 2). Likewise, oxcarbazepine combined with verapamil had no significant impact on muscular strength of animals as assessed by the grip-strength test (Table 2).

Table 2. Effects of verapamil and its combination with oxcarbazepine on long-term memory, skeletal muscular strength and motor performance in mice

Treatment (mg/kg)	Retention time (s)	Grip-strength (N)	Motor coordination impairment (%)
Vehicle	180 (180; 180)	82.38 ± 5.88	0
Verapamil (20) + vehicle	180 (170; 180)	79.50 ± 5.47	12.5
Oxcarbazepine (7.5) + vehicle	180 (180; 180)	84.75 ± 5.69	0
Oxcarbazepine (7.5) + verapamil (20)	175 (155; 180)	77.77 ± 5.91	25

Results are presented as: 1) median retention times (in seconds; with 25th and 75th percentiles in parentheses) from the passive avoidance task, assessing long-term memory in mice; 2) mean grip-strengths (in Newtons ± SEM) from the grip-strength test, assessing muscular strength in mice; and 3) percentage of animals showing motor coordination impairment in the chimney test in mice. Each experimental group consisted of 8 animals. Statistical analysis of data from the passive avoidance task was performed with nonparametric Kruskal-Wallis ANOVA test, whereas those from the grip-strength test were analyzed with one-way ANOVA. The Fisher's exact probability test was used to analyze the results from the chimney test. The drugs were administered i.p. at times scheduled from the MES test and at doses corresponding to their ED_{50} values against maximal electroconvulsions (for more detail see explanations to Table 1)

INFLUENCE OF VERAPAMIL ON TOTAL BRAIN CONCENTRATION OF OXCARBAZEPINE

HPLC method revealed that total brain concentrations of oxcarbazepine were significantly elevated (by 46%; $P<0.05$) when oxcarbazepine was administered in combination with verapamil (20 mg/kg) as compared to when oxcarbazepine was administered alone (Table 3).

Table 3. Effect of verapamil on total brain concentrations of oxcarbazepine in mice

Treatment (mg/kg)	Brain concentration (μg/ml)
Oxcarbazepine (7.5) + vehicle	1.015 ± 0.312
Oxcarbazepine (7.5) + verapamil (20)	1.484 ± 0.355 *

Data are presented as means ± SD of at least 8 separate determinations. Total brain concentrations of oxcarbazepine were determined with HPLC. Data were statistically verified by using the unpaired Student's *t*-test. The drugs were administered i.p. at doses corresponding to their ED_{50} values from the MES-induced seizures. For more detail see explanation to Table 1. *$P<0.05$ vs the respective control group (Oxcarbazepine + vehicle-treated animals)

DISCUSSION

Results clearly indicate that verapamil significantly enhanced the antiseizure action of oxcarbazepine in the MES test in mice and these findings are in agreement to those observed previously, showing that verapamil significantly potentiated the anticonvulsant action of oxcarbazepine against pilocarpine-induced limbic seizures in rats [9]. It is important to note that doses of verapamil used in this study (up to 20 mg/kg) did not significantly affect the threshold for electroconvulsions in mice [17, 18, 29, 30]. Moreover, verapamil administered alone at doses up to 20 mg/kg neither protected the animals against MES-induced seizures nor affected the anticonvulsant action of carbamazepine, phenobarbital, lamotrigine, topiramate, valproate, and phenytoin against MES-induced seizures in mice [10, 17, 29, 30]. Thus, the enhancement of the antielectroshock action of oxcarbazepine by verapamil confirmed the results obtained by other authors in pilocarpine-induced seizure model [9].

Pharmacokinetic estimation of oxcarbazepine concentrations with HPLC revealed that verapamil significantly increased total brain oxcarbazepine concentrations in experimental animals and our findings are consistent with those reported earlier by Clinckers et al. [9], who documented that

