CLINICAL AND EXPERIMENTAL STUDIES WITH MYANESIN*

(A Preliminary Report)

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IN December, 1946, following an investigation of numerous a-substituted ethers of glycerol, Berger and Bradley[1] reported on the pharmacological properties of a:b dihydroxy-y-(2 methylphenoxy) propane. This compound, which they named myanesin, produced transient relaxation and paralysis of skeletal muscles in animals, and showed a wide margin of safety between paralyzing and lethal doses. They also found that in small amounts it effectively antagonized strychnine convulsions, and from this inferred that the drug exerted a depressant action on the reflex excitability of the spinal cord. Shortly after, in a series of 112 clinical cases, Mallinson[2] discussed its value and safety as a muscle-relaxing agent when used as an adjunct to anæsthesia.

These observations prompted the present study to gather information on the site or sites of action of this drug, in order to evaluate more fully its therapeutic usefulness. For this purpose clinical trials, aided by electroencephalograms, have been carried out on a number of patients, and certain experimental data have been recorded. The results have been sufficiently interesting to warrant a preliminary report.

I. Clinical Procedure

Myanesin was administered alone to patients in an arbitrary dosage of 30 mgm. per kg. of body weight. The drug was given into an arm vein in 10% solution at a rate of 1 to 2 c.c. per minute. Clinical reactions were noted closely, and on seven patients electroencephalograms were recorded before, during and after injection, using the standard scalp surface and ear electrodes, as well as the basal electrode placed in the posterior nasopharynx for recording the electrical activity of deep-lying cerebral structures.

Case Studies

The cases to be reported can be classified into three groups: (1) patients suffering from diseases of the extrapyramidal nervous system; (2) those having frequent recurrent intractable pain; (3) patients with known spinal cord lesions.

Extrapyramidal Diseases

Case 1

Mrs. F., aged 46. Weight 150 pounds. Dose 2,000 mgm. For twelve years this patient had suffered from a marked "pill-rolling" tremor at rest and increased muscle tone involving all extremities, but principally the right arm and leg. There was also a mask-like facies. These symptoms had led to a clinical diagnosis of paralysis agitans. On two separate occasions she was given 20 c.c. of myanesin over a ten minute period. After 900 mgm. the tremor and spasm disappeared and remained completely absent for 30 minutes. During the next 45 minutes there was a gradual return of the spasm and tremor, although the patient reported that these symptoms remained less severe than usual for 12 hours. Voluntary motor power was not impaired during the time in which the drug was acting. The electroencephalogram recorded from cortical leads only showed no alteration in pattern during or after the administration.

Case 2

Mr. M., aged 56. Weight 156 pounds. Dose 2,000 mgm. Since 1941 this patient had been gradually developing a spastic paraplegia. At the time of examination he could not walk unassisted. In 1942 he began to have a Parkinsonian-like tremor of the left arm, without increased muscle tone, and this persisted. It was believed that these symptoms represented two distinct lesions, the spastic paraplegia being the result of a disease of a separate part of the motor system than that causing the tremor, which seemed clearly of the type attributed to the extrapyramidal system. On two occasions he was given 20 c.c. of myanesin, and each time after 800 mgm. the tremor of the hand ceased completely and remained absent for 45 minutes. Following this the tremor began to return, but the patient

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stated that it was improved for 24 hours. However, no decrease in the degree of spasticity of the legs was noted, and the patient found it no easier in his attempts to walk after the injection. Voluntary motor power, as measured objectively by the dynamometer, was not decreased during or after the administration. The electroencephalogram showed some decrease in the amplitude of the brain waves when the full dose of myanesin had been given, but no basic alteration in the pattern of the waves was seen.

CASE 3

Mr. C., aged 39. Weight 150 pounds. Dose 2,000 mgm. In 1922 this patient was struck in the right eye by a hockey stick, was unconscious for a few minutes, and blind for 48 hours. He appeared to recover completely, but in 1937 began to have marked Parkinsonian-like tremors of the left face, left arm and left leg. These persisted in spite of several forms of therapy. There was no spasm or increased tone associated with the tremor. He was given 20 c.c. of myanesin, and after 1,000 mgm. the coarse tremor of the extremities and face stopped; but there persisted even after the full injection a "pill-rolling" tremor of the left hand. This had been masked before injection by the presence of the coarse tremor. The normal tremor began to return after 60 minutes, and was back to its previous severity after 75 minutes. Motor power was not diminished during the procedure. Certain abnormal electrical waves recorded from the basal leads of the electroencephalogram disappeared during the absence of the coarse tremor. The waves from the cortical leads were unchanged during the administration.

