EFFECT OF ANTIDEPRESSANTS ON THE CONVULSANT ACTION OF THIOSEMICARBAZIDE, STRYCHINE, AND METRAZOL

S. M. Golgovina and N. I. Andreeva

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Data on the effect of antidepressants on convulsions (audiogenic, induced by electric shock, metrazol, strychnine, and other convulsants) are few in number and contradictory in nature [3, 4, 7, 13].

According to available evidence, readiness of the brain to produce convulsions is connected to some degree with disturbances in the system of biogenic monoamines [1], and elevation of the brain cAMP and cGMP levels also has been observed during convulsive episodes [5]. Various antidepressants have an influence on aminergic neurotransmission [2].

It was accordingly interesting to make a comparative study of the effects of several modern antidepressants on convulsions induced by convulsants differing in their mechanism of action: thiosemicarbazide, strychnine, and metrazol.

The convulsant effect of thiosemicarbazide is due to inhibition of glutamate decarboxylase activity followed by lowering of the GABA level in the brain [8]. In a dose of 20 mg/kg (subcutaneously) thiosemicarbazide causes fatal convulsions in all experimental mice [11]. The convulsant effect of strychnine is associated with blocking of glycinergic receptors [15]. It is also considered to have a blocking action on the GABA-benzodiazepine receptor complex [6]. The convulsant action of metrazol is effected at the synaptic level and is perhaps determined by its inhibitor action on the chloride ionophore [12]. Metrazol, like the other convulsants, depresses glutamate decarboxylase activity and the GABA level in the brain [9, 10].

TABLE 1. Effect of Antidepressants on Convulsant Action of Thiosemicarbazide (20 mg/kg, subcutaneously) in Mice

Preparation	Dose, mg/kg	Number of mice	Latent period of onset of convulsions		Latent period of death		Number of mice which survived	
			min (M ± m)	percent of control	min (M ± m)	percent of control	absolute	%
Distilled water (control)	—	60	58±1,8	100	73±5,8	100	3	5
Pirlindol	50	60	74±1,8*	127	94±5,2**	129	5	8
Inkazan	50	40	56±2,3	96	78±6,1	107	5	12,5
Imipramine	50	30	66±2,0**	113	69±3,4	95	4	14,6
Amitriptyline	25	40	83±3,9*	144	102±5,8*	138	13	32,5*
	50	30	100±4,1*	172	122±5,9*	167	19	63*
Maprotiline	50	40	67±2,0**	116	121±5,7*	166	2	5
Viloxazine	50	30	72±1,4*	124	118±4,0*	161	0	—
Nomifensine	50	40	68±1,8**	117	105±4,5*	144	1	2,5
Caroxazone	50	30	56±1,7	96	87±6,2	119	0	—
Mianserin	50	40	83±4,0*	143	95±3,0*	130	0	—
Trazodone	50	30	73±2,8*	125	93±5,2	128	1	3

Legend. Here and in Table 2: *P < 0.001, **P < 0.01 compared with control.

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TABLE 2. Effect of Antidepressants on Convulsant Action of Strychnine (3 mg/kg, subcutaneously) in Mice

Preparation	Dose, mg/kg	Number of mice	Latent period of onset of convulsions		Latent period of death		Number of mice which survived	
			min (M ± m)	percent of control	min (M ± m)	percent of control	absolute	%
Distilled water (control)	—	30	7,9±0,3	100	7,9±0,3	100	2	7
Pirlindol	50	30	8,5±0,5	107	9,3±0,6***	117	1	3
Inkazan	50	30	9,0±0,4	114	9,3±0,4	114	6	20
Imipramine	50	30	9,3±0,4**	118	9,3±0,4**	118	3	10
Amitriptyline	25	40	10,2±0,5*	129	12,4±1,4*	157	6	15
	50	30	16,3±0,6*	206	34,3±2,1*	434	15	50*
Viloxazine	25	30	9,8±0,8*	124	12,4±0,8*	157	8	27***
	50	30	10,8±0,5*	137	13,7±0,5*	174	10	33**
Nomifensine	50	30	7,8±0,5	99	7,8±0,5	99	4	13
Maprotiline	50	30	7,7±0,6	97	7,7±0,6	97	2	7
Caroxazone	50	30	7,9±0,5	102	7,9±0,5	102	5	17
Mianserin	50	30	10,7±0,5*	135	10,7±0,5*	135	2	7
Trazodone	50	30	9,2±0,5***	117	9,2±0,5***	117	5	17

Legend. ***P < 0.05 compared with control.

