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Department of Experimental and Clinical Pharmacology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland

MARIUSZ J. ŚWIĄDER

Influence of topiramate and its combination with valproate on the locomotor activity in mice

Wpływ topiramatu i jego kombinacji z waplroninianem na aktywność motoryczną u myszy

Epilepsy affects more than 50 milion persons world-wide. Until recently, physicians have a relatively limited armamentarium of antiepileptic drugs (AEDs) to treat patients with seizure disorders. These agents include phenytoin (PHT), carbamazepine (CBZ), valproate (VPA), benzodiazepines and ethosuximide. In some patients, seizure control with this group of "established" AEDs cannot be achieved at doses that are devoid of various types and severities of AED-related adverse effects. Therefore, from late 80`s newer second-generation antiepileptic drugs have been abundant with clinical approvals. Topiramate (TPM) is one of newer AEDs, possessing multiple diverse mechanisms of action, of which, the inhibition of voltage-sensitive Na+ channels [1]; potentiation of gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission through binding to a novel site on the GABAA-receptor complex [2]; blockade of excitatory neurotransmission through a negative modulatory effect on Ca^{2+}-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) and kainate subtypes of glutamate receptors [3]; inhibition of neuronal L-type high-voltage-activated Ca^{2+} channels [4]; and inhibition of the carbonic anhydrase isoenzymes CA II and CA IV, may account largely for its broad-spectrum anticonvulsant activity [5].

In experimental models of epilepsy, the drug is active against maximal electroshock (MES)-induced seizures [6], considerably reduces seizure activity and afterdischarge duration in amygdala-kindled rat [7], and protects the animals against pentylenetetrazole-induced seizures [8]. Moreover, in genetically epilepsy-prone rats, TPM reduces tonic seizures and decreases spike-wave discharges [9].

The aim of this study was to evaluate the effects of TPM, administered alone and in combination with valproate (VPA), on the exploratory and spontaneous locomotor activities in mice. Previously, it has been reported that TPM (administered at a constant dose of 5 mg/kg) potentiated the anticonvulsant activity of antiepileptics in the MES-test in mice [10]. In the present study, we studied the effects of TPM (5 mg/kg), VPA (203 mg/kg) and their combination on the exploratory and spontaneous locomotor activity of mice. To-date, the effect of TPM and VPA in combination on the locomotor behaviors in mice has never been assessed. The alterations in locomotor functioning of animals following a single exposure to TPM alone or combined with VPA would allow us to determine the adverse-effect profile of these AEDs.

MATERIALS AND METHODS

A n i m a l s. The experiments were carried out on male Swiss mice weighing 20-25 g. The animals were housed in colony cages with free access to food and tap water. Temperature in experimental room was 22 ± 1°C and the mice were on a natural light-dark cycle. After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to experimental groups (consisting of 8 animals). Each mouse was used only once. All experimental procedures were approved by Local Ethics Committee of Lublin.

D r u g s. The following AEDs were used: TPM (Topamax; Cilag AG, Schaffhausen, Switzerland) and VPA (Dipromal, Polfa Rzeszσw, Poland). The AEDs were suspended in distilled water and administered intraperitoneally (i.p.) in a volume of 0.1 ml/kg body weight. VPA was given – 30 min and TPM - 120 min prior to the test, as presented elsewhere [11].

LOCOMOTOR ACTIVITY MONITORING

Locomotor activity of animals was assessed with a Digiscan Animal Activity Monitor System (Omnitech Electronics, Columbus, OH, USA). Each monitor consisted of a 41 x 41 x 32 cm Plexiglas open field box with a grid of infrared beams mounted horizontally every 2.5 cm and vertically every 4.5 cm. Photocells located on the wall directly opposite each photo-beam were activated when the animal interrupted the beam. Each box was partitioned with acrylic cross into four (20 x 20 x 32 cm) quadrants. Mice were tested in the opposite quadrants of each unit (i.e. two mice per box). The photocells of each activity box were connected to the Digiscan analyzer that transmitted the number of beam breaks (activity data) to a computer. During operation, the pattern of beam interruptions was recorded and analyzed by IBM-PC compatible computer. Interruption of any beam was recorded as an activity score. All activity data were collected during two consecutive 15-min periods. Cumulative counts were compiled and downloaded every 15 min into the data collection software, which organized these counts into different motor indices. Three representative motor indices were analyzed as follows: 1) total distance traveled in cm – measuring the amount of forward activity of animals; 2) ambulatory activity – measuring the total number of beam interruptions that occurred in the horizontal sensors during a given sample period; and 3) rearing activity – measuring the total number of vertical photo-beam interruptions within the sample period.