CASE 4

Mr. N., aged 58. Weight 170 pounds. Dose 2,000 mgm. For several years this man had had a combined coarse tremor and athetosis involving the head and both arms. Associated with this had been a constant noise in the left ear. He was believed to be suffering from a familial type of basal ganglia disease which was present in three other members of his family. He was given 20 c.c. of myanesin, and after 600 mgm. the tremor and athetosis stopped completely. At the same time the patient volunteered that the noise in his ear had disappeared. The symptoms began to return after 45 minutes, but were improved for 4 hours. No loss of voluntary motor power was seen during the administration. There was no change in brain wave activity seen from the cortical leads of the electroencephalogram. Recordings from the basal lead were not made.

CASE 5

Mr. F., aged 49. Weight 135 pounds. Dose 1,800 mgm. Since the age of eight this intelligent patient had suffered from generalized gross athetotic movements which required considerable muscular effort for their control. He had a scissors-type gait and found walking a trying procedure. Several types of medication and one operation had failed to influence the condition. He was given 18 c.c. of myanesin, and after 1,000 mgm. his athetotic movements were much less pronounced. When the injection was completed, the patient stated that he felt pleasantly relaxed, and that in his estimation the abnormal movements were reduced by 80 to 90%. Those remaining were controlled easily by voluntary muscular effort, which was not impaired by the drug. Walking was considerably less strenuous than he normally found it. The gross athetosis began to return after 75 minutes, but the patient believed that the movements were less pronounced for the following three days.

CASE 6

Master A., aged 9. Weight 50 pounds. Dose 700 mgm. This congenital spastic had a mental age of approximately four months. He could not feed himself, could not sit up, and could not talk. The trunk and all extremities were spastic. Encephalogram showed greatly enlarged ventricles. He was given 7 c.c. of myanesin, and at the end of the injection appeared asleep, with the trunk and extremities completely flaccid. However, both intercostal and diaphragmatic respiratory movements were unimpaired, and there was immediate reaction to pinprick by withdrawal of the limb and loud crying. The spasticity began to come back after 30 minutes, with return to the former state in 40 minutes.

CASE 7

Mr. M., aged 20. Weight 135 pounds. Dose 1,700 mgm. Beginning shortly after birth this young man had a tremor with accompanying spasticity of the left arm and leg. In the last five years he had also developed a tremor of the right arm. He was believed to be suffering from a disease of the extrapyramidal nervous system. On three occasions he was given 17 c.c. of myanesin, and after 800 mgm. both the tremor and spasticity disappeared and remained absent for one hour. Improvement in the symptoms was noted for 48 hours. Voluntary motor power, measured objectively by the dynamometer, was not impaired during or after the administrations. The electroencephalogram showed evidence of relaxation while the myanesin was active, but there was no basic change in the pattern of the brain waves from cortical or basal leads.

INTRACTABLE PAIN OF CENTRAL ORIGIN

CASE 8

Mrs. T., aged 35. Weight 82 pounds. Dose 1,200 mgm. Three months prior to hospital admission this patient had developed a spastic paraplegia of the lower extremities with rapidly progressive muscle atrophy. She also had severe paroxysms of burning pain, lasting about 45 seconds, which began in the lower back and abdomen and spread like a wave down both legs. This pain recurred every 4 to 6 minutes and was accompanied by marked spasms of the abdominal muscles and flexor muscles of the legs. There was no evidence of spinal block by manometric study, and x-rays and myelogram were normal. The diagnosis was obscure, but, on the supposition that it might be the strong muscular contractions which were causing the pain, the patient was given 140 units of intocostrin. This provided complete muscular paralysis, except for continuing diaphragmatic action, but had no effect on the severity or time interval of the regular attacks of pain. On three different occasions she was given 12 c.c. of myanesin, and in each instance after 500 mgm. there was complete relief from the painful spastic attacks for 45 minutes, and the lower extremities became flaccid. After this period the attacks began to recur as before. The electroencephalogram recorded before myanesin was representative of that seen in tense, anxious patients. This tense picture disappeared when the drug was being given, but there was no change noted in the basic pattern of the electrical waves.

