ORIGINAL PAPER
ORYGINALNY ARTYKUŁ NAUKOWY

Health Problems of Civilization 2017, Volume 11, Issue 3
ISSN 2353-6942

ANTICONVULSANT POTENCY OF 10 VARIOUS P-ISOPROPOXYPHENYLSUCCINIMIDE DERIVATIVES IN THE MAXIMAL ELECTROSHOCK-INDUCED SEIZURE THRESHOLD MODEL IN MICE

PRZECIWDRGAWKOWE DZIAŁANIE 10 RÓŻNYCH POCHODNYCH P-IZOPROPOKSYFENYLOBURSZTYNIMIDÓW W MODELU PROGU MAKSYMALNEGO WSTRZĄSU ELEKTRYCZNEGO U MYSZY

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zebranie funduszy

Summary

Background. To compare the anticonvulsant potency of 10 various p-isopropoxyphenylsuccinimide (IPPS) derivatives [i.e., IPPS (IPPS); N-(morpholinomethyl)-IPPS (MM-IPPS); N-(anilinomethyl)-IPPS (AM-IPPS); N-hydroxymethyl-IPPS (HM-IPPS); N-(p-acetylphenyl)-IPPS (AP-IPPS); N-(p-ethoxycarbonylphenylmethyl)-IPPS (ECPM-IPPS); N-(m-bromoanilinomethyl)-IPPS (BAM-IPPS); N-(o-carboxyanilinomethyl)-IPPS (o-CAM-IPPS); N-(m-carboxyanilinomethyl)-IPPS (m-CAM-IPPS); N-(p-carboxyanilinomethyl)-IPPS (p-CAM-IPPS)] in the maximal electroshock-induced seizure threshold (MEST) test in mice. **Material and methods.** Linear regression analysis of doses of IPPS derivatives and their threshold increases in the MEST test in mice allowed to calculate TID20 values i.e., doses of the tested IPPS derivatives that elevate by 20% the seizure threshold in IPPS-treated mice over the threshold in control animals. **Results.** All the studied IPPS derivatives (i.e., IPPS, MM-IPPS, HM-IPPS, AP-IPPS, AM-IPPS, ECPM-IPPS, o-CAM-IPPS, m-CAM-IPPS, p-CAM-IPPS and BAM-IPPS) increased in a dose dependent manner the threshold for maximal electroshock-induced seizures in mice. The TID20 values in the MEST test for IPPS, AP-IPPS, AM-IPPS, BAM-IPPS, o-CAM-IPPS, m-CAM-IPPS, p-CAM-IPPS, ECPM-IPPS, HM-IPPS, and MM-IPPS were 60.44 mg/kg, 86.30 mg/kg, 44.69 mg/kg, 103.34 mg/kg, 22.43 mg/kg, 52.84 mg/kg, 80.85 mg/kg, 109.75 mg/kg, 32.62 mg/kg and 53.50 mg/kg, respectively. **Conclusions.** The studied IPPS derivatives with respect to their anticonvulsant potency in the MEST test can be arranged as follows: o-CAM-IPPS > HM-IPPS > AM-IPPS > m-CAM-IPPS > MM-IPPS > IPPS > p-CAM-IPPS > AP-IPPS > BAM-IPPS > ECPM-IPPS.

Keywords: p-isopropoxyphenylsuccinimide, electroshock, maximal electroshock-induced seizure threshold, threshold increasing dose by 20%

