THE PHARMACOLOGICAL ACTION OF ESERIDINE

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LITERATURE

The few original papers dealing with this alkaloid, both from the chemical and pharmacological side, were not available. In consequence, recourse was had to the articles on the subject by Henry (5) and by Sharp (6).

From these it appears that the alkaloid was first discovered by Eber in 1888 and first obtained in crystal form by Behringer. Merck has stated that eseridine and geneserine, first obtained by Polonovski and Nitzberg in 1915, are identical.

It is further stated that eseridine was recommended as a substitute for physostigmine as being less vigorous in action but that this advantage has been denied by Schweber on the grounds that both are too toxic to the heart. Geneserine is alleged not to possess the miotic action, so characteristic of physostigmine.

The author, having recently published a description of the action of physostigmine, considered that it might be of interest to examine the action of eseridine, a closely related alkaloid, along the same lines.

EXPERIMENTAL

The alkaloid was procured from Merck and was labelled "Eseridine Tartrate (Geneserine)."

a. Minimum lethal dose

This has been determined in rabbits and dogs by subcutaneous injection in the flank, and, very roughly, in toads by endolymphatic injection

Rabbits

WEIGHT	DOSE	TOTAL DOSE	RESULT
kgm.	*mgm. per kgm.*	*mgm.*	
0.750	30	22.5	Died in ten minutes
0.870	20	17.4	Died in twenty minutes
1.200	15	18.0	Died in twenty-five minutes
1.220	12.5	15.3	Died in forty minutes
1.000	10	10.0	Recovered

The M.L.D. is therefore approximately 12.5 mgm. per kilogram, practically ten times as great as that found for physostigmine. The symptoms observed were very similar to those caused by the latter drug. There was usually passage of semi-liquid feces, dyspnea and tremors of the muscles, often so pronounced as to be distinguished only with difficulty from convulsions. Later paralysis set in, the hind limbs being affected first. Miosis was well marked until shortly before death when the pupil dilated. Finally, the respiration ceased and the animal died in asphyxia with a few weak convulsions.

Post-mortem, the heart was found to be beating, though only feebly and irregularly. In most cases, it was found that faradic stimulation of the phrenic nerve gave rise to a twitch only of the diaphragm, which on direct stimulation responded with a strong tetanic contraction. Similar stimulation of the sciatic and brachial nerves caused strong tetanic contractions in the limb muscles in most cases. When the electrodes were applied to the spinal cord, usually no response was obtained but occasionally weak contractions of the back muscles occurred.

Dogs

WEIGHT	DOSE	TOTAL DOSE	RESULT
kgm.	*mgm. per kgm.*	*mgm.*	
4.20	15.0	63	Died in forty minutes
4.50	13.5	61	Died in three hours
3.50	12.5	44	Recovered
4.50	10.0	45	Recovered

The M.L.D. for dogs therefore is approximately 13.5 mgm. per kilogram, and again about ten times as great as that found for

physostigmine. The symptoms observed were exactly similar to those described in connection with the latter drug. Tremors were rather later in appearing but were well marked, as was also miosis.

Post-mortem, the same observations were made as described above for the rabbit and as were seen with physostigmine.

It may be deduced then that, in both the dog and the rabbit, the cause of death in eseridine poisoning is asphyxia, due to paralysis of the central nervous system, perhaps aided to some extent by paralysis of the neuro-muscular junctions of the phrenic nerves. It is therefore identical in action with physostigmine.

Toads. Eseridine was found to be poisonous to Bufo regularis, only in very large doses. In consequence, the M.L.D. was not determined with any attempt at accuracy but was found to be of the order of 3 grams per kilogram. The symptoms observed were similar to those caused by physostigmine. First the animal ceased to move about voluntarily; then it was unable to turn over when placed on its back. The respiration and reflexes became weaker, both ceasing at about the same time. Finally, the heart ceased and the animal died. Post-mortem, faradic stimulation of the nerves was ineffective but the muscles responded to direct stimulation.

b. Isolated heart

Toad. The isolated heart of B. regularis was perfused by means of Symes' method (7). Eseridine was found to possess a very weak depressant action, no effect being produced by solutions weaker than 1:5000, though a solution of 1:1000 practically arrested the heart. This depression was found to be unaffected by atropine and the action must, therefore, be exerted directly on the heart muscle.

