

Assessment of combined treatment with vigabatrin and antihypertensive drugs against electroconvulsions in mice

Krzysztof Łukawski¹, Grzegorz Raszewski¹, Stanisław J. Czuczwar^{1,2}

¹ Department of Physiopathology, Institute of Rural Health, Lublin, Poland

² Department of Pathophysiology, Medical University of Lublin, Lublin, Poland

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Abstract

Introduction and objective. It is likely that cardiovascular drugs will be used in epileptic patients because heart failure and hypertension are common comorbid conditions with epilepsy. Experimental studies show that some cardiovascular drugs can affect the protective activity of antiepileptics.

Objective. The aim of this study was to examine the effects in mice of angiotensin-converting enzyme (ACE) inhibitors (captopril and perindopril), angiotensin AT₁ receptor antagonists (losartan and candesartan) and diuretics (hydrochlorothiazide and ethacrynic acid) on the anticonvulsant activity of vigabatrin (VGB), a second generation antiepileptic drug.

Materials and methods. Adult Swiss mice were used in the study. The anticonvulsant action of VGB was assessed in the maximal electroshock seizure threshold test. Combined treatment with VGB and antihypertensive drugs was also tested for adverse effects in the passive avoidance task and chimney test. All drugs were administered intraperitoneally.

Results. Captopril (50 mg/kg), perindopril (10 mg/kg), losartan (50 mg/kg), candesartan (8 mg/kg), hydrochlorothiazide (100 mg/kg) and ethacrynic acid (100 mg/kg) did not influence the protective action of VGB. The combined treatment with VGB (700 mg/kg) and antihypertensive drugs showed a strong tendency towards impaired retention in the passive avoidance task, and in the case of the combination of VGB with ethacrynic acid it reached statistical significance ($P < 0.05$). Mice were not disturbed in the chimney test following applied treatment.

Conclusions. From the preclinical point of view, the use of the tested antihypertensive drugs in patients treated with VGB seems neutral regarding its anticonvulsant activity.

Key words

vigabatrin, ACE inhibitors, AT₁ receptor antagonists, diuretics, seizures

INTRODUCTION

Vigabatrin (VGB), an ethyl analogue of γ -aminobutyric acid (GABA), was the first of the newer generation of anticonvulsants. VGB is an antiepileptic drug used in more than 50 countries as adjunctive therapy for the treatment of refractory complex partial seizures in adults [1]. In animal experiments, VGB shows potent anticonvulsive effects in amygdala kindling, and in models of audiogenic and chemical seizures evoked by pentylenetetrazole, picrotoxin and strychnine [2]. Epidemiological studies have revealed that heart failure and hypertension are common comorbid conditions with epilepsy [3]. Therefore, it can be assumed that a concomitant use of antiepileptic drugs (AEDs), such as VGB and antihypertensive drugs, is likely in epileptic patients and may affect the anticonvulsant activity of AEDs. This has already been shown as regards other AEDs in animal studies [4, 5].

The presented study sought to assess the effect of a number of antihypertensive drugs on the anticonvulsant action of VGB in the maximal electroshock seizure threshold test (MEST test) in mice. VGB has been demonstrated to be effective in this test in earlier reports [6]. The study was performed with the use of angiotensin-converting enzyme

(ACE) inhibitors, captopril and perindopril, angiotensin AT₁ receptor antagonists, losartan and candesartan, and diuretics, hydrochlorothiazide and ethacrynic acid. All these drugs are widely used in clinical practice as antihypertensive agents, with the exception of ethacrynic acid due to its side-effect profile, and this loop diuretic is rather employed in the treatment of edematous states [7]. It was included in the current study because of anticonvulsant-like properties in previous reports in which it suppressed sound-triggered seizures in post-ischemic audiogenic seizure-prone rats [8] and potentiated, similarly to losartan, the anticonvulsant action of valproate against maximal electroshock (MES) in mice [4, 9]. In turn, captopril and hydrochlorothiazide enhanced the protective activity of carbamazepine in the MES test [5, 10]. Besides, captopril was reported to suppress audiogenic seizures in mice [11]. To the best of the authors' knowledge, the mentioned antihypertensive drugs have not been tested with VGB in animal models of seizures. In addition, in the current study, the concomitant treatment of VGB and antihypertensive drugs was examined in the passive avoidance task [12] and the chimney test [13] to assess long-term memory and motor coordination, respectively.

