Brit. J. Pharmacol. (1952), 7, 655.

THE ACTION OF *ALPHA-BETA*-DIHYDROXY-*GAMMA*-(2-METHYLPHENOXY)-PROPANE (MYANESIN) ON THE SPINAL CORD OF THE CAT

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(Received July 14, 1952)

Berger and Bradley (1946) first showed that $\alpha\beta$-dihydroxy-γ-(2-methylphenoxy)-propane (Myanesin, Tolserol, Mephenesin) produced muscular relaxation in animals and that it controlled strychnine induced convulsions more effectively than hexobarbitone. They concluded that myanesin acted by " depressing the reflex excitability of the spinal cord." This report led to the use of the drug clinically as a relaxant in anaesthesia (Mallinson, 1947) and in the control of spastic neurological conditions (Schlesinger, Drew, and Wood, 1948). The results were disappointing, because myanesin was either ineffective or transient in its action and because some toxic effects were noted.

Henneman, Kaplan, and Unna (1949), Henneman and Scherrer (1949), and Kaada (1950) studied the effect of the drug on the facilitation and inhibition of the mechanically induced knee jerk caused by electrical stimulation of other parts of the nervous system, such as the brain-stem reticular formation, cerebellum, and cerebrum. Kaada also studied its effect on the complex reflex discharges in the ventral root elicited by electrical stimulation of the dorsal root of the same segment of the spinal cord. Both authors are in general agreement that while myanesin in doses of 25–50 mg./kg. diminishes or abolishes both facilitation and inhibition of the knee jerk resulting from electrical stimulation of other parts of the central nervous system, except in very large doses it has no effect on the knee jerk itself. They concluded that myanesin exerts its effect specifically on the internuncial cells of the central nervous system, apparently at all levels.

This paper reports the results of an analysis of the action of myanesin on the spinal cord of the cat, using the methods developed in previous work on the action of tubocurarine and strychnine on the spinal cord (Bernhard and Taverner, 1951 ; Bernhard, Taverner, and Widén, 1951 ; Taverner, 1952). Monosynaptic and polysynaptic reflex discharges and cord dorsum potentials were evoked by electrical stimulation of appropriate sensory fibres in motor and sensory nerves in unanaesthetized preparations. Special attention has been paid to the blood pressure because myanesin is known to cause a fall in the arterial blood pressure (Berger and Bradley, 1946).

Material and Methods

Cats were used in all experiments. The standard electro-physiological technique employed has been fully described in previous papers. The cord dorsum potentials were recorded by a monopolar silver wire electrode resting on the dorsal surface of the spinal

cord with an indifferent electrode on adjacent muscle. The temperature of the paraffin lake was maintained at 38° C. ± 0.5° C. by means of heaters above and below the preparation. The arterial blood pressure was recorded from the right common carotid artery.

Myanesin, in 1 per cent solution, was injected slowly through an indwelling polythene tube in the left brachial vein. The rate of injection was controlled by direct observation of the blood pressure tracing, but was always 10 mg./kg./min. or less. *d*-Tubocurarine (0.1 per cent) and strychnine hydrochloride (0.01 per cent) were given by the same route. In certain experiments designed to control the influence of blood pressure changes on the preparation, dextran (Berger) was also injected intravenously either to restore the blood pressure to its previous level after the administration of myanesin or to raise the blood pressure above its basal level. Decerebration or spinal section was carried out under ether anaesthesia, but when the experiments were performed two to three hours later its effects had disappeared. Apart from heparin (Evans) 1/10,000 in the blood pressure cannulae, no other drugs were administered to the cats.