When the depression of the heart by eseridine was fully established, it was found that arecoline added to the perfusing fluid produced a further degree of depression. Similarly, adrenaline produced its usual action. These experiments show that the vagus and sympathetic nerve ends in the heart are unaffected by the drug.

A few experiments were performed in which, the heart being perfused with eseridine in situ, the vagus nerve in the neck was stimulated with the faradic current. It was found that perfusion for a few minutes with a solution of 1:2000 rendered the stimulation ineffective. On reperfusion with Ringer's solution, the vagus soon recovered. As the nerve ends have been shown to be unaffected by the drug, this action must be located in the ganglion cells of the vagus. The weakest solution which produced this effect was found to be 1:3000 but a considerable time was required.

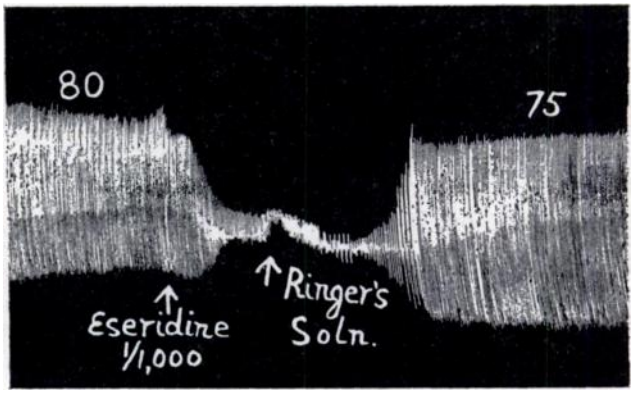

FIG. 1. TOAD HEART PERFUSED WITH ESERIDINE 1:1000

Almost complete arrest of the heart. With Ringer's solution, heart recovers practically completely.

Rabbit. The isolated heart was perfused by means of Gunn's apparatus (2) and the coronary flow measured by means of Condon's magnet tipper (1). The weakest solution to produce any appreciable effect on the rate or strength of beat was found to be 1:10,000. With stronger solutions, depression, affecting the amplitude more than the rate of the beat, was obtained and was found to be unaffected by atropine. The depression must therefore be attributed to direct action on the cardiac muscle. Recovery on reprefusion with Locke's solution was usually complete, though the general level of the tracing on the drum was frequently lowered.

The rate of the coronary flow was increased, by about 15 per cent in the case of 1:10,000 but with the stronger solutions by as much as 60 per cent.

The action of eseridine on the isolated heart of the toad and of the rabbit is exactly similar in nature to that of physostigmine though of a much lower degree of intensity.

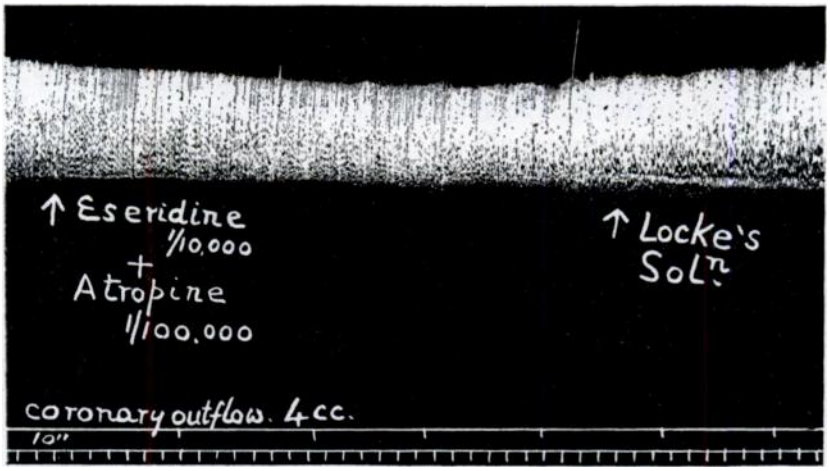

FIG. 2. RABBIT HEART, PERFUSED WITH ESERIDINE 1:10,000 AND ATROPINE 1:100,000

Very slight degree of depression. Coronary flow increased by about 15 per cent. Recovery with perfusion with Locke's solution.

c. Smooth muscle

Rabbit intestine. The usual method of Magnus was employed. It was found that the addition of eseridine to the bath in all strengths from 1:5,000 to 1:50,000 produced an increase in the size of the excursions of the lever and, with the higher concentrations, a rise of tone. This increase of amplitude and tone was immediately abolished by atropine and must be attributed to action on the parasympathetic mechanism. As this rise was equally well obtained after complete paralysis of the ganglion cells by nicotine, the action must be located in the nerve ends themselves.