CASE 9

Mrs. C., aged 56. Weight 112 pounds. Dose 1,000 mgm. In January, 1947, this patient developed a sudden hemiplegia due to cerebral thrombosis. About six weeks later she began to have two to four attacks a day of severe pain in the hemiplegic arm, often associated with flexor spasms. Each attack lasted about two hours and did not respond to any type of therapy except large amounts of opiates. The pain was believed to be "thalamic" in nature. On three different occasions she was given 10 c.c. of myanesin, and in each instance with 400 mgm. there was complete relief of pain and associated muscle spasm. Twice the pain recurred after 40 minutes, while the third time the patient was comfortable for 4 hours. Voluntary motor power was not decreased during or after the administration.

CASE 10

Mr. B., aged 44. Weight 130 pounds. Dose 1,700 mgm. In 1945 this patient developed a severe post-herpetic trigeminal nerve neuralgia, principally over the ophthalmic division. The pain persisted constantly, in spite of such therapeutic measures as trigeminal rhizotomy, stellate ganglion block, Gasserian ganglion block, sphenopalatine block, and fever therapy. It was concluded that the origin of the pain was probably central. He was given 17 c.c. of myanesin, and after 400 mgm. stated that he had complete relief from his pain, although a drawing sensation remained in the side of his face. The pain began to return after 70 minutes, and was back to its former severity in another 30 minutes. Voluntary motor power and sensation to pinprick were unaltered while the effects of myanesin were active. In the electroencephalogram no gross alterations were seen in the pattern of the brain waves, but there was some increase in the normal alpha rhythm during and after the administration.

LESIONS OF THE SPINAL CORD

CASE 11

Mr. M., aged 16. Weight 125 pounds. Dose 1,000 mgm. For three years this patient had had clinical signs of a complete spinal lesion with paraplegia and spasticity of both lower extremities. He had a long-standing history of tuberculosis. X-rays of the spine showed a tuberculous lesion involving the 6th, 7th, and 8th thoracic vertebræ. He was given 10 c.c. of myanesin, and following injections no change was noted in the degree of spasticity.

CASE 12

Mr. P., aged 63. Weight 156 pounds. Dose 2,000 mgm. For three months this patient had complained of a numbness and tingling in the left arm and shoulder. X-rays of the cervical spine showed gross bony changes on the left side about the 5th, 6th and 7th cervical vertebræ. The diagnosis was a lesion causing pressure on the cervical nerve roots. He was given 20 c.c. of myanesin, with no effect on the degree or character of his numbness and tingling.

GENERAL SIDE REACTIONS

Up to the present myanesin has been administered on some 50 different occasions. Certain reactions common to each patient were observed while the drug was being given, and these may be noted as follows:

1. *Cardiovascular system.*—With one important exception, no significant alterations in pulse or blood pressure were evident during or after the injection. In three patients with hypertension, no fall in pressure was noted. Almost all patients complained of a hot or flushed feeling during administration and usually the face and neck became reddened temporarily. One patient who was receiving the drug in the sitting position developed a sudden syncope after administration of 2.0 c.c. This was explained as an acute cerebral anæmia coincident with the noted signs of widespread vasodilatation while in the sitting posture.

2. *Respiratory system.*—There were no subjective complaints of difficulty in breathing and no evidence was noted of intercostal paresis. In two patients there was slowing of the respiratory rate, but it did not fall below twelve per minute.

3. *Mental reactions.*—With the dosage given, none of the patients went to sleep, nor were any sleep patterns seen in the electroencephalograms. At all times questions were answered correctly, but in some cases slowing of speech was apparent. During administration no apprehension was felt, but most patients complained of feeling "dopey", "relaxed" or "heavy". After completion of the injection the dopiness disappeared within 2 to 3 minutes, but the relaxed feeling persisted for about an hour. Most patients exhibited a mild degree of euphoria during this latter period.

