EFFECT OF DIAZEPAM, CARBAMAZEPINE, SODIUM VALPROATE, AND THEIR COMBINATIONS WITH VITAMINS ON EPILEPTIC ACTIVITY

G. N. Kryzhanovskii* and A. A. Shandra

UDC 616.853-085.214.22.015.2:
615.356/-036.8-092.9

KEY WORDS: nicotinamide; pyridoxal phosphate; α-tocopherol; diazepam; carbamazepine; sodium valproate; antiepileptic action.

It was shown previously [1, 3-5] that nicotinamide (NA), pyridoxal phosphate (PP), and α-tocopherol (α-TP), each separately but more especially in combination, have a marked antiepileptic action. These vitamin preparations, in combination with synthetic antiepileptic agents (phenobarbital, phenazepam), potentiate the action of the latter [5, 7]. The potentiating action of members of both classes of drugs allows the doses of synthetic antiepileptic agents to be reduced.

The present investigation is a continuation of those cited above, with the aim of developing pathogenetic combination therapy [2] and studying the anticonvulsant action of diazepam (DP), carbamazepine (CP), sodium valproate (SV), and their combinations with NA, PP, and α-TP, on a model of generalized seizure activity.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 18-24 g. Generalized clonicotonic convulsions were induced by intraperitoneal injection of metrazol in a dose of 100 mg/kg. The effects observed were recorded visually for 30 min after injection of the convulsant. The severity of the clonic and tonic convulsions and the number of animals dying during them also were taken into account. The intensity of the seizure reactions was expressed in points [5]. DP, CP, and SV were injected 1 h, NA 15 min, PP 30 min, and α-TP 24 h before injection of metrazol (all were injected intraperitoneally). The numerical results were subjected to statistical analysis by parametric and nonparametric methods.

EXPERIMENTAL RESULTS

Metrazol in a dose of 100 mg/kg induced generalized clonicotonic convulsions in all animals, which died in the course of 30 min (Table 1). DP in a dose of 0.5 mg/kg protected some animals against tonic and clonic convulsions and significantly reduced their severity and mortality. It was shown previously that administration of NA (250 mg/kg), PP (10 mg/kg), and α-TP (100 mg/kg) separately in the above doses caused a significant increase in the latent period of convulsions but had no significant effect on the intensity of the seizures or mortality among the animals [5]. When DP was injected together with NA the ability of DP to reduce the number of animals with tonic convulsions and to reduce their severity and mortality, was considerably potentiated. When a combination of PP and DP was used, a tendency was observed toward potentiation of the anticonvulsant effects of DP. A combination of DP, NA, CP, and α-TP protected 50% of animals against clonic convulsions and completely abolished tonic convulsions (Table 1). The results obtained with combinations of PP with DP, CP, and SV are not included in Table 1. CP (50 mg/kg) did not prevent clonic convulsions but considerably reduced the number of animals with tonic convulsions and the severity of the seizures, and reduced almost by half the mortality among the animals (Table 1). A combination of CP with NA protected more than 70% of animals against tonic convulsions and significantly reduced the severity of the seizures and mortality among the animals compared with CP alone.

*Academician of the Academy of Medical Sciences of the USSR.

Laboratory of General Pathology of the Nervous System, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. Department of Pathological Physiology, N. I. Pirogov Odessa Medical Institute. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 11, pp. 545-547, November, 1985. Original article submitted January 12, 1985.

 0007-4888/85/0011-1498$09.50

TABLE 1. Effect of Diazepam, Carbamazepine, Sodium Valproate, and Their Combinations with Nicotinamide, Pyridoxal Phosphate, and α-Tocopherol on Metrazol Seizures in Mice