RESULTS

Effect on spinal reflexes in unanaesthetized preparations

Stimulation of the low threshold afferent fibres in the gastrocnemius nerve is followed, after an interval of 2.5–3 msec., by a synchronous reflex discharge in the S1 ventral root. The work of Lorente de Nó (1935), Renshaw (1940), and Lloyd (1943) has shown that this discharge represents activity in two neurone (mono-

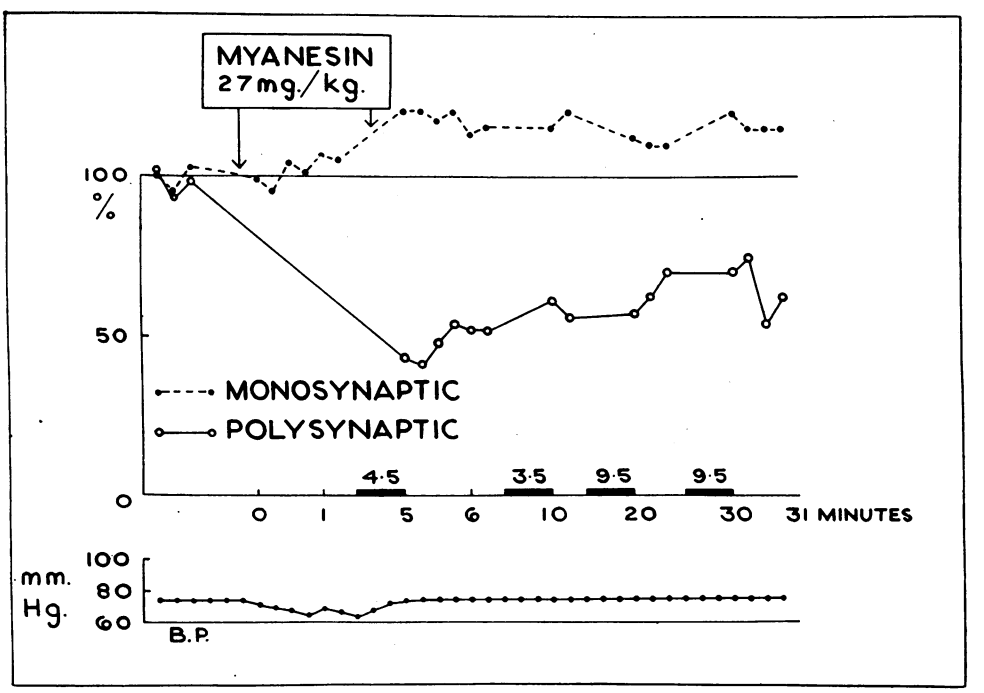

FIG. 1.—Effect of myanesin (27 mg./kg.) on the amplitude of the monosynaptic and polysynaptic reflexes in a decerebrate cat. Ordinates: amplitude as percentage of pre-injection level. Abscissae: time in minutes from start of injection. Bars show periods when recording suspended.

synaptic) arcs and reflects into the muscle from which the afferent fibres arise. This type of reflex arc is the basis of the myotatic reflexes (tendon jerks). If the stimulus is applied to a cutaneous nerve, such as the sural, an asynchronous, irregular discharge appears in the ventral root after 4–5 msec. and persists for 10 msec. or more. Lloyd (1943) has shown that this discharge represents activity in more complex reflex arcs with interpolated internuncial neurones (polysynaptic reflexes) which are the basis of responses such as the flexor and crossed extension reflexes.

Fig. 1 shows the effect of myanesin on the monosynaptic and polysynaptic reflex discharges in a decerebrate cat ; 18 mg./kg. body weight of myanesin had been previously injected and produced a transient and slight fall in the amplitude of the polysynaptic reflex only. Myanesin in a dose of 27 mg./kg. was injected slowly into the left brachial vein and the monosynaptic reflex response was recorded throughout (dotted line). The polysynaptic reflex response was recorded after the injection. Towards the end of the injection the monosynaptic response increased slightly in amplitude and reached a value of 120 per cent of the pre-injection amplitude. This effect on the monosynaptic response is inconstant, but has been seen in all types of preparation, decerebrate, high spinal, and low spinal. Its occurrence seems to depend on the excitability of the preparation and on the dose of myanesin. It usually appears with doses between 20 and 30 mg./kg. In this preparation a further dose of 36 mg./kg. of myanesin was given thirty minutes later, while the monosynaptic response was still augmented. The monosynaptic response fell to its original level during the course of this injection, but returned to its previous level of 120 per cent five minutes later.