4. *Neurological reactions.*—Apart from relief of presenting symptoms, as described in the case studies above, the principal neurological alteration seen in all patients was a coarse nystagmus present in all directions, associated with inability of the eyes to converge. This began after about 10 c.c. of myanesin had been given and lasted for 20 minutes following injection. According to Bender and O'Brien,[3] with personal observations by the latter, this myanesin nystagmus is indistinguishable clinically from barbiturate nystagmus, and may be central in origin. As noted above, voluntary motor power, determined clinically and by objective measurement, was not decreased in any patient. Also, pain reaction to pinprick showed no alteration. Superficial and deep reflexes were unchanged.

5. *Urinary changes.*—Within eight hours of administration, ten patients noted that their urine was reddish-brown in colour. One case reported dysuria and frequency for several hours. Examination of the altered urine showed no leucocytes or erythrocytes, but the orthotolidine test for blood was strongly positive, and small quantities of albumen (30 to 100 mgm. %) were present. These findings indicated that in some patients the administration of myanesin produced hæmolysis of blood. No traces of blood were seen in specimens passed more than eight hours after injection.

6. *Local irritation.* — Seven patients experienced about the site of injection some degree of inflammatory reaction which appeared clinically to be a localized thrombophlebitis. The soreness and redness disappeared completely within 48 hours of its appearance. For this

reason, however, no subcutaneous or intramuscular injections were attempted.

ELECTROENCEPHALOGRAPHIC INTERPRETATIONS

The electroencephalographic studies carried out with seven of the patients showed no evidence of significant alteration in the electrical activity of the cortex with the maximum doses of myanesin employed. In certain cases which displayed increased nervous tension, the increase in normal alpha rhythm following myanesin suggested a degree of general relaxation. However, no slow waves, which might indicate a depression of cortical function, were observed. Abnormal waves recorded from the base of the brain—probably diencephalic in origin—disappeared from the electroencephalogram with the disappearance of the clinical signs and symptoms.

CLINICAL OBSERVATIONS

1. It is apparent that involuntary movements of the type seen in diseases of the basal ganglia can be abolished for short periods by intravenous myanesin.

2. Intractable pain of central or thalamic origin may also be stopped for a short time by this drug.

3. Spasm and paræsthesias due to lesions of the spinal cord are not affected by myanesin.

4. The preservation of voluntary motor power and sensation, along with the lack of change in electrical activity in the cortical leads of the electroencephalogram, indicate that this compound exerts no direct action on the cortex of the brain.

5. In those cases where myanesin has a beneficial action, it requires only a fraction (6 to 10 c.c.) of the total dose to produce the desired effect. This tends to show that the drug has a selectivity of action.

6. The eye changes seen in all patients point to a site of action somewhere in the brain stem between the cortex and the medulla.

7. In the doses and at the rate administered, there is no indication that myanesin has a severe toxic action.

8. Myanesin cannot be considered an anæsthetic drug when used in the method described.

II. EXPERIMENAL PROCEDURE

Twenty-five experimental studies on eight cats were carried out with the object of studying the action of myanesin on (1) nerve conduction, (2) the neuromuscular junction and (3) synaptic transmission within the cord. These experiments were performed three to twenty-four hours after transection of the spinal cord at the lower thoracic levels. The nerve and muscle action potentials were recorded on the cathode ray oscilloscope.

NERVE-MUSCLE PREPARATIONS

In the first series of experiments the sciatic nerve was exposed completely on one side from the sciatic notch, and all its connections severed except that to the tibialis anticus muscle. A stimulating electrode was placed on the sciatic trunk as close to the sciatic notch as possible. One bipolar silver recording electrode was placed on the nerve to the tibialis anticus muscle near its entrance to the muscle. Another recording electrode was inserted into the muscle itself. When the nerve was stimulated, both the nerve and muscle action potentials were recorded by means of the standard vacuum tube amplifiers and a cathode ray oscilloscope. Fig. 1 shows a record of the normal nerve and muscle action potentials, and indicates the conduction time of the stimulus from nerve to muscle. The nerve conduction velocity, as measured from the stimulus artefact to the nerve action potential, was found normally to be about 90 metres per second.