verapamil elevated oxcarbazepine concentrations in the rat brains [9]. In the present study verapamil elevated total brain oxcarbazepine concentrations by 46%, which was associated with a 39% reduction of the ED_{50} value for the antiepileptic drug in the MES test in mice. Thus, one can ascertain that the pharmacokinetic interaction between oxcarbazepine and verapamil was entirely responsible for the observed enhancement of the antiseizure action of oxcarbazepine in the MES test in mice. To explain the pharmacokinetic nature of interaction between oxcarbazepine and verapamil, one should consider the fact documenting that verapamil blocks P-glicoprotein in the blood-brain barrier and interacts with organic anion transporter 2 [1, 22]. Verapamil, by blocking P-glycoprotein in the blood-brain barrier, contributes to the increase in oxcarbazepine concentrations in the brain tissue and thus, the elevated concentrations of oxcarbazepine in the brain seem to be responsible for the enhanced anticonvulsant action of the drug in the MES test. A similar situation was documented earlier in the pilocarpine-induced limbic seizure model in rats [9], because local perfusion with verapamil promoted the passage of concomitantly administered oxcarbazepine through the blood-brain barrier and accumulation of oxcarbazepine into the brain that contributed to the suppression of pilocarpine-induced limbic seizures in rats [9]. Moreover, a clinical report documented an improvement in seizure control in a pharmacoresistant patient after addition of verapamil to the AED regimen [41], despite the known poor penetration of verapamil through the blood-brain barrier [20, 42].

As regards molecular mechanisms underlying seizure activity, it should be stressed that an initial seizure increases excitatory synaptic neurotransmission (especially, glutamate that is the main excitatory neurotransmitter of the brain) [3]. Prolonged seizures and status epilepticus trigger glutamate surge or spread of excessive uncontrolled glutamatergic neurotransmission, which results in sustained depolarization that is initiated by the activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) receptors [3]. Excess of glutamate over-stimulates NMDA (N-methyl-D-aspartate) receptor-dependent inward synaptic currents, thereby enhancing excitability and elevates intracellular Ca^{2+} concentration [3]. The Ca^{2+} flux into the intracellular space represents the first stage of epileptic neuronal events that may lead to synchronous burst firing of multiple neurons [39]. It is noteworthy that Ca^{2+} enters the presynaptic terminal and binds to calmodulin, a major Ca^{2+} receptor protein in the neurons. The Ca^{2+}-calmodulin complex regulates several aspects of synaptic activity, e.g. excitatory neurotransmitter release and neuronal function [8]. With sustained depolarization, magnesium (Mg^{2+}) block is released from NMDA receptors and this impends the energy-dependent reuptake of glutamate, which results in a rise in intracellular Ca^{2+} concentration [8]. The Ca^{2+} entry into neurons and the subsequent loss of Ca^{2+} homeostasis are believed to underlie excitotoxicity and neuronal cell death [38]. At a cellular level, epileptic depolarizations of neurons were found to be depressed by Ca^{2+} channel blockers [16].

On the other hand, oxcarbazepine and its rapidly formed 10-monohydroxy derivative (MHD), at therapeutically relevant concentrations, reduce high-frequency repetitive firing of neurons by an action on Na^{+} channels and enhance K^{+} current [32, 34, 47]. Moreover, oxcarbazepine and MHD inhibit high-voltage–activated N-type Ca^{2+} channels and reduce glutamatergic transmission [5, 40, 46]. Thus, it seems that both oxcarbazepine and verapamil should cooperate in terms of reduction of seizure activity in experimental animals.

Furthermore, it was found that verapamil did not affect the acute adverse-effect potential of oxcarbazepine in animals challenged with the chimney test, passive avoidance task, and grip-strength test. These observations are consistent with our recent studies, showing that verapamil, when combined with lamotrigine and topiramate, did not alter acute adverse effects in experimental animals subjected to the chimney test, step-through passive avoidance or grip-strength tests [29, 30]. It is noteworthy that there exists a strong correlation between the acute adverse-effect (neurotoxic) profiles of AEDs, shown experimentally in animals, and neurological dysfunctions reported in

clinical settings in humans [13, 35]. Since the combinations of oxcarbazepine with verapamil did not produce acute adverse (neurotoxic) effects in the preclinical study, the combination may occur advantageous in clinical settings. Thus, one can ascertain that the acute application of verapamil at doses up to 20 mg/kg at 30 min. before the test seems to be safe and tolerable. In clinical settings, the chronic administration of verapamil is associated with some side effects, including headaches, facial flushing, dizziness, swelling, increased urination, fatigue, nausea, ecchymosis, lightheadedness, and constipation [6, 49]. It should be stressed that verapamil as the L-type calcium channel blocker is clinically used in the treatment of hypertension, angina pectoris, cardiac arrhythmia, and most recently, cluster headaches [14, 43, 49]. In cardiac pharmacology, verapamil belongs to class IV antiarrhythmic agents [14, 49]. Since calcium channels are especially concentrated in the sinoatrial and atrio-ventricular nodes, verapamil decreases impulse conduction through the atrio-ventricular node and thus it protects the ventricles from atrial tachyarrhythmias [25]. Calcium channels are also present in the smooth muscle that lines blood vessels. By relaxing the tone of this smooth muscle, verapamil dilates the blood vessels and therefore the drug is used in treating hypertension and angina pectoris [6]. The reduction of arterial pressure in the tested animals should be borne in mind as a potential negative influence of verapamil on cardio-vascular system of the tested animals, but this effect was highly unlikely when verapamil was administered at doses up to 20 mg/kg.