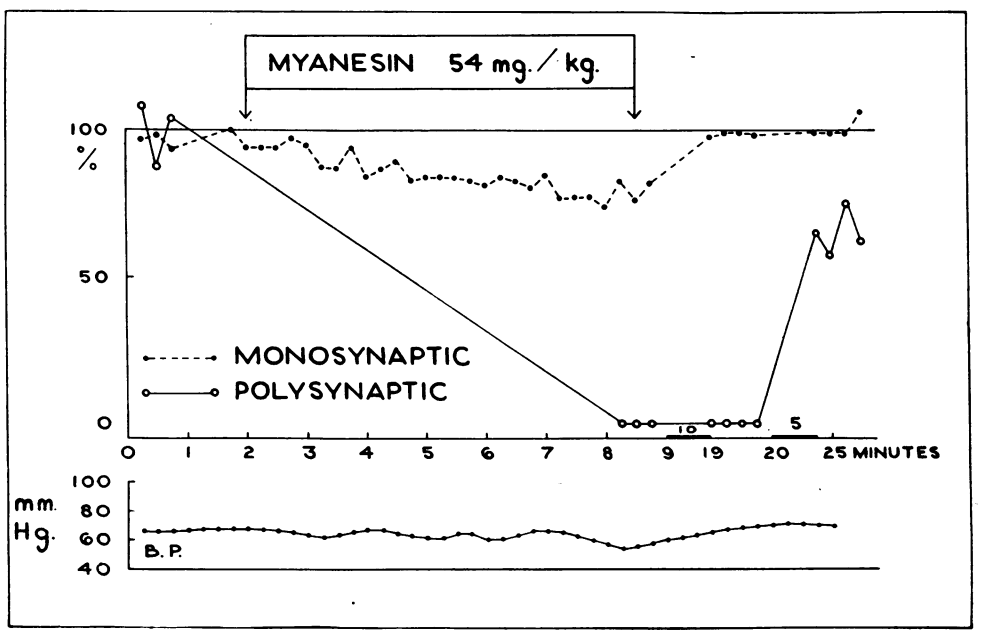

FIG. 2.—Effect of myanesin (54 mg./kg.) on the amplitude of the monosynaptic and polysynaptic reflexes of the same preparation as Fig. 1.

The solid line in Fig. 1 shows the effect of 27 mg./kg. of myanesin on the polysynaptic reflex. Immediately after the injection the response fell to 40 per cent of the pre-injection level. It then began to recover slowly, and thirty minutes later was 75 per cent of the pre-injection level. The next injection of 36 mg./kg. reduced it to 25 per cent of the original level. After this dose the reflex again began to recover but after a longer interval.

Fig. 2 shows the effect of a further injection of 54 mg./kg. of myanesin, making a total of 136 mg./kg. in the same preparation. The monosynaptic response fell to 70 per cent of the pre-injection level during the injection, but fifteen minutes later had attained its previous level. Immediately after the injection the polysynaptic reflex had disappeared ; seventeen minutes later it had reached 75 per cent of the original level.

Fig. 3 shows the effect of the drug on the monosynaptic and polysynaptic reflexes in a decerebrate cat with section of the spinal cord in the upper cervical region ; 21 mg./kg. of myanesin was injected intravenously and the polysynaptic reflex fell to 50 per cent of its original value, but the monosynaptic response was unaffected. The blood pressure remained at 60 mm. Hg during and after the injection, but fell to 50 mm. Hg at a time when the reflexes were normal. It is unlikely that the blood pressure fall is responsible for the reflex changes, because in that event the monosynaptic response would fall in parallel with the polysynaptic response (Taverner, 1952).