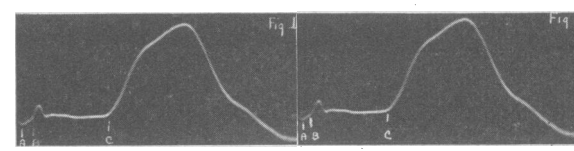

Fig. 1.—Showing normal nerve and muscle action potentials. Recorded at 3.2 millivolt gain per inch and 2.5 milliseconds velocity per inch. (A) Stimulus artefact; (B) beginning of nerve action potential; (C) beginning of muscle action potential; (AB) nerve conduction velocity; (BC) neuromuscular conduction time. **Fig. 2.**—Recording 2 minutes after intravenous injection of 20 mgm. of myanesin per kilogram body weight. Gain and velocity as in Fig. 1. There is no change in nerve and muscle action potentials, in neuromuscular conduction time, or in nerve conduction velocity.

When myanesin in doses from 10 to 30 milligrams per kilogram of body weight were administered intravenously, there were no changes in nerve and muscle action potentials, in neuromuscular condition time, or in nerve conduction velocity (Fig. 2). In doses of 40 mgm. per kilo, the alterations in the record were slight and equivocal. However, on giving doses of 50 mgm. per kilo, there was marked depres-

sion of the nerve and muscle action potentials and a definite prolongation of the nerve-muscle transmission time (Figs. 3a, 3b, 3c and 3d).

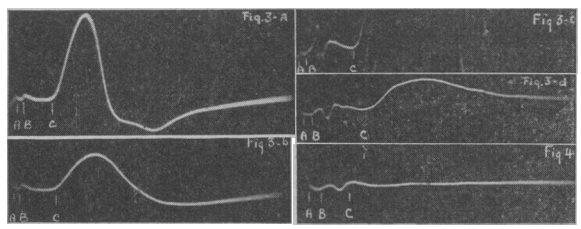

Fig. 3A.—Showing normal nerve and muscle action potentials before injection of myanesin, with gain at 3.2 m.v. and velocity of 5 m.s. per inch. **Fig. 3B.**—Record taken 2 minutes after injection of 50 mgm. of myanesin per kilo. Voltage and velocity as in Fig. 3A. Note pronounced fall in muscle action potential. **Fig. 3C.**—To show the normal nerve and muscle action potentials with a gain of 12.8 m.v. and a velocity of 2.5 m.s. per inch. The muscle action potential rises far off the record. **Fig. 3D.**—Record made 3 minutes after injection of 50 mgm. of myanesin per kilo. Voltage and velocity as in Fig. 3C for adequate comparison. Note diminution of nerve action potential (B), prolongation of neuromuscular transmission time (BC), and prolongation of nerve conduction time (AB). **Fig. 4.**—Record after injection of 70 mgm. of myanesin per kilo. There is almost complete absence of nerve and muscle action potentials.

When 70 mgm. per kilo were injected, there was complete absence of nerve and muscle action potentials (Fig. 4), and in addition no visible muscle contraction was seen.

CONTRALATERAL CORD TRANSMISSION

A second series of studies were made in which the sciatic nerves were exposed on both sides and records obtained when stimulating one sciatic nerve and recording the nerve action potentials from the other sciatic nerve after conduction of the impulses through the spinal cord. With injections of 10 to 40 mgm. per kilo intravenously, no change from the normal was seen in the nerve action potential (Fig. 5a and 5b). When 50 mgm. per kilo were given, there was depression of the nerve action potential (Fig. 6). With a dosage of 70 mgm. per kilo, there was complete obliteration of the nerve action potential (Fig. 7).

In all the experiments the drug began to act within 30 seconds of administration, and the effects persisted for about seven minutes. In doses of 20 and 30 mgm. per kilo the cats became somewhat drowsy and relaxed, but could be roused easily by stimulation. When 50 mgm. per kilo were given, the cats did not respond to painful stimulation and appeared deeply anæsthetized. The animals died with a dosage of 60 to 70 mgm. per kilo.