TABLE 3. Effect of Antidepressants on Convulsant Action of Metrazol (125 mg/kg, subcutaneously) in Mice

Preparation	Dose, mg/kg	Number of mice	Latent period of onset of convulsions		Latent period of death		Number of mice which survived	
			min (M ± m)	percent of control	min (M ± m)	percent of control	absolute	%
Distilled water (control)	—	60	4,7±0,4	100	8,4±1,1	100	4	6,6
Pirlindol	50	40	5,2±0,45	110	10,4±1,1	123	2	4
Inkazan	50	40	5,2±0,4	110	8,1±1,1	96	2	4
Imipramine	50	30	5,3±0,45	112	10,0±0,8	119	3	10
Amitriptyline	50	50	6,3±0,8	134	11,1±1,0	132	18	36*
Maprotiline	50	30	4,7±0,4	100	9,1±1,1	108	4	13,3 n.d.
Viloxazine	50	30	4,9±0,45	104	3,5±0,36	42	4	13,3 n.d.
Nomifensine	50	40	3,7±0,4	79	6,2±1,0	74	2	4
Caroxazone	50	30	6,3±0,8	134	11,7±1,3	139	1	3,3
Mianserin	50	30	5,7±0,4	121	8,9±1,1	106	0	0
Trazodone	50	30	7,3±0,6*	155	9,3±1,2	111	2	6,6

Legend. *P < 0.001 compared with control. n.d.) Not determined.

EXPERIMENTAL METHODS

Experiments were carried out on albino mice of both sexes weighing 18-20 g. The antidepresssants tested, which are typical tricyclic and atyptical monoamine oxidase (MAO) inhibitors with reversible action, were given internally in a dose of 50 mg/kg (sometimes 25 mg/kg) 30 min before subcutaneous injection of thiosemicarbazide (20 mg/kg) and 60 min before subcutaneous injection of strychnine (3 mg/kg) and metrazol (125 mg/kg).

The latent period of onset of convulsions and of death (in minutes) and also the number of animals which survived were recorded.

For statistical analysis of the results Student's t test was used; the error of the arithmetic mean was determined at the P = 0.05 level.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that the drug with the strongest protective action against convulsions induced by thiosemicarbazide was amitriptyline in doses of 25 and 50 mg/kg. It considerably delayed the time of onset of convulsions and the time of death of the animals and protected 32% of the animals from death in a dose of 25 mg/kg and 50% in a dose of 50 mg/kg.

Mianserin, viloxazine, and maprotiline in a dose of 50 mg/kg also prolonged the survival of the animals but did not protect them from death. A rather weaker protective effect was given by pirlindol, nomifensine, and trazodone (in a dose of 50 mg/kg). Inkazan and caroxazone had virtually no effect on the convulsant activity of thiosemicarbazide.

The antidepressants chosen for testing were arranged in about the same order of their anticonvulsant effect against strychnine (Table 2). The most active drug in this test also was amitriptyline. In a dose of 50 mg/kg it appreciably delayed the time of onset of convulsions and of death and protected 50% of the animals from death. A clear protective effect also was exhibited by viloxazine in doses of 25 and 50 mg/kg. Mianserin, imipramine, and trazodone were somewhat less active, but they only lengthened the latent period of onset of convulsions. Maprotiline and nomifensine, however, did not reduce convulsant activity. Pirlindol did not delay the onset of convulsions but delayed death a little. Inkazan and caroxazone had virtually no effect on the convulsant action of strychnine.

Only amitriptyline in a dose of 50 mg/kg protected 36% of the animals from death from convulsions induced by metrazol (Table 3). The remaining compounds had no such action. The antidepressants had virtually no effect on the time of onset of the convulsions or the time of death. Trazodone lengthened the latent period of onset of the convulsions a little but the effect was only weak.

These investigations thus revealed differences in the strength and selectivity of the anticonvulsant action of the antidepressants studied. Amitriptyline was the most active against convulsions of all types studied. Viloxazine also protected the animals from death from strychnine convulsions. Imipramine, unlike anitriptyline, had only a weak anticonvulsant action and lengthened the latent period of onset of thiosemicarbazide and strychnine convulsions only slightly, and did not protect the animals from death. Mianserin, amprotiline, and viloxazine appreciably lengthened the survival of animals with thiosemicarbazide convulsions, but likewise did not protect them from death.

Pirlindol had weak anticonvulsant activity (it lengthened the latent period of onset of thiosemicarbazide and strychnine convulsions a little), but inkazan and caroxazone had virtually no effect on the action of the convulsants.

Anticonvulsant activity, consequently, is not a common property of all antidepressants. The strength and selectivity of the anticonvulsant action of each preparation separately are evidently determined by its individual chemical and pharmacologic properties. The most effective of the antidepressants tested, namely amitriptyline, is also the most active in its effect on the various mediator systems and, in particular, on cholinergic neurotransmission [14].

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