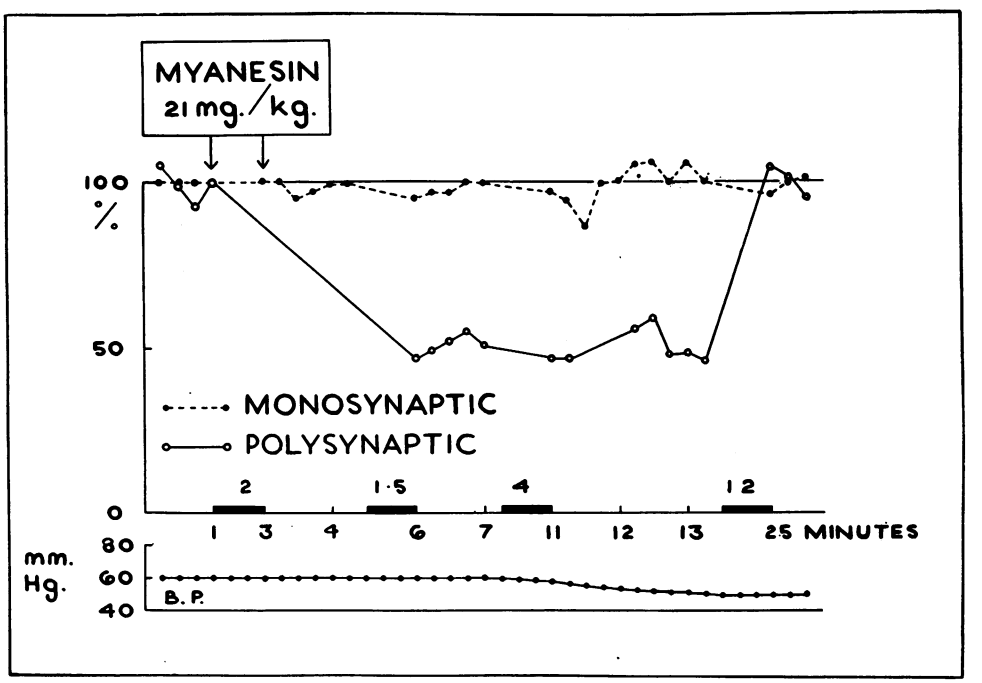

FIG. 3.—Effect of myanesin (21 mg./kg.) on the amplitude of the monosynaptic and polysynaptic reflexes in a decerebrate cat with spinal section in the upper cervical region.

If the spinal cord is severed at the level of T12–L1 segments, the action of myanesin is unchanged. Doses of 15–30 mg./kg. reduce the amplitude of the polysynaptic response to less than 50 per cent, but this action is transient and recovery occurs in 10–20 minutes. The monosynaptic response is unaffected or slightly increased by these doses. Doses of 50 mg./kg. in low spinal preparations depress the polysynaptic response to zero and the monosynaptic response to about 75 per cent of its original value. Recovery begins in both after 10–20 minutes, but is of longer duration than with the smaller doses. Care must be taken with these preparations to avoid depressing the initially low blood pressure of 60 mm. Hg or less to below the critical level of about 40 mm. Hg.

Effect on spinal reflexes in strychninized preparations

It is known that strychnine increases the amplitude of the polysynaptic reflex in all types of preparation. It has recently been shown by Bernhard, Taverner, and Widén (1951) that strychnine increases the amplitude of the monosynaptic reflex in low spinal preparations, but decreases it in high spinal and decerebrate preparations.

The spinal reflexes augmented by strychnine are more sensitive to the action of myanesin than the spinal reflexes in the unanaesthetized non-strychninized preparation. Fig. 4 shows the effect of a small dose of myanesin on the monosynaptic (dotted line) and polysynaptic (continuous line) reflexes in a curarized (1.5 mg. tubocurarine/kg.) low spinal preparation. An injection of strychnine hydrochloride

