Relaxation of Decerebrate Rigidity by Orphenadrine. (29163)

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Orphenadrine has been reported to cause a decrease in the flexor reflex of thalamic cats. In contrast, it had no effect on the flexor reflex of decerebrate cats(1). The technique of decerebration, whether by brainstem section or by ligation of the basilar artery, employed in the cited study was not specified. Certain drugs, such as chlorpromazine(2), have a much more profound effect on the rigidity following intercollicular section than on the "alpha" rigidity produced by ligation of the basilar artery. This differential action on Sherringtonian decerebrate preparations can be correlated with depression of gamma (fusimotor) neuron activity.

The observation that scopolamine produces significant, but limited, relaxation of the decerebrate rigidity following intercollicular section(3) prompted the investigation of 2 other tertiary anticholinergic compounds, diphenhydramine, and its o-methyl analog, orphenadrine, for their effects on decerebrate rigidity.

Methods. Ten adult cats of both sexes were decerebrated in the intercollicular plane by electro-coagulation under pentobarbital anesthesia (30 mg/kg intraperitoneally) one or two days prior to assessment of drug action according to the method of Smith *et al*(4).

The force developed by the ankle extensor muscles of the decerebrate cat opposing forced flexion of the foot through an angle of 20° was measured using a force-displacement transducer and polygraph. The flexion was maintained for 10 seconds and repeated every 30 seconds. The magnitude of the phasic and tonic components of the reflex was assessed(3). Aqueous solutions of orphenadrine citrate* or diphenhydramine hydrochloride were administered intravenously using a timed interrupted infusion (*i.e.*, each dose increment was injected slowly over a period of one minute, a dose calculated to double the total previously administered given 5 minutes later, etc.). The complete or 100% depression of the reflex response was taken as that response observed after administering ether to the point of respiratory arrest.

Results. Cumulative doses of orphenadrine between 0.5 and 4.0 mg/kg caused a limited, but dose-related, decrease in the phasic and tonic components of the stretch reflex of decerebrate cats (Fig. 1). In 3 of 6 cats the degree of depression by orphenadrine of reflexes opposing ankle flexion was limited to 20-40%; no detectable effects were observed in one; in the remaining 2 cats a maximum depression of 75% was observed. The tonic component was consistently somewhat more sensitive than the phasic to orphenadrine induced depression (Fig. 1).

After cumulative doses of 4-8 mg/kg of orphenadrine the reflex responses were consistently transiently increased during and immediately following the injection period. This increase with the larger doses appeared concomitantly with erratic spontaneous movements of the fore- and hindquarters and was eventually followed, in different cats, by a sustained increase, no net change, or a further decrease in the magnitude of the reflex response. This variability in response to the larger doses is indicated by the wider ranges in the values depicted with 4 and 8 mg/kg total dose in Fig. 1.

Diphenhydramine, in contrast to orphenadrine, failed to exhibit any depressant activity in doses up to 4 mg/kg in each of 3 preparations. Larger doses consistently caused a marked increase in the reflex, followed in some instances by a decrease; this sequence of effects are those that would be expected to result from the marked fall in blood pressure occurring with such doses.

Comments. These results clearly demonstrate that orphenadrine in doses of 1 to 4 mg/kg can produce a limited degree of depression of the phasic and tonic components of the hyperactive stretch reflex of extensor

* Orphenadrine substance and commercial solutions were kindly supplied by Riker Laboratories, Inc.

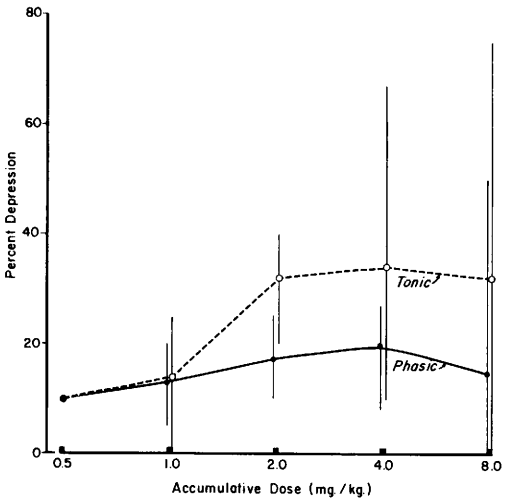

FIG. 1. Effects of orphenadrine on phasic and tonic components of the stretch reflex of decerebrate cats. Ordinate: Per cent depression of reflex response. Abscissa: Cumulative dose in mg/kg. Points are the means of at least 4 animals except for the point at 0.5 mg/kg which represents data from only one preparation. Bars indicate *range* of values obtained.

muscles of classically decerebrated cats. Larger doses, which must be considered as very large, if not excessive, in view of other known actions of this agent(5), cause a transient or sustained increase in the reflex.

These effects of orphenadrine resemble those previously obtained with scopolamine in that both caused a less than maximal depression of the reflex and that large doses of both agents were associated with an increase in the reflex(3). Orphenadrine was less potent than scopolamine: the PD50 for the tonic component ranged from 0.05-1.35 mg/kg for scopolamine whereas with orphenadrine maximal depressant effects were generally obtained with 2.0-4.0. On the other hand scopolamine consistently produced at least a 50% decrease in the reflex in all animals, but orphenadrine did not. Also, orphenadrine produced a depression of the phasic component only slightly less than that of the tonic component, whereas scopolamine produced no significant depression of the phasic component.

These data are consistent with the hypothesis that low doses of orphenadrine act to cause a decrease in the descending drive to gamma (fusimotor) motor neurons since it lacks effects on skeletal muscle or spinal cord(1,5). Studies on the effects of orphenadrine and scopolamine on the fusimotor system and muscle spindle afferent system for further elucidation of their reflex depressant actions are indicated.

The depression of decerebrate rigidity by orphenadrine documented by these findings may be analogous to the alleviation of skeletal muscle spasm by this agent observed in man(6), the effective antagonism of nicotine or Tremorine induced skeletal muscle hyperactivity, and the alleviation of canine tremor-rigidity syndrome(5). However, that the experimental rigidities of cats are the same as the superficially similar disease states in man has yet to be established(7).

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