Mode of Action of Phenaglycodol, A New Neurosedative Agent.† (22807)

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Among a series of diols studied by Gibson, Mills and Swanson*, phenaglycodol (2-p-chlorophenyl-3-methyl-2, 3-butanediol) was outstanding because of the relatively long duration of its anticonvulsant action. While the compound was being tested for antiepileptic activity, the ward attendants reported that the children had become much easier to handle. Further clinical investigation has confirmed the impression that phenaglycodol can be classified as a tranquilizing agent of the muscle relaxant group. Since it is more potent and longer acting than some of the currently known drugs of this type further study seemed indicated.

Methods. Considerable attention has been given to careful observation of changes in behavior of unanesthetized mice, cats and monkeys given phenaglycodol. In addition, we studied the effect of the drug on selected multisynaptic reflex arcs in the cat. Flexion reflex was elicited at 10-second intervals by a 0.2 millisec. square wave 10-volt pulse to the posterior tibial nerve and recorded from the anterior tibial tendon with an isotonic lever in cats anesthetized with 50 mg/kg of chloralose. The knee jerk was obtained by tapping the patella tendon with a solenoid tapper. This monosynaptic reflex was modified by mid-brain stimulation(1,2). The biphasic pulses of an integrated square wave(3) of 1 millisec. duration at 20-50 cycles/sec. were led to a concentric bipolar electrode or to a monopolar electrode with the stereotaxic frame as an indifferent electrode. Points in the mesencephalic reticular formation were located by trial and error, which gave either facilitation or inhibition. Inhibition was induced by caudate stimulation. In the bulbar reticular formation, stimulation caused inhibition of the knee jerk and usually, apnea. In spinal cats, a comparison was made of the effect of phenaglycodol on predominantly monosynaptic inhibition of the knee jerk by ipsilateral sciatic stimulation, with the effect on a multisynaptic inhibition by contralateral stimulation of the nerve to the quadriceps muscle(1). Electrical activity of the brain was recorded in unrestrained cats from surface and deep electrodes chronically implanted. Some experiments were done on cats immobilized with suspension of dimethyltubocurarine butyrate in oil. The surface electrodes were 2-56 stainless steel machine screws that were placed in the skull to reach, but not penetrate, the dura. The deep electrodes were of 24-gauge stainless steel wire insulated to within 1 mm of the tip with Epoxylite Electrode Insulating Varnish. In chronic animals, Cannon miniature plugs or Winchester subminiature sockets were secured to the skull with dental acrylic resin. The surface electroencephalograms were picked up from bipolar connections or from one screw and an "indifferent" electrode over the frontal sinus. For the most part, the deep electrodes were recorded as a unipolar derivation with the indifferent electrode. The deep electrodes were placed in the septal region, the mesencephalic reticular formation, the ventro-posterior lateral and medial dorsal nuclei of the thalamus, the amygdala, and the caudate nucleus.

Results. Mice, after the injection of phenaglycodol in doses of 55 to 80 mg/kg intraperitoneally, show a reduction in spontaneous activity and sit quietly in the center of the observation area. Although muscle weakness can be demonstrated, the animals are usually not ataxic. With larger doses, there is a rapid loss of pinnal and righting reflex while the corneal reflex is still brisk. The onset of this action is smooth and there is little of the ataxic running about usually seen with phenobarbital.

Cats given doses of 20 mg/kg intraperitoneally also became quiet. It was often

† The trade-mark for Eli Lilly and Company for phenalglycodol is 'Ultran.'

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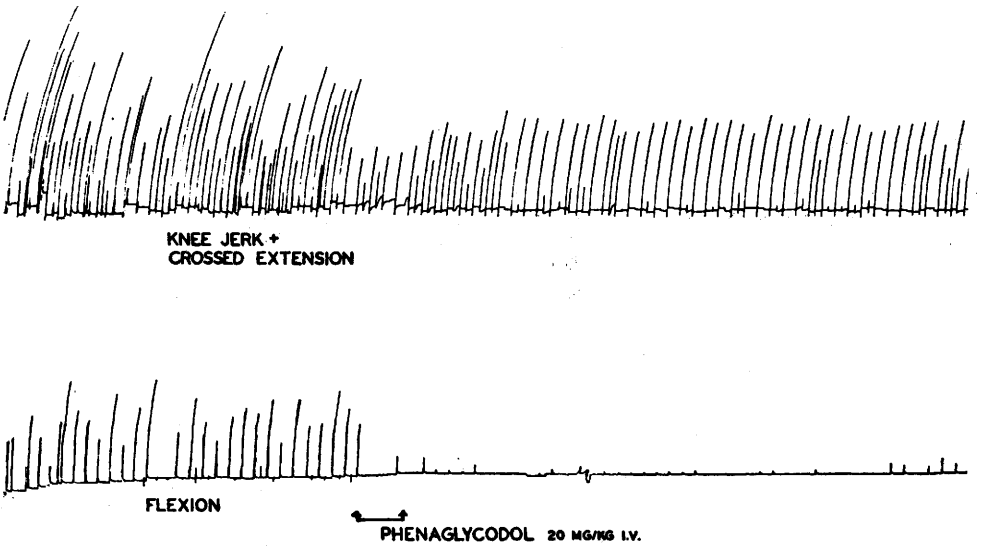