In conclusion, verapamil potentiated the antiseizure action of oxcarbazepine, although this effect resulted in the pharmacokinetic increase in total brain oxcarbazepine concentrations. The pharmacokinetic interaction between oxcarbazepine and verapamil is expected in clinical settings; therefore, the utmost caution is advised when combining these drugs in epileptic patients. If the results from this study can be extrapolated to the clinical settings, a novel therapeutic option in the management of epilepsy might be created for epileptic patients, who additionally require a treatment with verapamil for conditions other than epilepsy.

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SUMMARY

The aim of this study was to assess the influence of verapamil (an L-type calcium channel blocker) on the anticonvulsant potential of oxcarbazepine (a second-generation antiepileptic drug) in the maximal electroshock seizure (MES) test in mice. Electroconvulsions were evoked in Albino Swiss mice by a current (25 mA, 500 V, 50 Hz, 0.2 s stimulus duration) delivered via auricular electrodes. Adverse-effect profiles with respect to motor coordination, long-term memory and skeletal muscular strength were measured along with total brain oxcarbazepine concentrations. Verapamil (20 mg/kg, i.p.) significantly enhanced the anticonvulsant activity of oxcarbazepine in the MES test in mice, by reducing its ED_{50} value from 12.24 to 7.48 mg/kg ($P<0.01$). In contrast, verapamil (5 and 10 mg/kg) had no significant impact on the antiseizure action of oxcarbazepine in the MES test in mice. Moreover, verapamil (20 mg/kg) significantly elevated total brain oxcarbazepine concentrations in mice as measured with high-pressure liquid chromatography. The combination of oxcarbazepine with verapamil, at doses from the MES test, did not impair motor coordination in the chimney test, long-term memory in the passive avoidance task, or skeletal muscular strength in the grip-strength test in mice. In conclusion, the utmost caution is advised when combining oxcarbazepine with verapamil due to a possible pharmacokinetic increase in total brain oxcarbazepine concentrations in patients receiving both drugs.

STRESZCZENIE

Celem pracy było oszacowanie wpływu werapamilu (blokera kanałów wapniowych typu L) na przeciwdrgawkowy potencjał okskarbazepiny (leku przeciwpadaczkowego drugiej generacji) w teście maksymalnego wstrząsu elektrycznego (MES) u myszy. Drgawki elektryczne u myszy Albino Swiss wywoływano prądem (25 mA, 500 V, 50 Hz, 0,2 s czas trwania stymulacji) dostarczanym przez elektrody uszne. Profile działań niepożądanych w odniesieniu do koordynacji ruchowej, pamięci długotrwałej i szkieletowej siły mięśniowej mierzono wraz z całkowitymi mózgowymi stężeniami okskarbazepiny. Werapamil (20 mg/kg, i.p.) istotnie nasilał przeciwdrgawkową aktywność okskarbazepiny w teście MES u myszy, zmniejszając jej wartość ED_{50} z 12,24 do 7,48 mg/kg ($P<0,01$). Przeciwnie, werapamil (5 i 10 mg/kg) nie miał istotnego wpływu na przeciwdrgawkową aktywność okskarbazepiny w teście MES. Ponadto werapamil (20 mg/kg) istotnie podwyższał całkowite mózgowe stężenie okskarbazepiny u myszy, mierzone wysokosprawną chromatografią cieczową. Kombinacja okskarbazepiny z werapamilem w dawkach z testu MES nie upośledzała koordynacji ruchowej w teście komina, pamięci długotrwałej w teście biernego unikania i siły mięśni szkieletowych w teście chwytania. W podsumowaniu, szczególna uwaga jest zalecana podczas łączenia okskarbazepiny z werapamilem z powodu możliwego farmakokinetycznego wzrostu całkowitego mózgowego stężenia okskarbazepiny u pacjentów otrzymujących oba leki.