THE MECHANISM OF PYRAMIDON-INDUCED CONVULSIVE SEIZURES

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Yu. I. Detsik and I. I. Fedorov [1] revealed the epileptogenic properties of Pyramidon in experiments on dogs, rabbits and cats, and put forward the suggestion that this preparation might be used in the treatment of schizophrenia. At present intravenous injection of Pyramidon in convulsive and subconvulsive doses has found clinical application in psychiatry for treatment of chronic forms of schizophrenia [4].

The aim in the present study of the convulsivant action of Pyramidon has been to elucidate the conditions on which the appearance of convulsive seizures depends.

Under novocaine analgesia the subcutaneous vein in the shin of a pup was exposed and a freshly prepared 4% solution of Pyramidon injected into it. After this the animal was closely watched.

Data presented in Table 1 show that intravenous administration of Pyramidon to pups aged up to 1 month did not result in convulsive seizures. Reaction to the injection of Pyramidon consisted of the following. Immediately following the injection, agitation, squealing and sometimes slight tremor were noted. Pups aged over 2 weeks exhibited in addition copious salivation; many were doubly incontinent and tonic extension of limbs was also seen; this resembled the tonic phase of a convulsive seizure. No epileptiform seizures were observed in pups under 1 month of age.

Pups over 1 month of age showed clear tonic contraction of all muscles but particularly in the extremities after administration of Pyramidon; increased salivation, severe panting and vomiting also became evident.

Typical epileptiform seizures following administration of Pyramidon were constantly observed in the case of pups older than 50 days and only in one experiment were they seen in a pup aged 30 days. The seizures were characterized by the presence of tonic and clonic phases and a period of automatic movements ("running on one spot").

Four pups aged 40 to 60 days were given Pyramidon in divided doses of 81, 124, 142, 165 mg/kg with no resultant seizures; as in pups aged under 1 month there was only tonic contraction of the muscles.

The epileptiform seizures in pups following administration of Pyramidon were characterized by the young animals often having not single but 2-3 seizures which sometimes passed into status epilepticus. Older pups were more sensitive to intravenous injection of Pyramidon. While doses of Pyramidon of 197-306 mg/kg were not lethal for pups under two weeks of age, doses of 90-165 mg/kg were lethal for pups aged $1^1/_2$-2 months.

In order to discover a relationship between the appearance of convulsive seizures and the rate of injection of Pyramidon 62 experiments on 16 dogs were carried out. Convulsive doses of Pyramidon were injected subcutaneously into the shin either slowly through a fine needle or with intervals of 0.5-2 minutes.

It must be remarked that while there are certain variations in doses of Pyramidon producing convulsions, for one and the same animal under similar conditions of administration the convulsive dose remains constant.

TABLE 1

Effect of Intravenous Injection of Different Doses of Pyramidon to Pups of Various Ages

No. of pup	Sex	Age in days	Weight (in kg)	Dose of Pyramidon (in g/kg body wt.)	Animal's state after administration of Pyramidon	Outcome
1	Female	2	0.41	0.24	No convulsions	Survived
2	"	6	0.64	0.119	" "	"
3	"	40	2.9	0.165	" "	Died
2	Male	15	0.73	0.219	" "	Survived
2	"	43	3.51	0.081	" "	"
3	Female	15	1.2	0.127	" "	"
3	"	29	2.31	0.105	" "	"
3	"	68	4.17	0.114	Typical convulsive seizure	"
3	"	83	4.45	0.121*	" " "	—
4	Male	46	2.9	0.124	No convulsions	Died
5	"	56	7.8	0.048*	Typical convulsive seizure	Survived
6	Female	56	6.2	0.058	Typical convulsive seizure	"
6	"	74	5.6	0.085*	" " "	"
7	"	6	0.51	0.69	No convulsions	Died
8	"	6	0.48	0.227	" "	Survived
8	"	9	0.54	0.222	" "	"
8	"	30	2.9	0.063	Typical convulsive seizure	"
9	"	17	1.5	0.107	No convulsions	"
9	"	19	1.62	0.079	" "	"
10	"	2	0.3	0.226	" "	"
11	Male	2	0.32	0.375	" "	Died on the third day
12	"	2	0.3	0.73	" "	Died
13	Female	2	0.32	0.306	" "	Survived
14	Male	11	0.71	0.197	" "	"
15	"	11	0.81	0.247	" "	Died
16	Female	50	1.42	0.099	Typical convulsive seizure	Survived
17	"	50	1.4	0.086*	" " "	"
18	"	15	0.89	0.135	No convulsions	Died
19	"	60	2.8	0.142	" "	Survived
20	Male	60	2.2	0.09*	Typical convulsive seizure	Died
21	"	60	2	0.06	" " "	Survived