After eseridine, adrenaline produced its usual inhibitory effect, thus showing that the sympathetic nerve ends are unaffected by the drug.

It has been shown (3) that physostigmine in sufficiently high concentration paralyses first the ganglion cells and secondly the smooth muscle of the rabbit's intestine. Similarly, eseridine, in a strength of 1:1600, was found to prevent the rise of tone which would normally follow the addition of nicotine to the bath, while both arecoline and barium chloride produced their ordinary effect. This can only be due to paralysis of the ganglion cells of the parasympathetic. Again, the rise of tone produced by eseridine in small amounts could be abolished by the addition of very large amounts. At this stage the rise of tone produced by both arecoline and barium chloride was only very short lasting. This effect must be due to partial paralysis of the plain muscle of the intestine.

Uterus. The uterus of the guinea pig was suspended in the usual manner. In concentrations of from 1:25,000 to 1:5,000, eseridine was found to be devoid of action. With higher concentrations, occasionally a slight degree of depression was observed, probably due to action on the smooth muscle itself.

Again, the action of eseridine has been shown to resemble that of physostigmine in kind though much weaker in degree.

d. Pupil

In the experiments for the determination of the M.L.D. in both rabbits and dogs, it was observed that the pupil became narrowed. Similarly, the direct application of a few drops of eseridine, in 2 per cent solution, to the conjunctiva produced a marked degree of miosis which lasted for about eight hours and then gradually disappeared. The narrowing of the pupil was readily abolished by atropine and must be attributed to stimulation of the parasympathetic mechanism of the pupil.

Conversely, it was found that, the dilation of the pupil produced by the prior administration of atropine remained unaffected by eseridine, while that caused by homatropine was readily abolished.

e. Motor nerve ends

In a decerebrated toad, the sciatic nerve was dissected out on both sides. Round one hind limb a strong ligature was passed, excluding the nerve, and tied tightly. Eseridine was then injected into the dorsal lymph sac, and both nerves stimulated faradically at intervals. With the injection of 4 grams per kilogram, it was found that, after the lapse of two hours, there was no response to stimulation of the nerve on the unligatured side while on the other side there was a strong tetanic contraction. With 3 grams per kilogram, this state was reached after about four hours. At the same time, direct stimulation of the muscle on either side was effective. Eseridine therefore paralyses the nerve ends of the toad as does physostigmine. In mammals, however, the tremors produced by eseridine should probably be attributed to stimulation of the motor nerve ends.

f. Striated muscle

The experiments were carried out in the manner previously described (4). Eseridine in a strength of 1:1000 produced no appreciable change in the amplitude of the contractions within a period of forty minutes. In a strength of 1:150, however, it reduced the amplitude by about one-half in one hour. Paralysis of the muscles was not observed in animals to which the M.L.D. had been administered intra-lymphatically. The action of eseridine on the striated muscles of the toad can only be considered as very weak.

g. Intact animal

Dogs anesthetised with medinal, were used for these experiments. The blood pressure was measured by a mercury manometer, connected with either a femoral or carotid artery. A cannula inserted into a femoral vein was used for intravenous injections. For plethysmographic experiments a loop of intestine was employed. The respiration was measured by means of a lever connected directly to the chest wall.