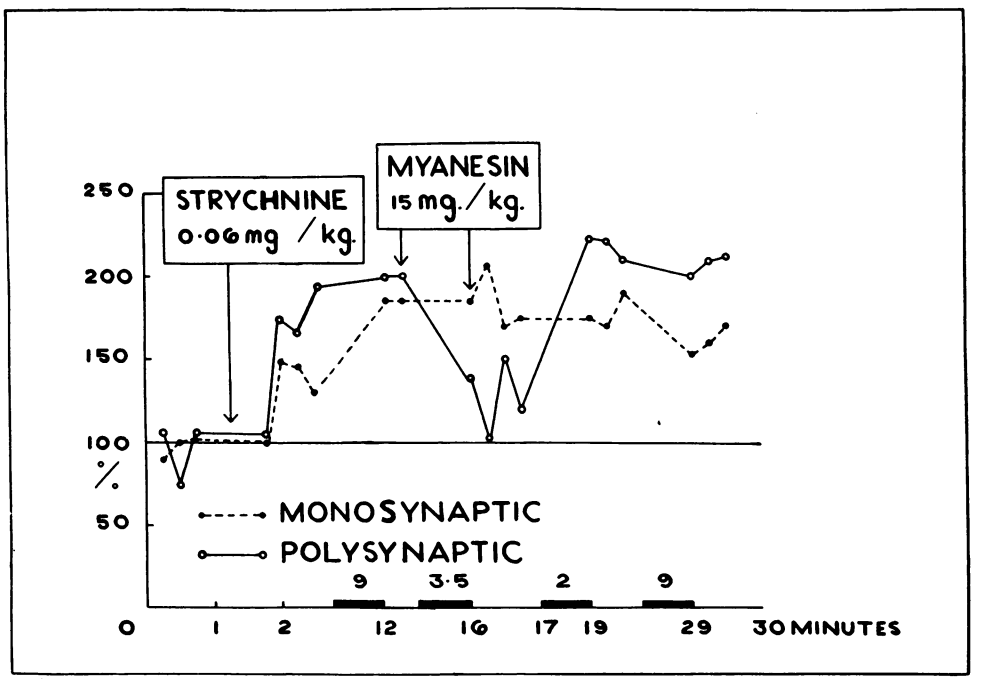

FIG. 4.—Effect of strychnine hydrochloride (0.06 mg./kg.) and myanesin (15 mg./kg.) on the amplitude of the monosynaptic and polysynaptic reflexes in a curarized (1.5 mg./kg.) decerebrate cat with spinal section at the junction of T12–L1 segments.

(0.06 mg./kg.) increased the amplitude of the polysynaptic response to 200 per cent and of the monosynaptic response to 185 per cent of the control level. 15 mg./kg. of myanesin was injected slowly, and temporarily reduced the polysynaptic response to the pre-strychnine control level. Five minutes later the polysynaptic response had returned to its augmented pre-myanesin level. The monosynaptic response was not significantly affected by this injection.

A second injection of 15 mg./kg. of myanesin had the same effect on the two reflexes. Two further injections of 15 mg./kg. reduced both responses to the pre-strychnine level, but ten minutes later they had begun to recover, although they did not attain the levels at first induced by the strychnine. Similar effects were obtained in all types of preparation. Slight depression of the polysynaptic reflex was sometimes observed after only 5 mg./kg of myanesin, but the action of myanesin in strychninized preparations is much more transient than in the non-strychninized cats. Strychnine augmented reflexes can only be kept under control by injections of myanesin repeated at short intervals.

Effect of myanesin on the cord dorsum potentials

It has long been known that electrical stimulation of cutaneous afferent fibres produces potential changes in the spinal cord (Gotch and Horsley, 1891 ; Gasser and Graham, 1933 ; Barron and Matthews, 1938 ; Eccles, 1946 ; Lloyd and McIntyre, 1944 ; Bernhard, 1949 ; and Bremer and Bonnet, 1949). Fig. 6 shows the potential changes recorded by a monopolar electrode on the dorsal surface of the S1 spinal segment after stimulation of the sural nerve. Bernhard (1952) has shown that the N1 potential represents activity in monosynaptically activated cell bodies in the dorsal grey matter, which do not participate in reflex transmission. This negative deflection is followed by an inconstant positivity (P deflection) which originates from propriospinal interneurones extending over several segments of the cord (Bernhard, 1952). This deflection is best seen in preparations with high reflex excitability, but is not essential for reflex transmission.