* Typical single convulsive seizures changed to status epilepticus.

In one case (experiment on the dog Damka) when the animal was agitated before the injection, a convulsive seizure occurred after a small dose of Pyramidon (25 mg/kg). The injection was repeated on the same dog 6 days later when it was placid. Convulsions took place after 42 mg/kg of Pyramidon had been given.

When Pyramidon is injected slowly the convulsive seizure develops after an appreciably larger amount of the substance than the epileptogenic dose usual for the given animal. Injected in divided doses, the epileptogenic dose becomes even larger. With this method of injection epileptiform seizures develop after amounts of Pyramidon 2-2$^1/_2$ times greater than that required to produce a seizure on rapid injection.

It was noticed that almost no toxic sequalae were observed in adult animals following repeated and frequent injections of Pyramidon. Half an hour after a convulsive seizure the animals behaved in a manner almost indistinguishable from the usual.

The development of convulsive seizures with smaller amounts of Pyramidon when it is injected rapidly evidently depends on the intensity of stimulation of receptors in the vascular bed. With rapid injection excitation of angioreceptors is greater since the solution of Pyramidon is diluted to a lesser extent than on slow injection.

In the next series of experiments Pyramidon was injected into the common carotid artery. With this method of administration more nearly optimal conditions are created for the action of Pyramidon on the carotid sinus area, vascular receptors of the brain and its meninges as well as directly on cerebral centers.

Experiments were performed on dogs and rabbits. 2 dogs (Burka and Rex) were given Pyramidon solution into the carotid artery externalized in a skin flap; in the other cases the common carotid artery was exposed under sterile conditions. 4% Pyramidon solution was injected into the artery and the wound closed. Results of these experiments are given in Table 2.

TABLE 2

Epileptogenic Doses of 4% Solution of Pyramidon on Injection into Common Carotid Artery

No. of Exp.	Description of animal	Weight in kg	Animal's	Artery receiving Pyramidon	Amt. Pyramidon (g/kg body wt.	State of the animal after injection
1	Bruka	15.6	4 years	Into right	0.0025	Convulsive seizure
2	Bruka	15.6	4 years	Into right	0.003	" "
3	Bruka	15.6	4 years	Into right	0.0043	" "
6	Bruka	15.6	4 years	Into right	0.0038	" "
12	Bruka	16.1	4 years	Into right	0.0039	" "
4	Rex	11.2	3 years	Into right	0.016	" "
5	Malyutka	7	5 years	Into right	0.0068	" "
7	Roza	17.7	4 years	Into right	0.0033	" "
8	Roza	17.7	4 years	Into left	0.0049	" "
9	Pup	5.6	2-5 months	Into right	0.0014	No convulsions
10	Female	5.6	2-5 months	Into left	0.085	Convulsions
11	Pup, male	6.1	2-5 months	Into left	0.013	No convulsions
13	Pup, male	6.1	2-5 months	Into left	0.062	Convulsions
14	Pushok	6.8	4 months	Into right	0.01	Convulsive seizure
15	Naida, male	3.2	4 months	Into right	0.093	" "
16	Zlaya	20.3	3 years	Into left	0.006	Convulsive seizure
17	Buran	16.5	3 years	Into right	0.031	" "
18	Lokhmach	20	2 years	Into left	0.07	No convulsions
19	Damka	15.6	4 years	Into left	0.005	Convulsive seizure
20	Damka	15.6	4 years	Into left	0.019	No convulsions
21	Damka	15.6	4 years	Into right	0.038	No convulsions
22	Bezymyanny	8	3 years	Into right	0.022	Convulsive seizure
23	Ryzhy	7.5	4 years	Into right	0.064	" "
24	Bely	7.8	3 years	Into right	0.082	" "
25	Gordy	11.5	4 years	Into left	0.142	3 convulsive seizures Dead from suffocation
26	Pup, 3 female	2.8	3 months	Into right	0.093	Convulsive seizure
27	Tsygan	20	5 years	Into right	0.1	3 convulsive seizures
28	Tsygan	20	5 years	Into left	0.008	Convulsive seizure
29	Ryabush	7	3 years	Into left	0.103	2 convulsive seizures
30	Zhuk	9.5	9 months	Into left	0.189	Status epilepticus
31	Pup, 4 female	2.6	3 months	Into right	0.015	Convulsive seizure
32	Aza	16.2	2 years	Into left	0.0056	" "
33	Aza	16.2	2 years	Into right	0.0066	" "

