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Anticonvulsant activity of conventional antiepileptic drugs unaltered by vinpocetine in mouse model of epilepsy

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Abstract: The objective of the study was to determine the effect of combined treatment with vinpocetine (VIN) (a commonly used nootropic drug blocking voltage-gated Na^+ channels) and conventional antiepileptic drugs: carbamazepine (CBZ), valproate (VPA), phenobarbital (PB), and phenytoin (PHT) against maximal electroshock-induced convulsions in mice. Vinpocetine (up to 30 mg/kg) did not present either its own anticonvulsant action or have any effect on the protective effect of antiepileptic drugs. This may indicate that not all Na^+ channel inhibitors are effective against electroconvulsions. On the other hand, concomitant treatment with vinpocetine and antiepileptics should not require any dose corrections in epileptic patients.

Key words: vinpocetine, antiepileptic drugs, electroconvulsions

INTRODUCTION

Vinpocetine is a widely known nootropic drug. On the cellular level it acts as a phosphodiesterase inhibitor, selective for PDE1, and a blocker of voltage-gated Na^+ channels [1]. The drug is as potent as phenytoin for blocking Na^+ channels in rat cortical neurons [2]. Thus, it inhibits the intracellular rise in Na^+ and Ca^+ cations [3] and glutamate release from the hippocampal nerve endings [4]. Vinpocetine possesses significant visceral antinociceptive properties, depending on activation of adenosine receptors [5]. According to Dutov et al. [6], vinpocetine exhibits antiepileptic potential against pentylenetetrazole (PTZ)-, strychnine-, and thiosemicarbazide-induced convulsions in mice, as well as in penicillin-evoked seizures in cats [6], and in PTZ- and neocortically-kindled rats [7]. It is sugested that its antiseizure action may be due to γ-aminobutyric (GABA) and serotoninergic mechanisms [6]. Vinpocetine, besides the neuroprotective and antiepileptic potential, also presents memory enhancing properties, and may perhaps be advantageous in the treatment of epileptic patients [4]. It should be mentioned that conventional antiepileptics – including carbamazepine, phenytoin and valproate – initiated hearing loss induced by PTZ. In contrast, vinpocetine prevented this undesirable effect [8].

In clinical conditions, concomitant treatment with antiepileptics and nootropics is often practiced. The aim of the study was to evaluate the effect of vinpocetine on the protective action of phenobarbital, carbamazepine, phenytoin and valproate against the maximal electroshock-induced convulsions in mice. Adverse effects in respect of motor impairment were assessed by the chimney test.

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MATERIALS AND METHODS

Animals. All experiments were performed on male Swiss mice, kept in colony cages with free access to food and tap water, under standardized housing conditions. The animals were randomly assigned to experimental groups consisting of 8 mice. Each mouse participated in only 1 experiment. All tests were performed between 09:00-14:00 p.m. to minimize confounding effects of circadian rhythms. All experimental procedures were approved by the Local Ethics Committee of the Medical University in Lublin.

Drugs. Vinpocetine (Sigma, St. Louis, MO, USA) and VPA (Polfa, Rzeszów, Poland) were dissolved in sterile saline, while carbamazepine, diphenylhydantoin (both drugs also obtained from Sigma, St. Louis, MO, USA), and PB (Polfa, Warsaw, Poland) were suspended in a 1% solution of Tween 80 (also from Sigma St. Louis, MO, USA). All drugs were administered *i.p.*, at times of their maximal anticonvulsant action against maximal electroshock-induced seizures.

Electroconvulsions. Electroconvulsions were evoked with the use of alternating current (50 Hz) produced by a Rodent Shocker Generator (Ataner, Lublin, Poland), and delivered by ear-clip electrodes. The stimulus duration was 0.2 s. The electroconvulsive threshold (CS_{50}) was the strength of current (in mA) necessary to produce tonic hind limb extension in 50% of the animals tested. The median effective dose (ED_{50}) was a drug dose (in mg/kg) providing a protective effect in 50% of the animals tested against maximal electroshock (25 mA). In order to evaluate CS_{50}s and ED_{50}s at least 4 groups consisting of 8 mice each were used. Subsequently, intensity-response and dose-response curves, were constructed respectively.