MATERIALS AND METHOD

The study was performed on male Swiss mice weighing 22–28 g. The mice were housed in colony cages with free access to food and tap water under standardized laboratory conditions

Address for correspondence: Krzysztof Łukawski, Department of Physiopathology, Institute of Rural Health, Jaczewskiego 2, 20-090 Lublin, Poland
E-mail: lukaw@mp.pl

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(12-h light-dark cycle, room temperature of 22±1°C). The animals were randomly assigned to experimental groups consisting of eight animals. Each mouse was used only once. The experimental procedures in this study were approved by the Local Ethics Committee for Animal Experiments and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

The following drugs were used: losartan potassium (Xartan, Adamed, Poland), candesartan cilexetil (Atacand, AstraZeneca AB, Sweden), captopril (Captopril Jelfa, Jelfa S.A., Poland), perindopril arginine (Prestarium, Servier, France), hydrochlorothiazide (Hydrochlorothiazidum, Polpharma S.A., Poland), ethacrynic acid (Ethacrynic acid, MP Biomedicals, USA) and vigabatrin (Sabril, Marion Merrell S.A., France). Drugs were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA) in distilled water. All drugs were administered intraperitoneally (*i.p.*) as a single injection, in a volume of 5 ml/kg body weight. Control animals received injections of the vehicle. The pretreatment times of the drugs before the tests were as follows: 240 min (vigabatrin), 120 min (losartan, candesartan, hydrochlorothiazide), 60 min (perindopril), 45 min (captopril) and 30 min (ethacrynic acid). The pretreatment times were based on previous reports on their biological activities [e.g. 5, 6, 10].

Electroconvulsions. Convulsions were assessed in the maximal electroshock seizure threshold test (MEST test). Electroconvulsions were produced by an alternating current (50 Hz, 500 V, stimulus duration of 0.2 s) delivered via ear-clip electrodes with the use of a generator (Rodent Shocker, Type 221, Hugo Sachs Elektronik, Freiburg, Germany). Full tonic extension of both hind limbs was taken as the endpoint. The convulsive threshold was evaluated as CS_{50} , which is the current strength (in mA) required to produce tonic hind limb extension in 50% of the animals tested. To calculate the convulsive threshold in the MEST test, at least three groups of mice (eight animals per group) were exposed to electroshocks of various intensities. An intensity-response curve was then calculated on a computer, based on the percentage of animals convulsing in experimental groups. In the MEST test, antihypertensive drugs at their subthreshold doses were examined with VGB administered at three different doses: 500, 600 or 700 mg/kg.

Passive avoidance test. On the first day, the training trial was performed in which the mice were pretreated with the studied drugs and individually placed in an illuminated box (12 × 20 × 15 cm) connected to a dark box (24 × 20 × 15 cm). The dark box was equipped with an electric grid floor and a doorway (4 × 7 cm) located at floor level in the centre of the connecting wall. Entry into the dark box was punished by an electric foot shock (0.6 mA for 2 s). On the next day (24 h after the training trial), the retention test was performed in which the same animals with no treatment were put again into the illuminated box, and time that the mice took to enter the dark box was recorded. The mice that avoided the dark compartment for 180 s were considered as remembering the task. The step-through passive avoidance task may give information about acquisition (learning) and recall (retrieval), which are components of long-term memory [12]. In the passive avoidance task, administration of test drugs before training may disrupt or improve learning by affecting acquisition and/or recall [12].

Chimney test. In this test, the mice had to climb backwards up a plastic tube (3 cm inner diameter, 25 cm in length). Motor impairment was indicated as the inability of mice to climb backward up the tube within 60 s.

Statistical analysis. CS_{50} values with their 95% confidence limits were calculated by computer log-probit analysis, according to Litchfield and Wilcoxon [14]. Subsequently, the 95% confidence limits were transformed to standard errors of the mean (SEM), as described previously [15]. Statistical analysis of data from the MEST test was performed with one-way ANOVA followed by the *post-hoc* Dunnett's test for multiple comparisons. A Kruskal-Wallis non-parametric ANOVA and Dunn's multiple comparisons test was applied to analyse data from the passive avoidance task. Fisher's exact probability test was used for the statistical evaluation of results from the chimney test. Group differences were considered statistically significant at $P < 0.05$.