EXPERIMENTAL OBSERVATIONS

From the above results certain observations can be made: (1) With doses of myanesin up to 40 mgm. per kilogram of body weight no measurable effect was shown on nerve and muscle action potentials, on transmission at the neuromuscular junction, on conduction along the sciatic nerve, or on synaptic transmission of impulses through the spinal cord. (2) in doses

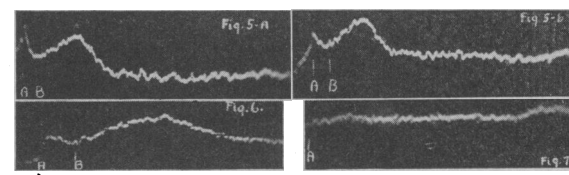

Fig. 5A.—Normal recording of nerve action potential after transmission through spinal cord. Gain is 12.8 m.v., with velocity of 2.5 m.s. per inch. (A) Stimulus artefact; (B) beginning of nerve potential. **Fig. 5B.**—Record 2 minutes after injection of 30 mgm. of myanesin per kilo. No change in potential is seen. **Fig. 6.**—Record 3 minutes after injection of 50 mgm. of myanesin per kilo. Note the depression of the nerve action potential. Gain and velocity as in Fig. 5. **Fig. 7.**—Record 3 minutes after injection of 70 mgm. of myanesin per kilo. Gain and velocity as in Fig. 5. There is complete obliteration of the nerve action potential.

of 50 mgm. per kilo and above, there was marked depression to absence of all the functions which were recorded. The diminution in response was generalized, and not directed specifically towards any one reaction. The dosage which produced these effects was close to the lethal dose for these animals. (3) Generalized reactions to myanesin were seen in cats with doses of 20 to 30 mgm. per kilo, and the minimal lethal dose was found to be 70 mgm. per kilo.

CONCLUSIONS

From the animal experiments it may be concluded that, until relatively large doses are given, myanesin has no effect on transmission of nerve impulses through the synapses of the spinal cord, on conduction of impulses along a nerve, or on transmission of impulses across the myoneural junction. These facts tend to be corroborated by the absence of clinical observations that the drug has any peripheral nerve action in a dosage of 30 mgm. per kilo.

In considering action on the cerebral cortex and brain-stem, most of the evidence accumulated is clinical in nature. The nystagmus seen

in every case suggests a possible action within these structures. However, in the doses specified, voluntary motor power and sensation are not interrupted, thus indicating that the corticospinal tract, and indeed the final common pathway to the periphery, are not affected. Also it is notable that the waves from the cortical leads of the electroencephalogram show little change with the drug administration. Thus there is little evidence of direct action on the cerebral cortex.

With regard to the subcortical area or diencephalon, the clinical results show that myanesin has a pronounced effect on pain of central or "thalamic" origin. In addition, the beneficial results seen in diseases of the extrapyramidal system indicate that the compound has an action in this portion of the brain-stem. Moreover, the small quantity of the drug required to produce these effects suggests that its action is selective for these portions of the nervous system.

It is impossible to state as yet any opinion regarding the therapeutic value of this compound. When given intravenously, it has a shortlived beneficial effect on certain diseases of the extrapyramidal nervous system and on pain of central origin. The localized thrombophlebitis at the site of injection and the transient evidence of hæmolyzed blood in the urine seen in some patients are untoward reactions which will bear careful evaluation against the beneficial effects of the drug. It is hoped that this preliminary report will prove an impetus for further investigation of drugs of this nature.

SUMMARY

1. The beneficial effects of a new drug, myanesin, on diseases of the extrapyramidal system and on pain of central origin, are reported.

2. The general side reactions of this compound are described.

3. Experimental studies to show the action of the drug on nerve conduction, neuromuscular conduction, and synaptic transmission within the spinal cord are recorded.

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REFERENCES

1. BERGER, F. M. AND BRADLEY, W.: The pharmacological properties of a:b dihydroxy-y-(2 methylphenoxy) propane (myanesin), *Brit. J. Pharmacol.*, 1: 265, 1946.
2. MALLINSON, F. B.: A new synthetic curarizing agent in anæsthesia, *The Lancet*, p. 97, January 18, 1947.
3. BENDER, COMDR. M. B. AND O'BRIEN, LIEUT. COMDR. F. H.: The influence of barbiturate on various forms of nystagmus, *Am. J. Ophthalmol.*, 29: 1541, 1946.