Streszczenie

Wprowadzenie. Porównać siłę przeciwdrgawkowego działania 10 różnych pochodnych p-izopropoksyfenylobursztynimidów (IPPS) [tj. (IPPS); N-(morfolinometylo)-IPPS (MM-IPPS); N-(anilinometylo)-IPPS (AM-IPPS); N-hydroksymetylo-IPPS (HM-IPPS); N-(p-acetylofenylo)-IPPS (AP-IPPS); N-(p-etoksykarbonylofenylometylo)-IPPS (ECPM-IPPS); N-(m-bromoanilinometylo)-IPPS (BAM-IPPS); N-(o-karboksyanilinometylo)-IPPS (o-CAM-IPPS); N-(m-karboksyanilinometylo)-IPPS (m-CAM-IPPS); N-(p-karboksyanilinometylo)-IPPS (p-CAM-IPPS)] w teście progu maksymalnego wstrząsu elektrycznego (MEST) u myszy. **Materiał i metody.** Analiza regresji liniowej dawek pochodnych IPPS i ich wzrostów progu w teście MEST u myszy pozwoliła policzyć wartości TID20 tj. dawki badanych pochodnych IPPS, które podnoszą o 20% próg drgawkowy u myszy, którym podano IPPS, ponad próg u zwierząt kontrolnych. **Wyniki.** Wszystkie badane pochodne IPPS (tj. IPPS, MM-IPPS, HM-IPPS, AP-IPPS, AM-IPPS, ECPM-IPPS, o-CAM-IPPS, m-CAM-IPPS, p-CAM-IPPS and BAM-IPPS) zwiększały w sposób zależny od dawki próg maksymalnego wstrząsu elektrycznego u myszy. Wartości TID20 w teście MEST dla IPPS, AP-IPPS, AM-IPPS, BAM-IPPS, o-CAM-IPPS, m-CAM-IPPS, p-CAM-IPPS, ECPM-IPPS, HM-IPPS i MM-IPPS wynosiły odpowiednio: 60,44 mg/kg, 86,30 mg/kg, 44,69 mg/kg, 103,34 mg/kg, 22,43 mg/kg, 52,84 mg/kg, 80,85 mg/kg, 109,75 mg/kg, 32,62 mg/kg i 53,50 mg/kg. **Wnioski.** Badane pochodne IPPS w odniesieniu do ich siły przeciwdrgawkowego działania można uporządkować następująco: o-CAM-IPPS > HM-IPPS > AM-IPPS > m-CAM-IPPS > MM-IPPS > IPPS > p-CAM-IPPS > AP-IPPS > BAM-IPPS > ECPM-IPPS.

Słowa kluczowe: p-izopropoksyfenylobursztynimid, wstrząs elektryczny, próg maksymalnego wstrząsu elektrycznego, dawka zwiększająca próg o 20%

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Submitted: 2017 Aug 17
Accepted: 2017 Aug 25

Kocharov SL, Panosyan HA, Marzęda P, Wróblewska-Łuczka P, Kochman E, Wlaź A, et al. Anticonvulsant potency of 10 various p-isopropoxyphenylsuccinimide derivatives in the maximal electroshock-induced seizure threshold model in mice. Health Problems of Civilization. 2017; 11(3): 195-201. doi: 10.5114/hpc.2017.70010.

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Introduction

A large number of publications and articles on the search for new substances possessing anticonvulsant action confirm the fact that treatment of epilepsy is still a topical problem and clinicians today do not possess a sufficient array of highly efficacious drugs devoid of any substantial unfavorable side effects. For this reason, there is an obvious need to search for newer antiepileptic drugs. Up-to-date, several classes of structurally unrelated organic compounds are used in therapy of epilepsy, but they all have certain drawbacks [1].

Despite the structural variety of anticonvulsant substances, some common structural elements responsible for the therapeutic activity have been determined. Such constituents are the nitrogenous heteroatomic system, at least one phenyl ring, and either additional phenyl nucleus or an alkyl substituent attached to the heterocycle [2, 3]. These attributes are, partially or fully, characteristic for a well-established antiepileptic drug – ethosuximide (3-ethyl-3-methyl-pyrrolidine-2,5-dione), which belongs to the succinimide class. However, this class of compounds is not exhausted as a source of new representatives with discussed activity [4-9].

Recently, a significant anticonvulsant activity of 3-(4-isopropoxyphenyl)-pyrrolidine-2,5-dione (3-p-isopropoxyphenylsuccinimide) was observed and this compound was introduced into medical practice in the former Soviet Union [10] under the trade name 'Pufemid'. In view of all the above, it was considered expedient to search for the influence of additional chemical modification of the molecule of 3-p-isopropoxyphenylsuccinimide on its biological properties, namely, on expected changes in the anticonvulsant activity. With this purpose, a series of p-isopropoxyphenylsuccinimide (IPPS) derivatives [i.e., IPPS (IPPS); N-(morpholinomethyl)-IPPS (MM-IPPS); N-(anilinomethyl)-IPPS (AM-IPPS); N-hydroxymethyl-IPPS (HM-IPPS); N-(p-acetylphenyl)-IPPS (AP-IPPS); N-(p-ethoxycarbonylphenylmethyl)-IPPS (ECPM-IPPS); N-(m-bromoanilinomethyl)-IPPS (BAM-IPPS); N-(o-carboxyanilinomethyl)-IPPS (o-CAM-IPPS); N-(m-carboxyanilinomethyl)-IPPS (m-CAM-IPPS); N-(p-carboxyanilinomethyl)-IPPS (p-CAM-IPPS)] were tested in an *in vivo* experimental model of epilepsy – the maximal electroshock-induced seizure threshold (MEST) [11-18]. To unequivocally assess the anticonvulsant potency of the tested candidate drugs in the MEST model, the calculation of TID_{20} value, i.e., doses of the compounds that increase the electroconvulsive threshold by 20% in drug-treated animals over the threshold in control animals, is recommended [19].