RESULTS

Electroconvulsions. VGB at doses higher than 500 mg/kg elevated the threshold for electroconvulsions. Captopril (50 mg/kg), perindopril arginine (10 mg/kg), losartan potassium (50 mg/kg), candesartan cilexetil (8 mg/kg), ethacrynic acid (100 mg/kg) and hydrochlorothiazide (100 mg/kg) injected solely did not affect the convulsive threshold. The antihypertensive drugs combined with VGB (500, 600 or 700 mg/kg) did not significantly raise the thresholds when compared to VGB alone groups. In the case of the combinations with VGB and losartan, increased CS_{50} values did not reach statistical significance (Tab. 1 and 2).

Passive avoidance and chimney test. In the passive avoidance task, VGB (700 mg/kg) alone and in combinations with captopril (50 mg/kg), perindopril arginine (10 mg/kg), losartan potassium (50 mg/kg), candesartan cilexetil (8 mg/kg), hydrochlorothiazide (100 mg/kg) or ethacrynic acid (50 mg/kg) showed strong tendency towards impaired retention. In the case of the combination of VGB (700 mg/kg) and ethacrynic acid (100 mg/kg), the treatment with these drugs significantly decreased latency ($P < 0.05$; Tab. 3).

Table 1. Effect of captopril, losartan and ethacrynic acid on anticonvulsant activity of vigabatrin against electroconvulsions

Drug (mg/kg)	$CS_{50} \pm SEM$				
	CAPT 50	LOS 50	EA 100		
vehicle	4.1 ± 0.40 (16)	4.9 ± 0.55 (24)	4.9 ± 0.39 (16)	4.8 ± 0.41 (24)	F(3,76) = 0.5888; P = 0.6242
VGB 500	5.1 ± 0.45 (24)	4.6 ± 0.36 (16)	5.4 ± 0.43 (16)	5.3 ± 0.51 (16)	F(3,68) = 0.5552; P = 0.6464
VGB 600	6.3 ± 0.51** (24)	6.4 ± 0.47 (16)	5.5 ± 0.38 (16)	6.8 ± 0.38** (16)	F(3,68) = 1.272; P = 0.2910
VGB 700	6.4 ± 0.44** (16)	7.3 ± 0.45** (16)	6.2 ± 0.46 (24)	7.2 ± 0.34** (8)	F(3,60) = 1.370; P = 0.2605
	F(3,76) = 4.710; P = 0.0045	F(3,68) = 6.215; P = 0.0009	F(3,68) = 1.711; P = 0.1730	F(3,60) = 6.107; P = 0.0011	

Results are shown as median current strengths (CS_{50} , in mA) with SEM values. Number of animals at those current strengths for which convulsant effects ranged between 4–6 probit (16 and 84%) according to Litchfield and Wilcoxon [14], indicated in brackets. Statistical evaluation of data was performed independently for rows and columns (one-way ANOVA and the *post-hoc* Dunnett's test).
VGB – vigabatrin; CAPT – captopril; LOS – losartan potassium; EA – ethacrynic acid.
** $P < 0.01$ vs. respective control values (columns).

Table 2. Effect of perindopril, candesartan and hydrochlorothiazide on anticonvulsant activity of vigabatrin against electroconvulsions

Drug (mg/kg)	CS ₅₀ ± SEM				
	PER 10	CAN 8	HCTZ 100		
vehicle	5.7 ± 0.56 (24)	5.4 ± 0.54 (32)	5.2 ± 0.64 (32)	5.9 ± 0.42 (24)	F(3,108) = 0.2982; P = 0.8267
VGB 500	6.3 ± 0.50 (16)	5.5 ± 0.22 (16)	6.7 ± 0.56 (24)	6.3 ± 0.24 (16)	F(3,68) = 1.204; P = 0.3151
VGB 600	7.1 ± 0.40 (16)	7.4 ± 0.25* (16)	7.9 ± 0.38* (16)	6.9 ± 0.62 (24)	F(3,68) = 0.7738; P = 0.5126
VGB 700	7.5 ± 0.22* (24)	7.7 ± 0.57** (24)	8.3 ± 0.80** (24)	7.9 ± 0.59* (24)	F(3,84) = 0.2801; P = 0.8396
	F(3,68) = 2.982; P = 0.0373	F(3,84) = 5.825; P = 0.0012	F(3,92) = 4.928; P = 0.0032	F(3,84) = 2.875; P = 0.0409	

