EFFECT OF NEUROTROPIC DRUGS ON MOTOR HYPERACTIVITY INDUCED IN DOGS BY BENACTYZINE

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Quantitative recording of motor activity in dogs showed that benactyzine (2 mg/kg intramuscularly) led to an increase in this activity which persisted for 2-3 h. The effect of benactyzine was abolished by intramuscular injection of galanthamine in a dose of 3 mg/kg. The most effective of the neuroleptics and tranquilizers studied was perphenazine. Chlorpromazine and diazepam not only did not abolish the hyperactivity induced by benactyzine, but they also caused the animals' condition to worsen. A further increase in hyperactivity was observed after diazepam and haloperidol. Levomepromazine abolished hyperactivity in some animals but potentiated other symptoms induced by benactyzine. It is postulated that motor hyperactivity produced by benactyzine is connected with anticholinergic mechanisms; the use of the drug for blocking the action of neuroleptics with marked cholinolytic properties is thus contraindicated.

KEY WORDS: motor hyperactivity; benactyzine; neuroleptics; tranquilizers; galanthamine.

Central cholinolytics and, in particular, benactyzine, may lead to psychomotor excitation if an overdose is given. Many investigations have been carried out for the experimental analysis of the action of benactyzine on higher nervous activity of animals of different species [1, 2]. Motor hyperactivity produced by benactyzine has been studied in rodents, relatively insensitive to central cholinolytics.

The object of this investigation was to develop a method of quantitative analysis of the motor activity of large laboratory animals and to use it to evaluate the effect of certain neurotropic drugs on motor hyperactivity induced by benactyzine in dogs.

EXPERIMENTAL METHOD

Experiments were carried out on 14 mongrel dogs of both sexes weighing from 8 to 15 kg. To record the animals' movements quantitatively they were placed in a chamber measuring 1.8 m^2 in area (115 × 175 cm). The floor of the chamber was made of 160 squares (10 × 10 cm) glued to porolon. When the dog moved about and pressed on the squares with its paws, it closed electrical contacts located under them. Pulses from all the contacts, led through a matrix and selecter, were recorded by a computer of the PP-16 type. If the dog lay down, closing six or more contacts, the computer was automatically disconnected by means of a shut-off relay. The same relay was connected to an automatic time marker, which recorded the animal's position continuously on paper tape throughout the experiment (lying and standing). The side walls of the chamber were made of flexible wire netting. Each of the four walls had a control pick-up with a contact closed when the dog touched the wall. The number of pulses from all the contacts on the walls was recorded on a type MES-54 magnetoelectric counter. The readings of the instruments were read out at 15-min intervals. The magnitude of the motor activity was thus measured in relative units characterizing the number of electric pulses from the system of contacts in the floor and side walls of the chamber.

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TABLE 1. Effect of Some Drugs on Motor Hyperactivity of Dogs Induced by Benactyzine (2 mg/kg)

Drug	Dose (in mg/kg)	Number of animals				
		total	tranquilizing effect present for 1 h	increase in motor activity	appearance of recurrences of hyperactivity	worsening of clinical condition
Chlorpromazine	0,5	3	1	1	1	3
Levomepromazine	0,75	3	1	1	1	3
Perphenazine	0,1	3	2	0	0	1
Haloperidol	0,08	5	1	4	1	0
Diazepam	1	3	1	3	1	3
Galanthamine	3	5	5	0	0	0

The animals' motor activity was recorded for 1 h, after which benactyzine was injected intramuscularly in a dose of 2 mg/kg, and one of the drugs for testing was injected 30 min later during the stage of motor hyperactivity. The total duration of the experiment was 7 h.

Central adrenolytic properties of the neuroleptics were evaluated with respect to changes in the toxicity of amphetamine for grouped mice. The central cholinolytic properties were studied by recording the EEG from the cortex of cats with preliminarily implanted electrodes on the Nihon Kohden encephalograph with automatic analysis every 10 sec.

EXPERIMENTAL RESULTS AND DISCUSSION

The results characterizing the effect of the compounds studied are summarized in Table 1.

Control tests in which benactyzine was given in a dose of 2 mg/kg showed that motor hyperactivity appeared in the dogs for the first 15-30 min and lasted for 2-3 h. The behavior of the dogs in this period was characterized by intensive purposeless motor activity and by disturbed movement coordination. The animals periodically barked, struck the walls of the chamber during their movements, and were unresponsive. Both the general condition of the dogs and the level of their motor activity were back to normal after 2-3 h.

Administration of chlorpromazine to one dog abolished the motor hyperactivity after 1 h, but after a further hour the motor activity increased again and remained increased until the end of the experiment. In another dog the normal motor activity was restored at the same times as in the control animals receiving benactyzine only. Finally, in a third dog, chlorpromazine sharply increased the motor hyperactivity. In all dogs receiving chlorpromazine the general state was much worse than in those receiving benactyzine only.

Levomepromazine abolished the motor hyperactivity induced by benactyzine in all the animals, but one dog very quickly developed a recurrence of severe hyperactivity which persisted for 3 h. The general state of the animals worsened just as much after levomepromazine as after chlorpromazine.

The effect of perphenazine was well marked in two of the three dogs. No recurrence was observed. Haloperidol, tested on five dogs, blocked hyperactivity for 1 h in only one dog. In four dogs motor activity was increased after administration of haloperidol. Prolonged hyperactivity, continuing for 5-6 h and higher in intensity than that recorded in animals receiving benactyzine only, was recorded in all the dogs receiving diazepam.

Motor excitation induced by benactyzine was abolished in all the experiments by galanthamine in a dose of 3 mg/kg. The effect of galanthamine appeared quickly and was characterized not only by the blocking of excitation but also by disappearance of other symptoms characteristic of the action of benactyzine. The animals became responsive, their movement coordination was restored, and they responded to external stimuli.

Chlorpromazine and levomepromazine, in the doses used, significantly ($P < 0.05$) reduced the toxicity of amphetamine for grouped mice, but no difference could be found between the action of the two drugs. Perphenazine, in a dose of 0.1 mg/kg, had no effect. The results are in good agreement with published data [3].

Experiments on five cats showed that chlorpromazine and levomepromazine, in doses used to block motor hyperactivity, led to the development of slow, high-voltage activity on the EEG with blocking of the arousal reaction. Intramuscular injection of eserine (0.1 mg/kg) or arecoline (0.3 mg/kg) completely a-

bolished the effect of chlorpromazine and levomepromazine. Perphenazine had a similar action only in a dose of 0.2 mg/kg.

The results indicate that chlorpromazine and levomepromazine, highly effective in other types of psychomotor excitation, not only will not abolish the motor hyperactivity induced by benactyzine, but indeed they potentiate the effect of the latter. The possibility of blocking motor excitation induced by benactyzine by means of a reversible cholinesterase inhibitor, together with the negative effect of neuroleptics with a marked central muscarinic cholinolytic activity, suggests a pathogenetic connection between benactyzine hyperactivity and the anticholinergic properties of that drug.

To abolish the psychomotor hyperactivity that may arise following overdosage of benactyzine, the use of galanthamine and neuroleptics of the perphenazine type must therefore be recommended. The use of neuroleptics with marked cholinolytic properties and of benzodiazepines in this case is contraindicated.

LITERATURE CITED

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