Previously, the anticonvulsant potency of modafinil, its sulfone and acid metabolites and GBR-12909 (a prototypical dopamine transporter blocker) in the MEST test were assessed by calculating the TID_{20} values for these agents [20]. Likewise, the anticonvulsant potency of a series of benzylamide derivatives (i.e., nicotinic acid benzylamide, picolinic acid 2-fluoro-benzylamide, picolinic acid benzylamide, (RS)-methyl-alanine-benzylamide, isonicotinic acid benzylamide and (R)-N-methyl-proline-benzylamide) was assessed in the MEST model by comparing the TID_{20} values for these compounds in mice [21].

The aim of this study was to calculate the TID_{20} values for 10 various IPPS derivatives in the MEST test in mice in order to assess their anticonvulsant potency in this seizure model.

Material and methods

Calculation of TID_{20} values from the MEST test

Threshold for maximal electroshock-induced seizures was recorded for at least 3 increasing doses of each p-isopropoxyphenylsuccinimide (IPPS) derivative as follows: 25, 50 and 100 mg/kg for MM-IPPS; 12.5, 25, 50 and 100 mg/kg for HM-IPPS; 25, 50, 100 and 150 mg/kg for AP-IPPS; 18.75, 37.5, 75 and 150 mg/kg for IPPS and AM-IPPS; 50, 100 and 150 mg/kg for BAM-IPPS and ECPM-IPPS; 37.5, 75 and 150 mg/kg for o-CAM-IPPS and m-CAM-IPPS; and 75, 100 and 150 mg/kg for p-CAM-IPPS. Subsequently, the particular doses of IPPS derivatives and their resultant percentage of threshold increase over the threshold for control (vehicle-treated animals) were graphically depicted and examined with linear regression analysis, as recommended earlier [19, 22]. Finally, the TID_{20} values were directly calculated from linear regression equations.

Results

TID_{20} values for various IPPS derivatives

MM-IPPS administered systemically (i.p.) in doses of 25, 50 and 100 mg/kg increased the threshold for MEST-induced seizures over the threshold for control animals by 10.5%, 19.5% and 34.7%, respectively (Figure 1A).

