GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Anticonvulsive and Neurotoxic Effects of Lamictal (Lamotrigine) in Combination with Other Anticonvulsive Preparations

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In the model of electroshock convulsions combined administration of lamictal with other anticonvulsants (sodium valproate, phenobarbital, Diphenine, carbamazepine, ethosuximide, diazepam, and riodipin) decreased ED_{50} of each preparation by 1.9-4.2 times. The effectiveness of combination with carbamazepine was the highest: its therapeutic index was higher than that of each ingredient preparation.

Key words: *lamictal (lamotrigine); anticonvulsants; maximum electroshock; complex pathogenic therapy*

Among novel antiepileptic preparations a particular place belongs to lamictal (LT or lamotrigine), a triazine derivative [1,7,15]. It differs from antiepileptic preparations by its effect on voltage-dependent Na channels in nerve presynaptic terminals, where it inhibits the release of excitative neurotransmitters (predominantly glutamate), although glutamate is released within the limits of physiological norm [11, 14]. In previous studies devoted to development of a complex pathogenic therapy of epilepsy, it was shown that in a number of cases combined administration of preparations modifying basic mechanisms of epileptogenesis makes it possible to decrease dosage of the drugs and to achieve a high therapeutic index (TI) of the combinations [2-5]. Therefore, it was interesting to evaluate the effectiveness of combined administration of LT with other antiepileptic drugs. There is evidence that LT has an appreciable therapeutic effect against the background of antiepileptic preparations when they are inefficient [1]. In this work we assess the effectiveness of combined administration of LT with other anticonvulsant preparations.

MATERIALS AND METHODS

Experiments were performed on 380 random-bred albino mice weighing 18-24 g. The animals were maintained under vivarium conditions on the standard ration. Anticonvulsant activity of preparations and their combinations was estimated in the maximum electroshock test [5]. Neurotoxicity of these substances was determined by the rota-rod test (6 rpm during 10 min). Effectiveness of individual preparations and their combinations was characterized by the dosage which prevented tonic convulsions of the hind legs in 50% animals (ED_{50}). This value and the dose respecting to the toxic effect in 50% animals (TD_{50}) was determined by the method [12] using computer software [9]. After combined administra-

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TABLE 1. ED_{50}, TD_{50}, and TI of Anticonvulsant Preparations

Combination	ED_{50} of preparations, mg/kg	TD_{50} of preparations, mg/kg	TI of preparations
LT	3.9 (2.8—5.5)	53.4 (37.9—75.3)	13.7
Sodium valproate	295.7 (271.1—322.5)	346.4 (305.7—392.6)	1.2
Diazepam	6.1 (3.7—10.1)	5.7 (3.7—8.8)	0.9
Phenobarbital	11.1 (8.6—14.2)	51.3 (40.8—64.6)	4.8
Diphenine	9.6 (7.7—11.9)	35.3 (26.2—47.5)	3.7
Carbamazepine	12.0 (8.1—17.7)	57.4 (47.9—68.8)	4.8
Ethosuximide	337.4 (245.9—463.0)	835.0 (659.2—1057.8)	2.5
Riodipin	35.1 (27.1—45.6)	51.3 (40.8—64.6)	2.7

Note. Here and in Table 2: the scatter of experimental values is given in parentheses.

tion of the preparations, both ED_{50} and TD_{50} were determined in the conditions when the ratio of their doses relative to ED_{50} (found previously for individual preparations) was the same. Analysis and resulting estimation of anticonvulsant and neurotoxic effect of combined administration were performed by modified [6] isobolographic method [13], and by calculation of the fraction indices: fraction effectiveness dose (FED) and fraction toxicity dose (FTD) [8,10]. The index value of less than 0.7 indicated synergism of action (of potentiating type). The interaction was additive when this value was in the range of 0.7-1.3. The values higher than 1.3 indicated antagonistic interaction. To estimate prospectiveness of the combinations, TI was calculated as the ratio between TD_{50} and ED_{50} both for individual preparations and for their combinations. All preparations were administered *per os*, so that to attain the highest activities at the same time. Sodium valproate (Sanofi) was injected 30 min before electroshock; diazepam and LT (Wellcome) 60 min; phenobarbital, Diphenine (pharmaceutical production) and calcium blocker 1,4-dihydropyridine riodipin (Foridon) — 3, 4, and 1.5 h, respectively. Sodium valproate was dissolved in physiological saline, other preparations were dissolved in 5% Tween-80. The entire volume of injected liquid was no more than 0.2 ml for individual or 0.4 ml for combined administration. Under similar experimental conditions, the solvents (physiological saline and/or Tween-80) were given to control animals.