As Table 2 shows, the epileptogenic dose of Pyramidon on its injection into the carotid artery of adult female dogs was 2.5-6.8 mg/kg i. e., 10-20 times smaller than with rapid single intravenous injection. It is characteristic that convulsions in these cases took place instantaneously: they resembled the result of sudden electric current stimulation.

In the case of a 4-months old female dog (Pushok) a convulsive seizure appeared after injection of 10 mg/kg, i. e., a dose a little larger than that which evokes seizures in adult female dogs with the same method of administration. In 2 female pups aged $2^1/_2$-3 months a convulsive seizure was produced by injection of 85-93 mg/kg Pyramidon into the common carotid artery; the onset of convulsions was not immediate but 20-30 seconds after the injection, i. e., after a period similar to that usually observed after intravenous injections of Pyramidon.

Male dogs did not exhibit enhanced sensitivity to Pyramidon injection into the common carotid artery.

Females, on the other hand, reacted to intracarotid injection of Pyramidon with convulsive seizures with very small doses – 2.5-6 mg/kg. The epileptogenic dose of Pyramidon was, in the majority of cases of male dogs, little different whether administered by the common carotid route or intravenously although the experimental conditions were identical in the case of male and female animals.

The specific sensitivity to injection of Pyramidon into the common carotid artery in female animals and its absence in the males are not absolutely constant. Both increases and decreases of sensitivity (Tsigan, Experiment No. 28, Damka, Experiments No. 20-21 respectively) were observed at different times. It also depends on age: no increased sensitivity to Pyramidon injected by the common carotid route was, as a rule, observed in pups up to 3 months old.

In addition to the described experiments similar studies were made on rabbits and gave consistent data: convulsive seizures occurred on injection of Pyramidon into the common carotid artery in doses which were epileptogenic when given intravenously; this was observed both in male and female rabbits.

It was then shown that injection of Pyramidon into the femoral artery and external carotid artery in dogs produced convulsions when given in the same doses as intravenously. Suboccipital injection was followed by convulsions after 60-90 seconds when 10-15 mg/kg of Pyramidon had been administered.

The fact that convulsions following Pyramidon injection into the common carotid artery occur in many animals, predominantly female, with minute doses of the substance and with extremely rapid onset suggests that this method of administration may involve chiefly the receptor apparatus of the carotid sinus zone and possibly vascular receptors of the brain. Definite elucidation of this question requires further study.

Moreover, the direct action of Pyramidon on the central nervous system cannot be denied since this substance exerts considerable influence on basic cortical processes [2, 3].

SUMMARY

The effect of Pyramidon was experimentally studied to clarify the conditions of the rise of epileptic-like seizures.

It was noted that the development of a convulsive seizure in dogs when intravenously injected with a 4% Pyramidon solution proceeded differently depending upon the age of the animal, Pyramidon dose, rapidity and frequency of injection, and the site of the injection.

LITERATURE CITED

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* In Russian.