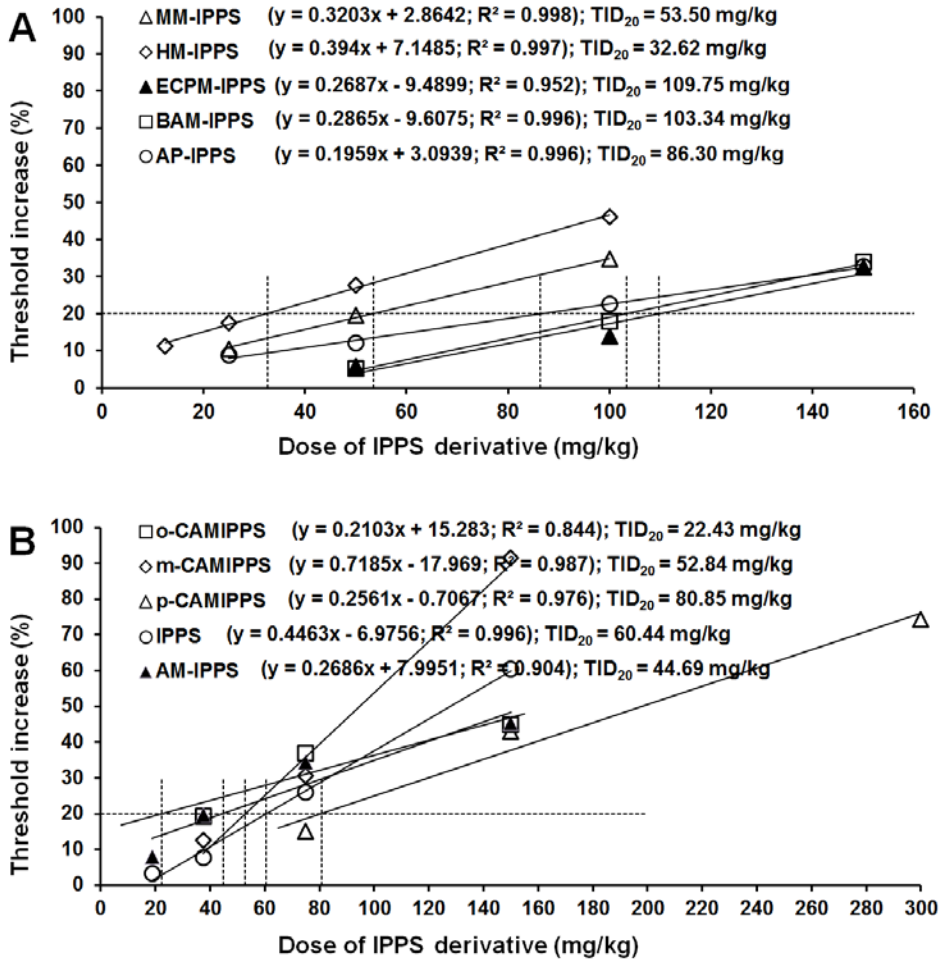

Figure 1A-B. Dose-threshold increase relationship for 10 various IPPS derivatives in the maximal electroshock seizure threshold (MEST) test in mice. Each point corresponds to a threshold increasing dose of IPPS derivative, which was experimentally determined in the MEST test in mice. Linear regression analysis allowed for the determination of equations for dose-threshold increase relationship for 10 IPPS derivatives (Fig. 1A, Fig. 1B). For each IPPS derivative, y – is the threshold increase in %, x – is the dose of the studied IPPS derivative, and R^2 – coefficient of determination. The dashed line parallel to the abscissa corresponds to the TID_{20} values of IPPS derivatives, (threshold increasing doses by 20%) in the MEST test

The calculated TID_{20} value from the linear equation was 53.50 mg/kg (Figure 1A; Table 1).

Table 1. Comparison of TID_{20} values for various IPPS derivatives in the MEST test in mice

Chemical name of IPPS derivative	TID_{20} (mg/kg)	Molecular Weight	TID_{20} (mM/kg)
N-(o-Carboxyanilinomethyl)-p-isopropoxyphenylsuccinimide (o-CAM-IPPS)	22.43	382.410	0.0587
N-Hydroxymethyl-p-isopropoxyphenylsuccinimide (HM-IPPS)	32.62	263.287	0.1239
N-(Anilinomethyl)-p-isopropoxyphenylsuccinimide (AM-IPPS)	44.69	338.400	0.1321
N-(m-Carboxyanilinomethyl)-p-isopropoxyphenylsuccinimide (m-CAM-IPPS)	52.84	382.410	0.1382
N-(Morpholinomethyl)-p-isopropoxyphenylsuccinimide (MM-IPPS)	53.50	332.390	0.1610
p-Isopropoxyphenylsuccinimide monohydrate (IPPS)	60.44	251.277	0.2405
N-(p-Carboxyanilinomethyl)-p-isopropoxyphenylsuccinimide (p-CAM-IPPS)	80.85	382.410	0.2114
N-(p-Acetylphenyl)-p-isopropoxyphenylsuccinimide (AP-IPPS)	86.30	351.387	0.2456
N-(m-Bromoanilinomethyl)-p-isopropoxyphenylsuccinimide (BAM-IPPS)	103.34	417.299	0.2476
N-(p-Ethoxycarbonylphenylmethyl)-p-isopropoxyphenylsuccinimide (ECP-M-IPPS)	109.75	410.460	0.2674

Results are doses of the drugs increasing the threshold for maximal electroshock-induced seizures in mice by 20% (TID_{20}) in mg/kg and mM/kg.

HM-IPPS in doses of 12.5, 25, 50 and 100 mg/kg elevated the threshold for MEST-induced seizures over the threshold for control animals by 11.2%, 17.5%, 27.7% and 46.1%, respectively (Figure 1A). The calculated TID_{20} value was 32.62 mg/kg (Figure 1A; Table 1).

AP-IPPS injected systemically (i.p.) in doses of 25, 50, 100 and 150 mg/kg raised the threshold for MEST-induced seizures over the threshold for control animals by 8.8%, 12.0%, 22.5% and 32.8%, respectively (Figure 1A). The TID_{20} value was 86.30 mg/kg (Figure 1A; Table 1).

BAM-IPPS administered i.p. in doses of 50, 100 and 150 mg/kg elevated the threshold for MEST-induced seizures over the threshold for control animals by 5.3%, 17.9% and 33.9%, respectively (Figure 1A). The TID_{20} value was 103.34 mg/kg (Figure 1A; Table 1).