RESULTS

Isobolographic analysis of anticonvulsant effects of two preparations after their combined administration showed that LT and carbamazepine, diazepam, or Diphenine act as synergists potentiating the effects of each other, because the "confidence fields" were inside the triangle formed by isobole and coordinate axes (Fig. 1). It was possible to decrease ED_{50} of each preparation by 4.2, 4.0, and 3.1 times, respectively (Tables 1 and 2). The FED index was less than 0.7, confirming the potentiating effects of these preparations (Table 2).

When LT was administered with phenobarbital, ethosuximide, sodium valproate, and riodipin, the interaction of these preparations was additive: ED_{50} could be decreased by 2.6, 2.4, 1.9, and 2.2 times, respectively (Table 1 and 2). The FED of these combinations pointed to the additive interaction of these preparations (Table 2).

In most cases FTD for LT combinations with anticonvulsant preparations indicated additive interaction, because it ranged from 0.7 to 1.3 (Table 2). An exception was the LT—carbamazepine combina-

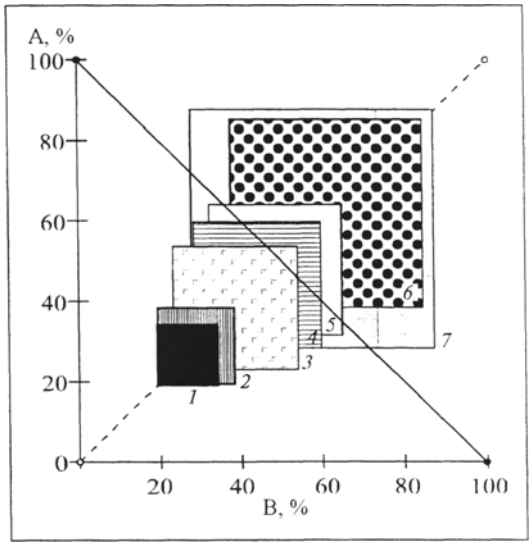

Fig. 1. Isobolographic analysis of effectiveness of preparations after combined administration. Ordinate and abscissa: ED_{50} of the preparations *A* and *B*. The line *AB* connecting ED_{50} of *A* and *B* preparations is theoretical isobole for an additive interaction. Combinations: *1*) lamictal (LT)+carbamazepine; *2*) LT+diazepam; *3*) LT+Diphenine; *4*) LT+phenobarbital; *5*) LT+ethosuximide; *6*) LT+sodium valproate; *7*) LT+riodipin.

TABLE 2. Pharmacological Parameters of Combinations of LT with Other Anticonvulsants

Combination	ED_{50} of preparations after combined administrations, mg/kg	FED index	TD_{50} of preparations after combined administrations, mg/kg	FTD index	TI of combination
LT+	0.91 (0.68—1.22)	0.47	18.6 (15.4—22.4)	1.35	20.3
carbamazepine	2.82 (2.10—3.77)		57.2 (47.5—68.9)		
LT+	0.98 (0.69—1.38)	0.50	3.4 (2.6—4.3)	0.98	3.5
diazepam	1.5 (1.1—2.2)		5.3 (4.1—6.8)		
LT+	1.26 (0.83—1.93)	0.65	8.8 (6.0—12.8)	0.77	6.9
Diphenine	3.11 (2.04—4.74)		21.6 (14.9—31.5)		
LT+	1.5 (1.0—2.1)	0.76	15.5 (11.7—20.4)	1.15	10.5
phenobarbital	4.2 (2.9—6.1)		44.2 (33.8—58.3)		
LT+	1.6 (1.1—2.3)	0.84	10.6 (7.6—14.7)	1.29	6.5
ethosuximide	141.0 (99.2—200.4)		914.2 (657.8—1270.6)		
LT+	2.1 (1.4—3.1)	1.06	5.4 (4.0—7.3)	1.29	2.6
sodium valproate	156.1 (104.7—232.4)		411.6 (306.4—552.9)		
LT+	1.8 (1.0—3.2)	0.95	6.2 (4.5—8.5)	1.20	3.4
riodipin	16.1 (9.2—28.4)		55.5 (40.4—76.2)		

tion (FTD index 1.35), implying a weak antagonism in the neurotoxic action.

In comparison with other anticonvulsant preparations, TI of LT was much higher (2.8- to 15.2-fold, Table 1). TI of the LT—carbamazepine combination was the highest among the studied combinations: 20.3, respectively, 1.5 and 4.2 times higher then TI of each preparation. TI of other combinations of LT with anticonvulsant preparations was lower then TI of LT, but higher (by 1.3-3.9 times) than TI of the second drug. Thus, the effectiveness of LT—carbamazepine combination was the highest. Potentiation of anticonvulsant effects of the preparations was accompanied by additive neurotoxic interaction, which made TI of the combination higher than TI of any ingredient. It should be noted that irrespective to a similar character of anticonvulsant and neurotoxic interaction after combined administration of LT with diazepam or Diphenine, TI of the combinations was lower than that of LT, which reflected a greater decrease in the LT TD_{50} in comparison with its ED_{50} in these combinations.

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