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A Neuropharmacological Investigation of the Convulsant Action of 4-Phenyl-4-Formyl-N-Methyl Piperidine (1762 IS)* (26599)

V. G. LONGO AND A. PINTO CORRADO (Introduced by F. W. Schueler)
Laboratorio di Chimica Terapeutica, Istituto Superiore di Sanità, Rome, Italy

During an investigation of a series of compounds synthetized for possible strychnine-like activity, one in particular, 4-phenyl-4-formyl-N-methyl-piperidine (1762 IS), was found to possess marked activity as indicated by preliminary screening(1).

In the present work, a more detailed analysis of the action of 1762 IS was made. The usual pharmacological procedures were used as well as more specific technics which included a study of the modifications of the electrical activity at the various levels of the cerebro-spinal axis, the effects of application of the substance to the cerebral and cerebellar cortex on the cortical electrical activity and its action on spinal integratory mechanisms.

Material and methods. Acute toxicity was determined by intraperitoneal and oral administration in mice and intravenously in rabbits. The LD_{50} was determined in mice using the probit method.

Eleven unanesthetized rabbits paralyzed with 5 mg/kg of gallamine intravenously were used for registration of the cortical and subcortical electrical activity according to a method described previously(2). In all animals arterial blood pressure was simultaneously recorded. Histological sections were prepared routinely to verify the exact location of the electrodes in the subcortical structures. Experiments in which the compound was applied topically were carried out in 8 rabbits unanesthetized and without neuromuscular paralysis. Disks soaked in various concentrations of the drug were applied on the sensorimotor area of the cortex and on the *lobulus medianus* of the cerebellum. Freshly made water solutions of the hydrochloride salt were used; the dosage is given in weight of the free base.

Experiments on the action of the drug upon the spinal cord were carried out in spinal (Th-10) cats lightly anesthetized with chloralose. After lumbar laminectomy, the appropriate ventral roots were cut and mounted on silver electrodes for recording purposes. The spinal cord was covered with warm paraffin oil. Mono- and polysynaptic reflexes were evoked by stimulation of the popliteal branch of the sciatic nerve. In the experiments dealing with the "primary" inhibition, a maximal monosynaptic reflex was evoked by stimulation of the central stump of the biceps and semi-tendinous nerves (BST). Inhibition of this reflex was obtained by stimulating the group Ia afferent fibers of the quadriceps

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nerve (Q). Further details of the technical procedure have been described previously(3).

Results. Acute toxicity. The LD_{50} in mice was found to be 42 mg/kg intraperitoneally and 284 mg/kg perorally. Mice injected with sublethal doses showed continuous running movements, elevation of the tail (Straub reaction), twitching and jerking. Death of the animals was preceded by muscular tremors and a tetanic spasm. In rabbits, doses of 1-2 mg/kg *i.v.* were found to bring about hyperreflexia, spasmodic continuous jerking and, in some instances, tetanic convulsions. Higher doses (3 mg/kg) provoked, in all animals, the characteristic tonic attack with opisthotonus and extension of the hind legs, which was normally followed by death. In those cases where the animal survived the initial attack, it was possible to elicit new attacks by a variety of external stimuli, *e.g.*, acoustical or visual and especially by touching the back of the animal.

Electroencephalogram. Doses of 1 to 2 mg/kg (which cause hyperreflexia in animals not treated with gallamine) result in a desynchronization of the tracing, characterized by an increase in frequency and a decrease in amplitude of the cortical waves, and by appearance of a regular 5 c/sec rhythm in the thalamic lead. The tracing of the electrospinogram, however, shows no change. Doses of 3 mg/kg bring about the appearance of a characteristic seizure consisting of 20-30 c/sec waves in the spinal, cerebellar and mesencephalic leads (Fig. 1). Concurrently, only desynchronization is noticed in the cerebral cortex. The thalamic lead exhibits synchronous and regular waves at 8-9 c/sec. In 4 out of 7 animals treated with higher doses (4-5 mg/kg) the spinocerebellar seizure developed into a "grand mal" EEG pattern in all leads.

An increase in blood pressure accompanied the alterations of the EEG and became particularly noticeable during the spino-cerebellar seizures. These seizures lasted for several minutes and were frequently interrupted by short periods of elecrtical silence accompanied by abrupt drops in blood pressure.

Topical application. At a concentration of 0.1%, 1762 IS applied to the cortex induced the appearance of spikes, at first in the region of the treated zone and thereafter spreading to the entire cortex. Spreading of the spik-

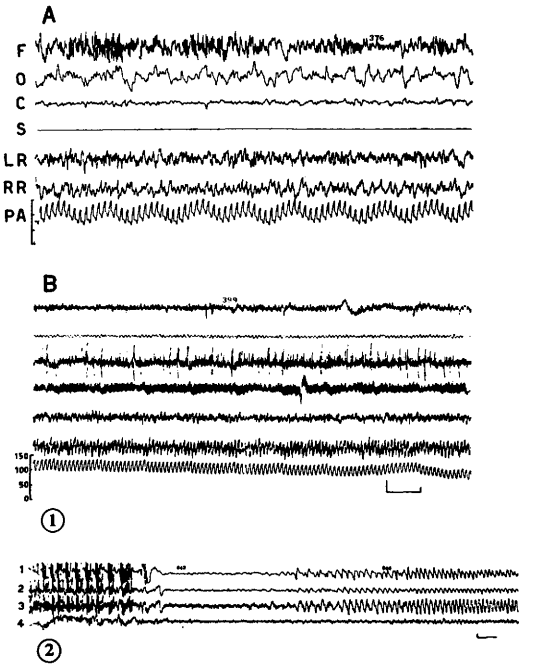

FIG. 1. A. Control tracing. Spindles are present in the sensorimotor cortex. No activity is registered from the spinal cord lead. B. Five min. after i.v. administration of 3 mg/kg 1762 IS. A sustained seizure, characterized by spikes at 20-30 c/sec., appears in the spinal, cerebellar and reticular leads; concurrently, there is desynchronization of the cortical tracing.