Experimental conditions	Dose of drugs, mg/kg	Number of animals	Number of animals with seizures		Severity of seizures, points	Mortality	
			clonic	tonic		abs.	%
Control (physiological saline + metrazol)	100	25	100	100	4,0	25	100
DP	0,5	20	85	70	2,9±0,2*	4	20
DP + NA	0,5+250	20	60	30	2,2±0,2*	0	
					P_1—P_2<0,05		
DP + PP	0,5+10	15	80	53	2,5±0,3*	3	20
DP + NA + PP + α-TP	0,5+250 10+100	20	55	0	1,5±0,2*	0	
					P_3—P_4<0,05		
CP	50	20	100	55	3,6±0,2*	11	55
CP + NA	50+250	15	100	27	3,1±0,2*	4	27
CP + PP	50+10	15	100	27	3,2±0,2*	5	33
CP + NA + PP + α-TP	50+250+10+100	20	70	25	2,6±0,2*	2	10
					P_5—P_6<0,05		
SV	200	20	100	60	3,6±0,1*	12	60
SV + NA	200+250	20	95	35	3,1±0,2*	6	30
					P_9—P_{10}<0,05		
SV + PP	200+10	15	100	50	3,4±0,1	6	40
SV + NA + PP + α-TP	200+250+10+100	20	90	20	2,5±0,2*	3	15
					P_{10}—P_{12}<0,05		

*P < 0.05 compared with control.

The anticonvulsant action of CP was potentiated also when given in combination with PP: the number of animals with tonic convulsions and their mortality both decreased. With a combination of CP, NA, PP, and α-TP a further reduction in severity of the seizures was observed down to 2.6 ± 0.2 points (P < 0.005) and in mortality.

In a dose of 200 mg/kg, SV considerably reduced the number of animals with tonic convulsions, as well as their severity and mortality among the animals. With a combination of SV and NA a greater reduction was observed in the severity of the seizures and in mortality from them compared with the effects of SV alone. PP also potentiated the anticonvulsant effects of SV. SV in combination with NA, PP, and α-TP had the strongest anticonvulsant effect: The number of animals with tonic convulsions was reduced significantly, the severity of the seizures diminished (to 2.5 ± 0.2 points), and fewer animals died.

These experiments thus showed that DP, CP, and SV significantly reduced the number of animals with seizures induced by metrazol and weakened their intensity, in agreement with data obtained by other workers [9, 13, 14]. The convulsant effects of metrazol are known to be associated with direct depolarization of the neuron membrane [15] and disturbance of the GABA–benzodiazepine receptor complex system [9]. The mechanism of the anticonvulsant action of DP, CP, and SV is associated with the effect of these substances on different components of GABA-ergic inhibitory control [10-12]. Studies of the effect of NA and PP on different models of epileptic activity led to the conclusion that the antiepileptic effect of these drugs also is realized through activation of the GABA-ergic system [4, 5, 7].

α-TP is a powerful natural antioxidant, which depresses enhanced lipid peroxidation (LPO) of neuronal membranes, reduces the free radical concentration, and depresses epileptic activity [1, 3, 5, 7] and also, it can be postulated, normalizes the state of the GABA–benzodiazepine receptor complex. The high anticonvulsant efficacy of combinations of DP, CP, SV, and the vitamins listed above can evidently be linked with these particular features of the action of the drugs.

The writers showed previously that NA, PP, and α-TP potentiate the antiepileptic action of phenobarbital and phenazepam [5]. Bourgeois et al. [8] confirmed our observations on potentiation of the anticonvulsant effects of phenobarbital by NA. The results of the present investigation, and also those obtained previously [3-6] indicate that these vitamin preparations potentiate the action of antiepileptic agents of various classes and with different models of epileptic activity. It can be postulated on the basis of the foregoing facts that different forms of epileptic activity are based on common pathogenetic mechanisms. These in-

clude insufficiency of GABA-ergic inhibitory control, intensification of LPO, disturbance of oxidation-reduction processes, and so on. Normalization of these mechanisms by the action of vitamins helps to depress the level of epileptic activity. The vitamin preparations studied, in the necessary doses, may thus be considered to potentiate the action of different kinds of antiepileptic agents, as a result of which the doses of synthetic drugs can be reduced. This situation is very important because of the need for prolonged treatment and the possibility of side effects and complications. The results of these investigations provide a new basis for consideration of the desirability of using anticonvulsant drugs and vitamins in the form of pathogenetic combination therapy. Yet this may apply not only to the treatment of epilepsy. Since the pathogenesis of every neuropathological syndrome characterized by hyperactivity of systems is based on the formation of a generator of pathologically enhanced excitation [2], it can be tentatively suggested that this proposed pathogenetic combination therapy may also be useful in the treatment of other neuropathological syndromes (diencephalic syndromes, pain syndromes of central origin, manic-depressive psychosis, etc.).

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