FIG. 1. Effect of phenaglycodol on spinal cord reflexes in cat. Upper trace is record of extension of the leg. Before drug, the leg extended in response to both tapping patella tendon and stimulation of contralateral posterior tibial nerve. After phenaglycodol the crossed extension disappeared while knee jerk became more consistent in amplitude.

noted that animals that were complaining about being confined in a cage seemed peaceful and content after phenaglycodol, in doses of 10 and 20 mg/kg. The animals given 40 mg/kg were ataxic and those on larger doses slept. No changes in respiration or in heart rate were noted.

Monkeys given phenaglycodol in doses of 50 to 100 mg/kg by stomach tube were less aggressive or less fearful. These animals often became playful and engrossed in their own activity. As with the other tranquilizing agents, there were a variety of patterns of behavior, depending not only on the dose of drug, but also on the character of the monkey, and on the observer and his previous experience with the colony. The larger dose caused some unsteadiness in movement. These doses were repeated daily for 6 months without appreciable change in intensity of effect. The animals usually recovered in 4 hours.

In cats anesthetized with chloralose, 20 mg/kg intravenously of phenaglycodol caused a small transient fall in blood pressure associated with some slowing of respiration. Heart rate and electrocardiogram were virtually unchanged. The pressor response to either carotid occlusion or epinephrine and the depressor response to either histamine or methacholine were unaltered. The contraction of the nictitating membrane after epinephrine or during preganglionic stimulation was not altered by phenaglycodol. Flexion reflex was usually reduced, but when the stimulus was supramaximal, there was not much change.

In experiments in which the posterior tibial nerve was stimulated, flexion reflex could be recorded ipsilaterally and crossed extension contralaterally. This stimulus was alternated with tapping of the contralateral patella tendon. Phenaglycodol in doses of 20 mg/kg intravenously caused little change in the knee jerk, but flexion and crossed extension were decreased (Fig. 1). These results were obtained in animals anesthetized with chloralose or dial-urethane solution. Further evidence of a selective depression of multisynaptic pathways in the cord was obtained from experiments in spinal cats. Phenaglycodol blocked the inhibition of the knee jerk caused by stimulation of the nerve to the contralateral quadriceps muscle but had little effect on the inhibition obtained by ipsilateral sciatic stimulation.