ECPM-IPPS administered systemically in the same doses of 50, 100 and 150 mg/kg increased the threshold for MEST-induced seizures by 5.7%, 13.9% and 32.6%, respectively (Figure 1A). The TID_{20} value was 109.75 mg/kg (Figure 1A; Table 1).

IPPS administered i.p. in doses of 18.75, 37.5, 75 and 150 mg/kg raised the threshold for MEST-induced seizures over the threshold for control animals by 3.4%, 7.8%, 26.0% and 60.5%, respectively (Figure 1B). The TID_{20} value was 60.44 mg/kg (Figure 1B; Table 1).

AM-IPPS administered intraperitoneally in the same doses of 18.75, 37.5, 75 and 150 mg/kg elevated the threshold for MEST-induced seizures by 8.0%, 19.8%, 34.5% and 45.3%, respectively (Figure 1B). The TID_{20} value was 44.69 mg/kg (Figure 1B; Table 1).

o-CAM-IPPS injected systemically (i.p.) in doses of 37.5, 75 and 150 mg/kg elevated the threshold for MEST-induced seizures over the threshold for control animals by 19.3%, 36.9% and 44.9%, respectively (Figure 1B). The TID_{20} value for o-CAM-IPPS was 22.43 mg/kg (Figure 1B; Table 1).

m-CAM-IPPS administered i.p. in the same doses of 37.5, 75 and 150 mg/kg increased the threshold for MEST-induced seizures by 12.5%, 30.6% and 91.6% over the threshold for control animals, respectively (Figure 1B). The TID_{20} value was 52.84 mg/kg (Figure 1B; Table 1).

The last tested IPPS derivative, p-CAM-IPPS, when injected i.p. in the doses of 75, 150 and 300 mg/kg raised the threshold for MEST-induced seizures by 15.0%, 42.93% and 74.4% over the threshold for control animals, respectively (Figure 1B). The TID_{20} value was 80.85 mg/kg (Figure 1B; Table 1).

Discussion

The main goal of this study was to compare the anticonvulsant properties of a series of IPPS derivatives and classify the compounds taking into account their anticonvulsant potency manifesting in elevation of the threshold for maximal electroshock-induced seizures in mice. In this study, we did not examine the anticonvulsant effects of various IPPS derivatives in the MEST test, but we only calculated the TID_{20} values from the antiseizure effects that have already been determined in our earlier studies. A novelty of our research is related to the determination of the anticonvulsant potency of 10 IPPS derivatives by calculating their TID_{20} values in the MEST test, which allowed us to compare the anticonvulsant potency of the tested IPPS derivatives. In the MEST test, researchers usually determine the threshold for maximal electroshock-induced seizures in mice receiving various doses of the examined compounds. Unfortunately, the threshold for control (vehicle-treated) animals differs in each day of experiment in the MEST test, therefore, researchers cannot directly compare the anticonvulsant effects produced by various compounds. Also classification of the compounds with respect to their antiseizure potency is impossible. To be able to compare the effects produced by various compounds in the MEST test, the calculation of TID_{20} values is recommended [22]. Sometimes researchers calculate TID_{50} values, i.e., doses of the compounds elevating the threshold by 50% as compared to the threshold value for control animals, but such calculations are very rare. To calculate the TID_{20} values for IPPS derivatives, we used linear regression analysis, which analyzed the increasing doses of 10 IPPS derivatives and their corresponding threshold increases in mice challenged with the MEST test. It is important to note that the TID_{20} values as determined in the MEST test are substantially lower than the experimentally determined ED_{50} values in the MES test [11-18]. Furthermore, we have reported that some of the studied IPPS derivatives when combined with classical antiepileptic drugs, they potentiated the anticonvulsant properties of the selected antiepileptic drugs (i.e., phenytoin, phenobarbital and valproate) in the mouse MES model in mice [11, 13-18]. More specifically, it has been found that AM-IPPS, AP-IPPS, HM-IPPS and MM-IPPS significantly potentiated the antiseizure activity of phenobarbital and valproate in the mouse MES model (Table 2).