Data are presented as median current strengths (CS₅₀ in mA) with SEM values. Number of animals at those current strengths for which convulsant effects ranged between 4 – 6 probit (16 and 84%) according to Litchfield and Wilcoxon [14], indicated in brackets. Statistical evaluation of data was performed independently for rows and columns (one-way ANOVA and the *post-hoc* Dunnett's test).

VGB – vigabatrin; PER – perindopril arginine; CAN – candesartan cilexetil; HCTZ – hydrochlorothiazide.

**P < 0.01; *P < 0.05 vs. respective control values (columns).

Table 3. Cardiovascular drugs and vigabatrin in the passive avoidance test

Drug (mg/kg)	n	Retention time (s)
control	8	180 (180, 180)
VGB (700)	8	19 (16, 180)
VGB (700) + CAN (8)	8	56 (22, 116)
VGB (700) + LOS (50)	8	33 (9, 111)
VGB (700) + PER (10)	8	28 (16, 65)
VGB (700) + CAPT (50)	8	78 (44, 135)
VGB (700) + HCTZ (100)	8	51 (25, 84)
VGB (700) + EA (100)	8	33 (20, 36)*
VGB (700) + EA (50)	8	34 (21, 51)

Results shown as median values (in s) together with 25th and 75th percentiles. n – number of animals; *P < 0.05 vs. control group (Kruskal-Wallis non-parametric ANOVA and Dunn's test).

In the chimney test, VGB (700 mg/kg) alone and in combinations with antihypertensive drugs did not impair motor coordination (Tab. 4).

Table 4. Cardiovascular drugs and vigabatrin in the chimney test

Drug (mg/kg)	n	% of animals
Control	8	0
VGB (700)	8	0
VGB (700) + CAN (8)	8	0
VGB (700) + LOS (50)	8	37.5
VGB (700) + PER (10)	8	0
VGB (700) + CAPT (50)	8	0
VGB (700) + HCTZ (100)	8	0
VGB (700) + EA (100)	8	37.5

Data presented as percentage of animals that failed to perform in this test. n – number of mice. Abbreviations in legends for Tables 1 and 2; P > 0.05 vs. control group (Fisher's exact probability test).

DISCUSSION

The presented results show that protective action of VGB against electroconvulsions is not affected by co-administration of antihypertensive drugs such as captopril, perindopril, losartan, candesartan, hydrochlorothiazide and ethacrynic acid in mice. VGB, as a structural GABA analogue, binds irreversibly to GABA-transaminase (GABA-T) which results in the inhibition of this enzyme and reduced metabolism of this inhibitory neurotransmitter [16]. Thus, VGB seems to

express its anticonvulsant activity primarily via the GABAergic system. However, its mechanism of action might not be solely due to elevated brain GABA levels. Following a single dose of VGB to audiogenic sensitive rats, Engelborghs et al. [17] observed maximal protective activity of this drug 4 h after its administration whilst GABA-T was maximally inhibited 24 h after the injection. These authors have considered that VGB possesses an additional action by reduction of brain excitatory amino acid levels and/or elevation of glycine levels.