In experiments in which the knee jerk was

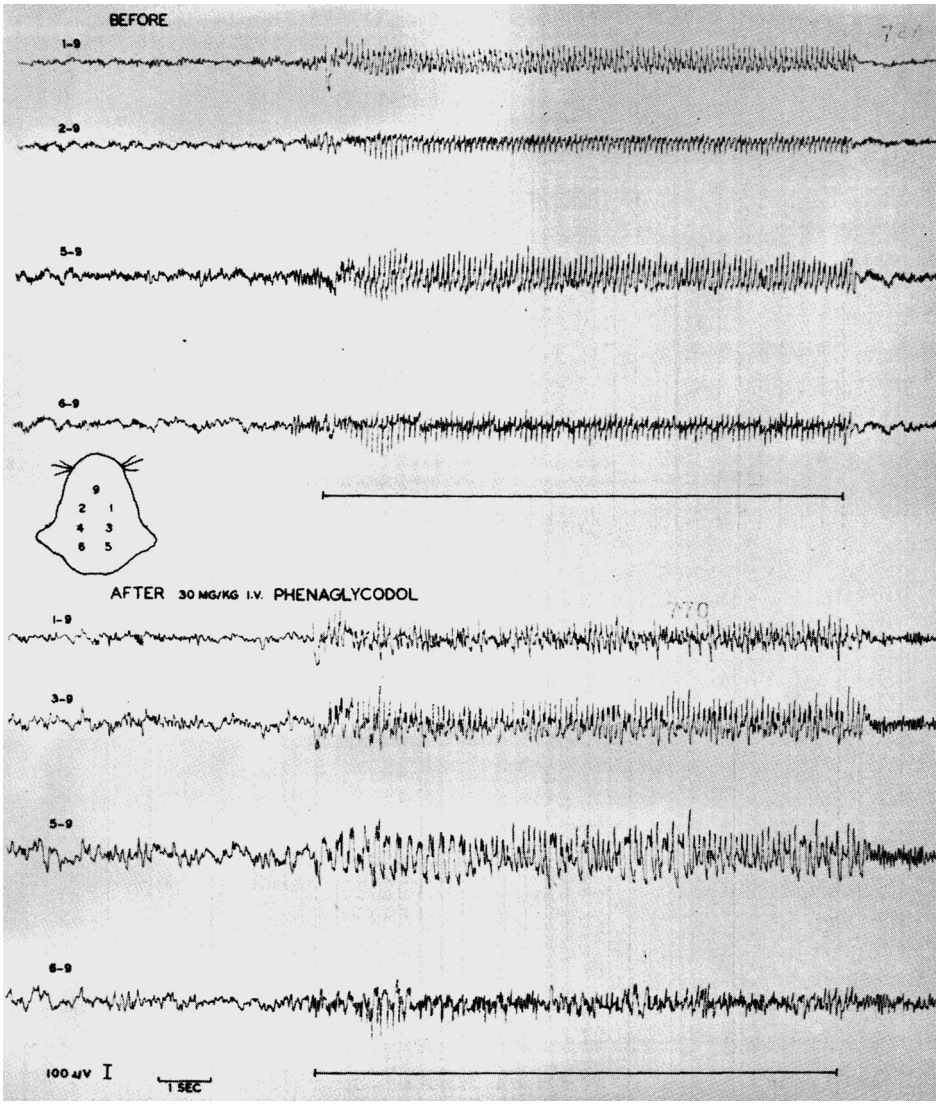

FIG. 2. Effect of phenaglycodol on EEG of cat showing change in form of recruiting response and of spontaneous record. Heavy line beneath records indicates duration of the 9 cycle/sec. stimulus.

inhibited or facilitated by supratentorial stimulation either from the mesencephalic reticular formation or from the caudate nucleus, doses of phenaglycodol of 10 to 20 mg/kg intravenously blocked the alteration of the knee jerk without changing the knee jerk itself. We did not detect a consistent difference in the effect of the drug on either facilitation or inhibition. When inhibition was obtained by stimulation of the bulbar reticular formation, however, phenaglycodol and mephenesin failed to block the change. It was characteristic of phenaglycodol that, when the drug caused a reduction in the activity of a polyneuronal arc, a simple increase in voltage of the stimulus would restore the response to or almost to the pre-drug level. The failure of phenaglycodol to block subtentorial inhibition may be related to the difference in the effect of a small increase in stimulus strength on the bulbar and mesencephalic reticular formation. In the former region a

small increase in voltage changes a barely discernible decrease in knee jerk to a complete block of the reflex. In contrast, small increase of voltage of mesencephalic stimulation caused less striking changes. This difference probably reflects the smaller number of interneurons involved in mediating the effect of bulbar stimulation.

In cats immobilized with dimethyl-tubocurarine butyrate in oil, low voltage fast activity was the usual pattern of the electroencephalogram. After phenaglycodol in doses of 10 to 20 mg/kg intravenously, this desynchronized record showed a greater degree of synchrony. The voltage increased from 30-50 μV to 100-150 μV, and the frequency slowed to 9-12 c/sec. In 3 cats of this type, 9 c/sec. stimulation in the nonspecific thalamic nuclei gave a typical recruiting response in the surface leads. The threshold for this response was not changed although the form was somewhat modified after phenaglycodol (Fig. 2).

In the unrestrained cats there was a greater variety in the resting EEG pattern, but the activation pattern was usually observed. After 20 mg/kg intraperitoneally of phenaglycodol the change to a higher voltage, slower frequency record was observed. We were unable to convince ourselves that any one of the surface or deep leads could be identified as the source or starting point for the synchrony. A somewhat similar pattern of action has been obtained with pentobarbital, 10 mg/kg, but the cat seemed somewhat more sleepy after this dose. Another difference was noted in that tapping or scratching of the cage would cause an EEG arousal response after phenaglycodol, but failed to do so after pentobarbital. From these observations it would appear that phenaglycodol lies somewhere between the muscle relaxants, which depress the recruiting response but leave EEG arousal unimpaired, and the barbiturates which depress arousal and do not depress and perhaps even enhance recruiting (4).

Discussion. It seems clear from the results of these experiments that phenaglycodol is a sedative that differs materially from the barbiturates in its mode of action. The pattern of action in mice, cats and monkeys demonstrates this distinction. More detailed studies on polysynaptic pathways indicate that phenaglycodol has properties in common with the interneuronal blocking agents such as mephenesin, at least at the level of the spinal cord. The changes in the electroencephalogram demonstrate an action on higher structures, but further work will be needed to localize this effect.

Summary. 1. Phenaglycodol, a compound originally selected for clinical trial on the basis of its anticonvulsant and effective tranquilizing actions, has been shown to have a quieting effect on mice, cats and monkeys. 2. Its effects on blood pressure, respiration and electrocardiogram are minimal. 3. In studies on selected reflex arcs it has been shown to be a selective depressant of polysynaptic pathways at the spinal and supraspinal level. 4. After doses of phenaglycodol causing sedation but not sleep in cats, the electroencephalogram shows a pattern of 9-12 c/sec. synchronous activity at both surface and deep electrodes.

1. Henneman, E., Kaplan, A., and Unna, K., *J. Pharmacol. Exp. Therap.*, 1949, v97, 331.

2. Magoun, H. W., and Rhines, R., *J. Neurophysiol.*, 1946, v9, 165.

3. Lilly, J. C., Hughes, J. R., Alvord, E. C., Jr., Galkin, T. W., *Science,* 1955, v121, 468.

4. King, E. E., *J. Pharmacol. Exp. Therap.*, 1956, v116, 404.

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