Table 2. Influence of various IPPS derivatives on the anticonvulsant potency of classical antiepileptic drugs in the MES test in mice

IPPS derivative	Classical antiepileptic drugs				References
	Carbamazepine	Phenytoin	Phenobarbital	Valproate	
AM-IPPS	0	0	↑	↑	[14]
AP-IPPS	0	0	↑	↑	[16]
BAM-IPPS	0	0	0	0	[17]
o-CAM-IPPS	↓	0	0	0	[12]
m-CAM-IPPS	0	0	0	0	[12]
p-CAM-IPPS	0	0	0	0	[12]
ECPM-IPPS	0	0	0	0	[11]
HM-IPPS	0	0	↑	↑	[15]
IPPS	0	↑	0	↑	[13]
MM-IPPS	0	0	↑	↑	[18]

↑ – increase in the anticonvulsant potency;
0 – no significant effect on the anticonvulsant potency;
↓ – decrease in the anticonvulsant potency.

Likewise, IPPS enhanced the anticonvulsant action of phenytoin and valproate in mice challenged with the MES test. In contrast, o-CAM-IPPS significantly reduced the anticonvulsant action of carbamazepine in the MES test in mice (Table 2). Only, BAM-IPPS, m-CAM-IPPS, p-CAM-IPPS and ECPM-IPPS had no significant impact on the anticonvulsant properties of all the tested classical antiepileptic drugs in the MES test in mice (Table 2).

On the other hand, it should be mentioned that IPPS derivatives tested in this study at doses reflecting their TID_{20} values did not produce any acute adverse effects in mice. More specifically, no significant impairment of motor coordination (ataxia) or alleviation of skeletal muscular strength (flaccidity) were reported in mice [11-18]. In other words, lack of any adverse effects associated with the treatment with IPPS derivatives contributes to their favorable pharmacological profiles in preclinical studies. Of note, in preclinical epileptology, researchers are obliged to indicate which of the tested compounds is the most favorable with respect to their suppression of seizures. Considering the calculated TID_{20} values for IPPS derivatives, the most favorable compound was o-CAM-IPPS with the lowest TID_{20} value of 22.43 mg/kg.

Additional explanations are required when discussing facts that some IPPS derivatives potentiated the anticonvulsant action of phenobarbital and valproate, whose main anticonvulsant action is associated with activation of GABA-ergic neurotransmission in the brain [23]. In contrast, IPPS derivatives did not enhance the anticonvulsant action of carbamazepine and phenytoin (except for IPPS), whose main anticonvulsant effects are mediated by the blockade of voltage-dependent sodium channels in neurons [23]. It can be suggested that IPPS derivatives can possess similar molecular mechanisms of action to those of carbamazepine and phenytoin. In such a situation, IPPS derivatives probably compete carbamazepine and phenytoin to bind to their target sites. This hypothesis can be confirmed at least partially by an observation of the effects of o-CAM-IPPS with carbamazepine in the mouse MES test. It was found that o-CAM-IPPS alleviated the anticonvulsant action of carbamazepine in mice. In contrast, two structurally similar IPPS derivatives (m-CAM-IPPS and p-CAM-IPPS) had no impact on the anticonvulsant action of carbamazepine in the mouse MES test in mice. It can be suggested that o-CAM-IPPS blocks specific binding of carbamazepine to its target in neurons and, in consequence, it reduced the antiseizure effects of the drug. Additionally, as documented in this study, all three CAM-IPPS derivatives (o-CAM-IPPS, m-CAM-IPPS and p-CAM-IPPS), despite almost identical chemical structure, had diverse TID_{20} values, ranging from 22.43 mg/kg (o-CAM-IPPS), 52.84 mg/kg (m-CAM-IPPS) to 80.85 mg/kg (p-CAM-IPPS). Of note, the TID_{20} value for p-CAM-IPPS was 3.6-times higher than that for o-CAM-IPPS (Table 1).

In this study we arranged the IPPS derivatives with respect to their anticonvulsant properties observed in the MEST test in mice. As shown in Table 1, the strongest anticonvulsant properties possessed o-CAM-IPPS with its TID_{20} value of 22.43 mg/kg, whereas the weakest properties were documented for ECPM-IPPS with its TID_{20} value of 109.75 mg/kg (Table 1). Undoubtedly, our classification allowed to indicate the most beneficial IPPS derivatives, which were characterized by strong anticonvulsant effects (low TID_{20} values) and lack of any adverse effects in experimental animals.

In conclusion, the compared IPPS derivatives with respect to their anticonvulsant potency in the MEST test can be arranged in ascending order as follows: o-CAM-IPPS > HM-IPPS > AM-IPPS > m-CAM-IPPS > MM-IPPS > IPPS > p-CAM-IPPS > AP-IPPS > BAM-IPPS > ECPM-IPPS.

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