E x p e r i m e n t a l d e s i g n. In this experiment, the mice were not habituated to the test apparatus, therefore the test procedure consisted of two independent, consecutive measures. After injection of vehicle or the respective AED doses, the mice were placed in the centre of individual cages and recording of their locomotor activities started throughout two consecutive 15 min-intervals. The first measure of animals' activity is the rate of habituation to a novel environment. Thus, during prolonged exposure to a new environment, animals typically spend progressively less time in movements and exploration. So, the second measure is considered as the rate of spontaneous activity of mice.

S t a t i s t i c s. Data from the locomotor activity test were statistically evaluated with the analysis of variance (ANOVA) followed by Bonferroni's post-hoc test for multiple comparisons.

RESULTS

Exploratory locomotor activity testing. TPM (5 mg/kg) combined with VPA (203 mg/kg) or given alone, either reduced the ambulatory activity scores, rearing activity score nor total distance traveled of the mice (Fig. 1).

Spontaneous locomotor activity testing. TPM combined with VPA reduced, however not significantly, the ambulatory activity scores in mice (Fig. 2A). Furthermore, TPM combined with VPA did not change the rearing activity scores in mice (Fig. 2). The both AEDs administered separately did not alter this parameter in animals tested (Fig. 2). Inversely, neither TPM nor VPA administered alone significantly shortened total distance traveled by animals (Fig. 2).

DISCUSSION

The presented results clearly indicate that TPM combined with VPA did not affect the exploratory and spontaneous locomotor activities in mice. Similarly, TPM given singly, at a dose of 5 mg/kg, also did not influence ambulatory and rearing activities, as well as, had no impact on total distance traveled by the mice. Moreover, neither the exploratory nor spontaneous locomotor activities of animals were altered after the injection of VPA alone.

Previously, it has been documented that TPM (5 mg/kg) enhanced the anticonvulsant activity of CBZ, VPA, PB and PHT [10]. Moreover, TPM administered alone or combined with AEDs (at doses providing a 50% protection against MES) resulted in no adverse effects, as measured in the chimney test (motor coordination) or passive avoidance task (long-term memory). Noteworthy, the investigated combination between TPM and CBZ was pharmacokinetic in nature, since it has been found that TPM considerably elevated the free plasma level of CBZ [10].

The complete unaffecting observed following administration of both AEDs, when compared to control (vehicle-treated animals), provides evidence that the combination may be useful in the clinical setting.

It should be highlighted that the electronically-monitored locomotor activity test in rodents seems to be a good screening allowing preselection of drugs affecting CNS and changing locomotor functioning in experimental animals.

CONCLUSIONS

1. Lack of any significant changes in the ambulatory locomotor activity of animals administered with TPM alone or in combination with VPA, during the exploratory and spontaneous activities testing, is of some clinical importance, worthy of further consideration.
2. Based on the animals behavioral study we could recommended co-adminisration of TPM with VPA.

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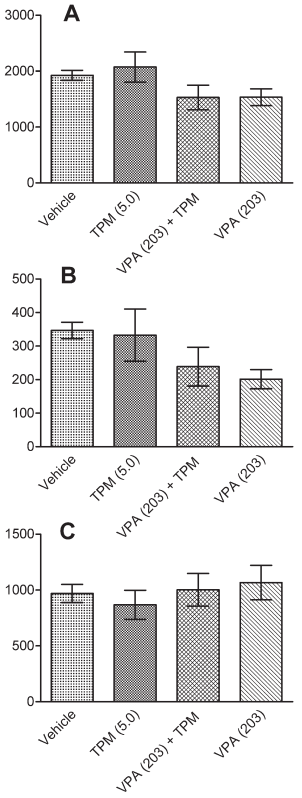