As mentioned in the Introduction, VGB exhibited potent anticonvulsive effects in amygdala kindling and in models of audiogenic and chemical seizures evoked by pentylenetetrazole, picrotoxin and strychnine [2]. In addition, VGB was effective against kainate-induced seizure activity in pubescent rats [18], and decreased the number and severity of seizures in the perforant pathway stimulation model of status epilepticus in the rat [19]. There are also reports demonstrating that VGB at doses higher than 500 mg/kg *i.p.* increases the threshold for electroconvulsions [6], which is in agreement with the current study. Lack of interactions between VGB and ACE inhibitors (captopril and perindopril) in the MEST test seems to support observations that these antihypertensive drugs do not positively influence the anticonvulsant activity of AEDs whose primary action is associated with GABAergic system [5, 11]. It is thought that pharmacological mechanisms of AEDs, which are related to sodium channels, NMDA receptors, AMPA receptors, voltage-dependent calcium channels or glycinergic system could be positively affected by certain ACE inhibitors in terms of seizure susceptibility [5, 11]. With regard to AT₁ antagonists, their influence on GABAergic neurotransmission is not clear. In one study, losartan decreased the intensity of pentylenetetrazol kindling, a GABA_A receptor antagonist [20]. On the other hand, losartan and telmisartan, another AT₁ antagonist, did not enhance the anticonvulsant action of phenobarbital [4] that suppresses seizures by potentiating the effects of GABA [16]. A potentiating effect of diuretics upon anticonvulsant activity of AEDs has been reported in a number of studies [9, 10], although the GABAergic system is rather not involved in this effect. The anticonvulsant action of loop diuretics, including ethacrynic acid, can be attributed to a blockade of K⁺-Cl⁻ co-transporters in the brain, especially KCC2 [21]. Thiazides which are structurally related to acetazolamide, a diuretic and AED, may exert their anticonvulsant activity through inhibition of carbonic anhydrase [10]. It is thought that drugs with diverse mechanisms of action may complete their own activities and, thus, produce a synergistic interaction [22]. However, this phenomenon did not occur in the presented study, at least in terms of antiseizure activity, as observed from the combined treatment with VGB and diuretics.

In the passive avoidance task, the combination of VGB (700 mg/kg *i.p.*) with ethacrynic acid (100 mg/kg *i.p.*) significantly impaired retention in mice (P < 0.05). Additionally, other mice subjected to acute VGB (700 mg/kg) treatment, both naive and injected with antihypertensive drugs, showed a strong tendency towards retention deficits; therefore, the observed impairment in learning should be attributed to an effect of VGB. A slight reduction in retention time was observed for mice injected with the lower doses of VGB (308.9 mg/kg *i.p.*) [23]. Mazurkiewicz et al. [24] reported that VGB, up to a dose of 500 mg/kg as single *i.p.* administration, did not affect the working memory task (delayed non-matching to position task), whereas at a dose of 1000 mg/kg *i.p.* it decreased the behavioral activity in rats.

It is noteworthy that delayed non-matching to the position task includes a long-term memory component (the animal must learn and remember the rules of the task to perform correctly on each trial) [24]. Based on the mentioned data, the effects of VGB on memory functions seem to be dose-dependent. It is thought that the passive avoidance is a hippocampal and amygdala dependent test [25]. It has been suggested that hippocampal GABA_A and GABA_B receptor activation may lead to retention deficits in the passive avoidance task [26]. Therefore, the enhancement of GABAergic neurotransmission following administration of VGB could be responsible for the impaired retention. On the other hand, VGB may interfere with performance in the passive avoidance test via its antinociceptive properties. Direct microinjection of VGB into the rostral agranular insular cortex in rats resulted in a clear and consistent analgesia [27]. Systemic (*i.p.*) administration of VGB suppressed the pain sensation in mice challenged with the formalin test [28]. Further, VGB *i.p.*, in a dose-dependent manner, lengthened the time to the first pain reaction in animals subjected to the pain threshold evaluation [23]. Considering that in the step-through passive avoidance test the animals have to acquire (learn) the task, based on an aversive (punitive) stimulus as a negative reinforcement, it can be concluded that if this stimulus is attenuated by an antinociceptive effect of a drug, the animals cannot learn the task properly [23]. However, because VGB at high doses showed some amnesic activity in tests in which aversive stimulus is not applied [24], a direct effect of VGB on memory system which could participate in the observed performance of mice in the passive avoidance test cannot be totally excluded.

CONCLUSIONS

The use of: losartan potassium, candesartan cilexetil, captopril, perindopril arginine, hydrochlorothiazide or ethacrynic acid in patients receiving VGB, is suggested to be neutral regarding its anticonvulsant action. Consequently, none of the tested antihypertensive drugs seems contraindicated in patients with epilepsy on VGB therapy.

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