In a series of experiments on unanaesthetized preparations myanesin was found to have no action upon the cord dorsum potentials except in large doses. Such doses exert a profound influence on the blood pressure, and these changes are probably responsible for any depression of the cord dorsum potentials.

Effect of myanesin on the cord dorsum potentials in strychninized preparations

Bernhard and Koll (1952) found that strychnine produces a marked increase in the amplitude of the P deflection. Larger doses of strychnine produce a succession of regular high voltage waves at frequencies of 10–30 sec. (Bremer, 1941).

The strychnine augmented P deflection is sensitive to myanesin. Fig. 5 shows the effect of the injection of 5 mg./kg. of myanesin into a curarized (1.5 mg./kg.) decerebrate preparation with section of the spinal cord in the upper cervical region. The maximum P deflection after the injection of 0.15 mg./kg. of strychnine hydrochloride is plotted as 100 per cent. Myanesin (5 mg./kg.) caused a prompt fall in the amplitude of the P deflection to 7 per cent of its augmented level. Three minutes later it had increased to 15–25 per cent of its previous level, but there was no further increase. Four further injections of smaller doses of strychnine (0.04–0.1 mg./kg.) rapidly increased the P deflection to its former size. After three of these injections myanesin in a dose of 5 mg./kg. promptly reduced the P deflection to zero and it did

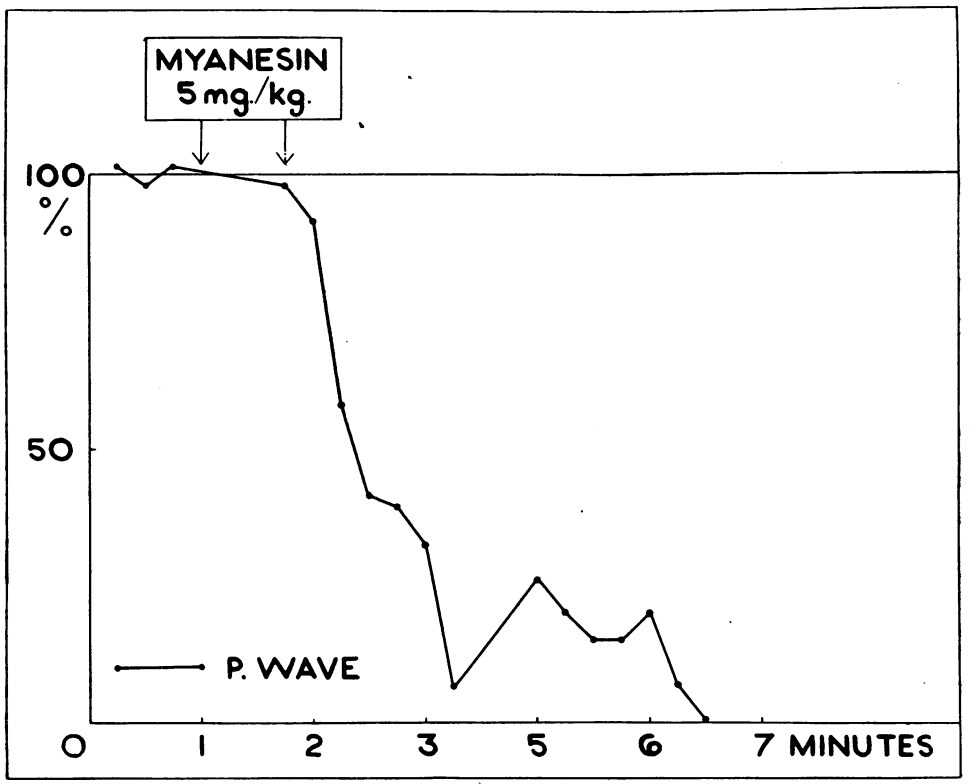

FIG. 5.—Effect of myanesin (5 mg./kg.) on the P component of the cord dorsum potentials elicited by stimulation of the sural nerve in a strychninized (0.15 mg./kg.) and curarized (1.5 mg./kg.) decerebrate cat with spinal section in the upper cervical region. Ordinates: Amplitude of P deflection expressed as maximal P deflection 100 per cent. Abscissae: Time in minutes.