Fig. 1. Influence of topiramate, valproate and its combination on the exploratory locomotor activity in mice

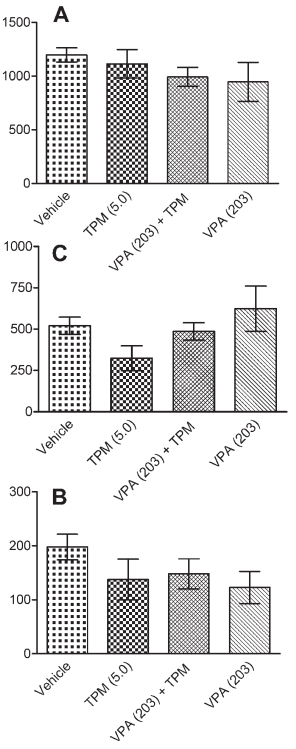

Fig. 2. Effect of topiramate alone or combined with valproate on the spontaneous locomotor activity in mice

Columns represent the means (± SEM as the error bars) of the ambulatory activity (A), rearing activity (B), and total distance traveled by animals (C) evaluated during the first period of time (0-15 min) – habituation to a novel environment. Means were calculated from at least of 8 determinations. Statistical evaluation of data was performed with one-way ANOVA followed by Bonferroni's post-hoc test. TPM – topiramate; VPA – valproate.

Columns represent the means (± SEM as the error bars) of the ambulatory activity (A), rearing activity (B), and total distance traveled by animals (C) evaluated during the second period of time (16-30 min) – related with spontaneous locomotion in animals. Means were calculated from at least of 8 determinations. Statistical evaluation of data was performed with one-way ANOVA followed by Bonferroni's post-hoc test. TPM – topiramate; VPA – valproate

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SUMMARY

The aim of this study was to determining the effect of topiramate (TPM - a newer antiepileptic drug) co-administered with valproate (VPA) on the exploratory and spontaneous activities in mice. Locomotor activity was monitored electronically using a Digiscan system with relation to the ambulatory and rearing activities, as well as total distance traveled by animals within two 15-min. periods. Results indicated that TPM (5 mg/kg) and VPA (203 mg/kg) administered alone did not alter the exploratory and spontaneous locomotor activities with respect to all parameters studied in mice. Similarly, the drug combination of VPA (203 mg/kg) with TPM (5 mg/kg) also did not influence either spontaneous or exploratory locomotor activities in animals. As the combination of TPM with VPA unchanged locomotion in experimental animals, it seems that clinical application of these drugs in combination is favorable.

Keywords: exploratory and spontaneous locomotor activities, valproate, topiramate, ambulatory and rearing activities, total distance, adverse-effect profile, mice.

STRESZCZENIE

Zamierzeniem pracy była ocena wpływu topiramatu (TPM – nowego leku przeciwpadaczkowego) podawanego łącznie z walproinianem magnezu (VPA) na poznawczą i spontaniczną aktywność ruchową u myszy. Aktywność ruchową monitorowano elektronicznie przy użyciu systemu Digiscan, oceniając ruchliwość poziomą, pionową oraz całkowity dystans pokonany przez zwierzęta w ciągu 2 okresów po 15 min. Wyniki wykazują, że TPM (5 mg/kg) i VPA (203 mg/kg) podawane osobno nie zmieniały poznawczej i spontanicznej aktywności ruchowej w zakresie wszystkich badanych parametrów u myszy. Podobnie, kombinacja VPA (203 mg/kg) z TPM (5 mg/kg) nie wpływała znacząco na aktywność ruchową poznawczą i spontaniczną u zwierząt. Wnioskując, skoro kombinacja TPM z VPA nie zmienia aktywności motorycznej u zwierząt doświadczalnych, wydaje się, że łączne podawanie tych leków w praktyce klinicznej może okazać się korzystne.

Słowa kluczowe: aktywność ruchowa poznawcza, aktywność ruchowa spontaniczna, walpronian, topiramat