Chimney test. The effects of antiepileptic drugs and their combinations with vinpocetine were quantified with the chimney test of Boissier et al. [9] In this test, the animals had to limb backward up a plastic tube (3 cm inner diameter, 25 cm

length). Motor impairment was indicated by the inability of mice to climb backward up the tube within 60 s. Results were presented as TD_{50} values – doses producing motor impairment in 50% of the animals.

Statistics. Statistical analysis of the data obtained in the electroconvulsive test was performed by computer probit analysis, according to Litchfield and Wilcoxon [10].

RESULTS

Effect of vinpocetine on the electroconvulsive threshold. Vinpocetine (up to 30 mg/kg) did not affect the electroconvulsive threshold (Table 1).

Table 1 Effect of vinpocetine (VIN) (on electroconvulsive threshold. CS_{50} (in mA) is the strength of current which produced convulsions in 50% of animals. Vinpocetine (VIN) was administered 30 min before the test

Treatment (mg/kg)	CS_{50} (mA)
Control	6.8 (6.1 - 7.5)
VIN (2.5)	7.2 (6.5 - 8.1)
VIN (5)	7.5 (6.5 - 8.6)
VIN (10)	7.6 (6.7 - 8.5)
VIN (20)	7.7 (7.0 - 8.6)
VIN (30)	7.1 (6.6 - 7.6)

Effect of vinpocetine on the protective action of conventional antiepileptic drugs. Vinpocetine (up to 30 mg/kg) did not influence the anticonvulsant action of phenobarbital, carbamazepine, diphenylhydantoin or valproate (Table 2).

Table 2 Effect of vinpocetine (VIN) on the protective action of conventional antiepileptic drugs. ED_{50} (in mg/kg) is the median effective dose producing protection against seizures in 50% of animals. Vinpocetine (VIN), carbamazepine (CBZ) and valproate (VPA) were administered 30 min, phenobarbital (PB) 60 min, and phenytoin (PHT) 120 min before the test

Treatment (mg/kg)	CS_{50} (mA)
PB + saline	25.8 (21.8 - 30.4)
PB + VIN (2.5)	19.2 (16.6 - 22.1)
PB + VIN (5)	19.6 (6.5 - 8.6)
PB + VIN (30)	20.6 (20.1 - 21.2)
CBZ + saline	10.4 (8.9 - 12.2)
CBZ + VIN (2.5)	9.6 (8.1 - 11.4)
CBZ + VIN (5)	9.8 (8.3 - 11.7)
CBZ + VIN (30)	9.5 (8.7 - 10.6)
PHT + saline	11.7 (10.1 - 13.4)
PHT + VIN (2.5)	10.3 (8.9 - 12.0)
PHT + VIN (5)	10.0 (8.8 - 11.3)
VPA + saline	226.2 (200.8 - 254.7)
VPA + VIN (2.5)	248.2 (224.3 - 275.0)
VPA + VIN (5)	256.4 (230.9 - 284.8)

DISCUSSION

The results obtained demonstrate that vinpocetine (up to 30 mg/kg) was ineffective against the electroconvulsive threshold test, and did not change the anticonvulsant properties of 4 conventional antiepileptic drugs (phenobarbital, carbamazepine, diphenylhydantoin, valproate) against maximal electroshock in mice, the optimal animal model of generalized tonic-clonic convulsions. This finding seems surprising because the most effective drugs in this model – including carbamazepine, diphenylhydantoin and valproate – act through the blocking of Na^+ channels. Vinpocetine was reported to be as potent an Na^+ channel inhibitor as diphenylhydantoin [2]. The effectiveness of vinpocetine against convulsions evoked by negative modulators of $GABA_A$ receptors [6, 7] suggests that the enhancement of GABA-ergic neurotransmission is more important for the antiseizure action of vinpocetine.

It should be stressed that vinpocetine did not potentiate the motor impairment produced by conventional antiepileptic drugs. This indicates that the nootropic may be safely induced in epileptic patients. Lack of changes in antiseizure potential of antiepileptics suggest that no dose adjustment of these drugs is necessary in the case of their combined treatment with vinpocetine.

CONCLUSIONS

1. Vinpocetine is not effective against electrically-evoked convulsions in mice.
2. Vinpocetine did not affect the anticonvulsant action of phenobarbital, carbamazepine, diphenylhydantoin and valproate against maximal electroshock in mice; therefore, no dose adjustment is needed during the combined treatment with vinpocetine and conventional antiepileptic drugs.

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