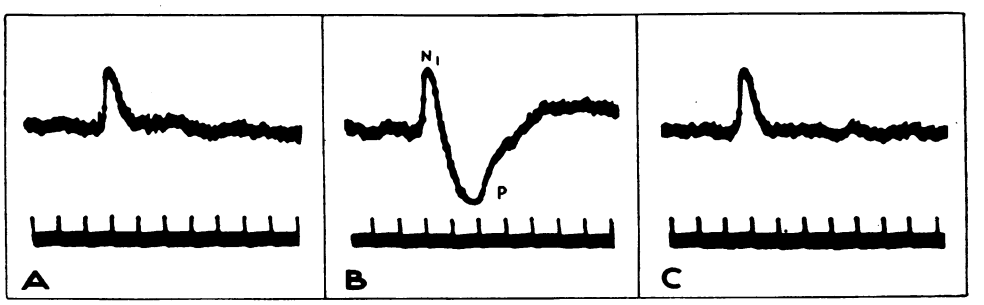

FIG. 6.—Effect of myanesin (5 mg./kg.) on the cord dorsum potentials in the same preparation as Fig. 5. A, Control. B, After strychnine hydrochloride 0.08 mg./kg. C, 3 minutes after myanesin (5 mg./kg.). N: N1 component. P: P deflection. Time: 10 msec.

not reappear until more strychnine was given. Fig. 6 is an extract from the photographic record of this stage of the experiment. Fig. 6A shows the cord dorsum potentials before strychnine, Fig. 6B after 0.08 mg./kg. of strychnine hydrochloride, and Fig. 6C three minutes after 5 mg./kg. of myanesin, when there is no trace of the P deflection. After the fourth injection of strychnine hydrochloride (0.1 mg./kg.) it was found that myanesin in a dose of 2.5 mg./kg. would depress the P deflection, but this action was transient and the P deflection had recovered after two minutes.

It has been shown by Taverner (1952) that strychnine increases the amplitude of the N1 potential to about 125 per cent in low spinal preparations. Myanesin in doses up to 25 mg./kg. in low spinal preparations has no effect on this strychnine augmentation of the N1 potential.

Discussion

The investigation of the action of myanesin on the spinal cord is complicated by the fall of blood pressure which may follow the too rapid intravenous injection of doses of more than 20 mg./kg. body weight. Below a critical level of approximately 40 mm. Hg both the monosynaptic and polysynaptic reflexes diminish in size and may disappear entirely. In the present investigation the drug has been injected slowly and the blood pressure tracing has been inspected throughout. Any fall in the blood pressure has been checked by temporarily stopping the injection. In this way the possibility that the observed changes in the reflexes were due to a fall in blood pressure has been excluded.

The previous investigations by Henneman *et al.* (1949) and Kaada (1950) were mainly directed to the effect of the drug on the facilitation and inhibition of the mechanically induced knee jerk which can be produced by electrical stimulation of other parts of the central nervous system. These authors were in general agreement that myanesin in doses of 25–50 mg./kg. diminished or abolished both facilitation and inhibition of the knee jerk for periods of 30–40 minutes but had no effect on the amplitude of the knee jerk itself. Kaada also reported that myanesin in doses of 10–40 mg./kg. had no effect on the monosynaptic and polysynaptic reflex discharges evoked by electrical stimulation of the mixed afferent fibres in the dorsal root. With doses of 40–60 mg./kg. he produced transient depression of the polysynaptic response, but to reduce the monosynaptic response he had to employ doses of 80–150 mg./kg.