Unanesthetized rabbit treated with gallamine. Leads. F: anterior sensorimotor cortex; O: optic cortex; C: *Lobulus medianus* of cerebellum; S: lumbar enlargement of spinal cord; LR: left retic ular midbrain formation; RR: right reticular midbrain formation; PA: femoral blood pressure.

Calibration: horizontal bar, 2 sec.; the left vertical bar indicates 100 μV for cerebellar and spinal tracing; the right vertical bar indicates 100 μV for the other leads.

FIG. 2. Convulsant action of 1762 IS applied topically to the right sensorimotor cortex of the rabbit. The tracing was recorded 15 min. after application of 1762 IS 0.1%. Clonus of the snout and movements of vibrissae were seen simultaneously with appearance of the burst of spikes. Few seconds after the seizure, waves of high voltage at 2 c/sec. appear in the record.

Unanesthetized rabbit without gallamine. Leads. 1: R anterior sensorimotor cortex – L anterior sensorimotor cortex; 2: L anterior sensorimotor cortex – L posterior sensorimotor cortex; 3: R posterior sensorimotor cortex – L posterior sensorimotor cortex; 4: R optic cortex – L optic cortex.

Calibration: 50 μV, 2 sec.

ing activity was consistently provoked by stimulation of the reflexogenic zones, such as the muzzle and the vibrissae of the opposite side when the drug was applied to the anterior sensorimotor cortex. Immediately after the seizures, there appears an unusual EEG picture consisting of waves of high voltage and of a frequency of 2 c/sec in all leads (Fig. 2). However, topical application (1%) on the cerebellum did not cause the appearance of cerebellar spikes.

Mono and polysynaptic reflexes and spinal "primary" inhibition. The influence of increasing doses of 1762 IS on the segmental reflexes was observed in 4 spinal cats. At a dose of 2-3 mg/kg the polysynaptic wave increased both in duration and in height, whereas the monosynaptic spike remained unchanged or was slightly reduced in amplitude. Higher doses (up to 5 mg/kg) further enhanced the polysynaptic component. Simultaneously, there was a more marked decrease of the monosynaptic reflex (to 60-70% of control).

The effect of 1762 IS on the spinal "primary" inhibition was studied in 3 animals. Three to 4 mg/kg blocked the inhibition of the BST monosynaptic reflex due to stimulation of the Q nerve. Concomitant with this effect, a slight decrease of the monosynaptic BST reflex occurred.

Discussion. These results have demonstrated that 1762 IS can be considered as another synthetic drug possessing strychnine-like properties. There exist, however, some slight differences between strychnine and 1762 IS which, even though not observed during toxicity studies in various laboratory animals, are evident from the results of electrophysiological procedures. From the point of view of its action on cerebral electrical activity, it has been noticed that, after the spino-cerebellar-mesencephalic seizure (which is characteristic of strychnine also), in about 50% of the treated animals, a "grand mal" EEG pattern developed in all leads. This picture is only rarely observed with strychnine(2,4). Also, a difference was found between the action of 1762 IS and of the alkaloid on the spinal cord. In previous investigations, using the same experimental conditions(2), both strychnine and a synthetic strychnine-like compound, 5,7-diphenyl-1,3-diazadamantan-6-ol, consistently provoked an enhancement of the monosynaptic reflex. On the contrary, 1762 IS causes a slight decrease of this reflex. This indicates that the block of the spinal "primary" inhibition can occur independently of enhancement of the monosynaptic reflex. Thus, it may be concluded that 1762 IS has a specific depressant action on the monosynaptic excitatory arch. or that it is inconsistent in its influence on the various spinal inhibitory systems.

These results indicate a strong similarity between 1762 IS and thebaine, the action of which, on the EEG and on spinal primary inhibition, has been described recently by Corrado and Longo(5). In this connection, it is of considerable interest that 1762 IS is the aldehyde corresponding to the 1-methyl-4-phenyl isonipecotic acid, whose ethyl ester is meperidine, which possesses significant analgesic properties. A marked structural similarity exists also between morphine and thebaine. With both pairs of drugs these modifications in structure lead from a predominance of analgesic activity to a predominance of convulsant strychnine-like activity.

Summary. In preliminary toxicity studies, a synthetic compound, 4-phenyl-4-formyl-N-methyl-piperidine (1762 IS) showed convulsant properties very similar to those of strychnine. More detailed neuropharmacological investigations dealing with the action of 1762 IS on cerebral electrical activity, on the mono- and polysynaptic reflexes and on the "primary" spinal inhibition have confirmed the similarities between this compound and strychnine. Some relationships between chemical structure and pharmacological properties are discussed.

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