The method of selective study of the monosynaptic and polysynaptic responses employed in this investigation is a more sensitive indicator of the action of myanesin on the spinal cord. The present findings confirm that polysynaptic reflexes are more susceptible than monosynaptic reflexes to the action of myanesin, but in addition they show that the polysynaptic response is temporarily depressed by doses of 20 mg./kg. Doses of approximately 50 mg./kg. abolish the reflex entirely, but it begins to recover within 15 minutes. Throughout the investigation the transient nature of the myanesin effect was striking and this may be of clinical importance.

The present results confirm the findings of Kaada and of Henneman that the monosynaptic response is relatively insensitive to the drug, but transient and slight depression was noted in some preparations with doses of approximately 50 mg./kg. The increase in the amplitude of the monosynaptic reflex which occurs frequently with doses of myanesin of the order of 20–30 mg./kg. is of interest because Henneman

et al. (1949) noted that in one experiment the injection of 10 mg./kg. increased the amplitude of the knee jerk and was followed by the appearance of clonus. They mentioned that similar phenomena have been reported several times in patients. In the present study this effect was observed in both decerebrate and low spinal preparations. It is probably due to the selective blocking of propriospinal interneurones which have an inhibitory effect on the monosynaptic reflex arc.

The anti-strychnine effect of myanesin was described by Berger and Bradley (1946) and confirmed by Kaada (1950), who reported that doses of 25–60 mg./kg. restored the augmented monosynaptic and polysynaptic responses to normal within a few minutes. The present findings provide further confirmation of this, but they show that a dose of only 15 mg./kg. will reduce the strychnine augmented polysynaptic reflex to normal for a few minutes, while doses of 30 mg./kg. have a similar transient effect on the monosynaptic reflex.

An even more striking example of the anti-strychnine effect of myanesin is provided by the studies of its action on the cord dorsum potentials. Doses of 5 mg./kg. of myanesin permanently abolish the strychnine augmentation of the P deflection but leave the originating structure susceptible to the stimulating action of further doses of strychnine. If Bernhard's (1951) view is accepted, that the P deflection represents activity in propriospinal interneurones, the present findings provide evidence for the conclusion of previous workers that myanesin exerts its action on the internuncial cells of the central nervous system. The fact that the drug is equally effective in low spinal preparations with all higher connections severed suggests that its chief site of action is on the propriospinal interneurones. Berger and Bradley (1946) have shown that myanesin has no action on the neuromuscular junctions in the doses employed in the present experiments.

Clinically, myanesin has been disappointing in the treatment of spastic states, extrapyramidal disorders, and tetanus (Schlesinger *et al.*, 1948 ; Bickers *et al.*, 1950 ; Ablett, 1952). It is evident that the doses used clinically could at best have only a transient effect on such conditions and under certain circumstances might even make them worse. The possibility of using continuous intravenous infusions of low concentrations of myanesin in the treatment of convulsive states produced by strychnine or tetanus toxin appears worthy of further consideration, but the hypotensive action of the drug may render this method impracticable.

Summary

1. The action of $\alpha\beta$-dihydroxy-γ-(2-methylphenoxy)-propane (myanesin) on the monosynaptic and polysynaptic reflexes and the cord dorsum potentials elicited by selective electrical stimulation of appropriate afferent fibres, in unanaesthetized cats before and after strychnine, has been investigated. Special attention has been paid to changes in arterial blood pressure produced by the drug.

2. The results of previous workers have been in general confirmed, but it has been shown that myanesin produces transient depressions of the polysynaptic reflex in smaller doses than previously reported.

3. Under certain conditions small doses of myanesin increase the amplitude of the monosynaptic reflex.

4. The anti-strychnine effect of myanesin has been confirmed, but it has been shown that the drug is effective against both the monosynaptic and polysynaptic reflexes in smaller doses than previously reported.

5. The action of myanesin on the cord dorsum potentials is described. In very small doses the drug permanently abolishes the strychnine augmentation of the P deflection.

6. The significance of the results is discussed.

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