Blood pressure. The only effect observed to follow the administration of small amounts of eseridine was a slight rise of blood

pressure which soon returned to normal. With larger doses, from 2.5 mgm. per kilogram upward, there was a rise of blood pressure, usually only small. This was soon replaced by a fall, often quite sudden in onset, which was found to be associated with a considerable degree of slowing of the heart rate. This was in no way affected by bilateral section of the vagi. With further

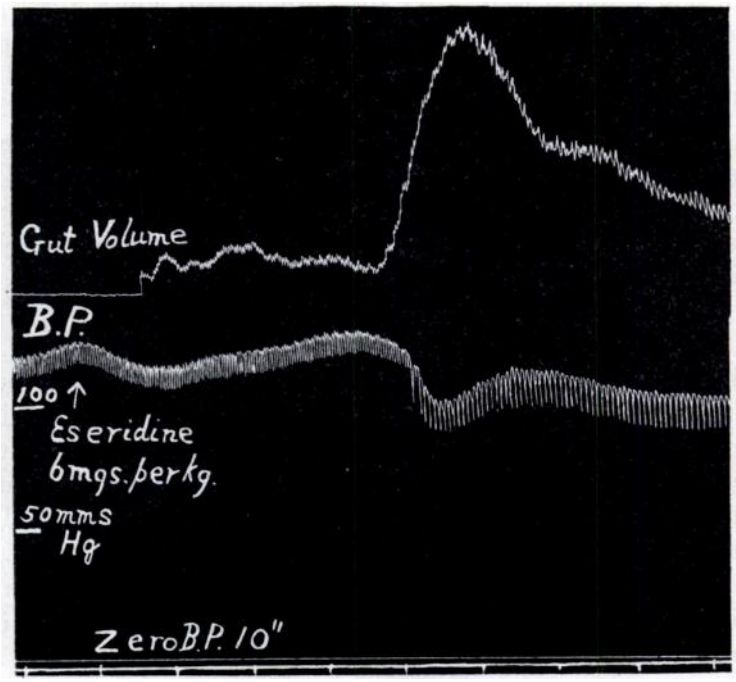

FIG. 3. BLOOD PRESSURE AND PLETHYSMOGRAPH OF GUT VOLUME OF DOG

Injection of 6 mgm. per kilogram of eseridine produces very slight rise of blood pressure, followed by sudden fall associated with great slowing of the heart rate. Synchronous with this is a large rise of intestinal volume which gradually disappears.

administration, the blood pressure continued to fall and the heart rate to decrease. On injection of atropine, the blood pressure rose rapidly to nearly the original height and the heart rate became greatly increased showing that the effect is due to peripheral stimulation of the vagus. When large amounts of eseridine, 10 mgm. per kilogram, had been given, the blood pressure,

though rising rapidly with atropine, often did not reach the original height or, if it did so, soon fell to a considerably lower level, probably due to action on the heart muscle directly.

Respiration. With small amounts of eseridine, less than 2.5 mgm. per kilogram, there was little or no apparent change in the rate or depth of the respirations. With larger amounts, dyspnea was well marked, associated with moist sounds in the chest. With doses of about 5 mgm. per kilogram, the respiration, at first dyspneic, gradually weakened and finally stopped. The blood pressure was usually fairly low at the time of arrest of the respira-

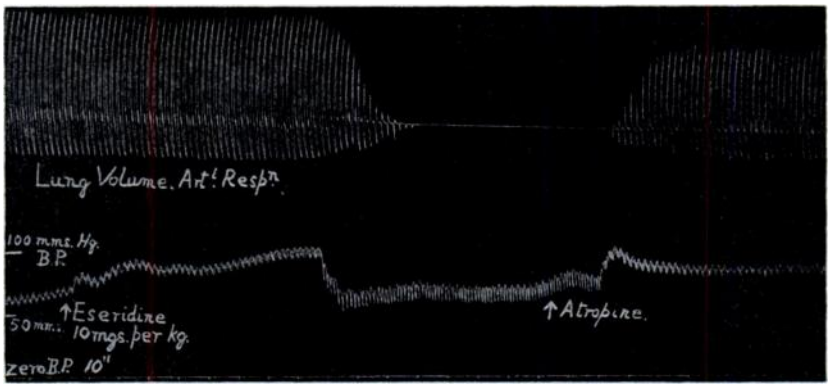

FIG. 4. BLOOD PRESSURE AND LUNG VOLUME OF DOG

Injection of 10 mgm. per kilogram of eseridine causes slow rise of blood pressure with no change in lung volume. This is interrupted by sudden fall of blood pressure with great slowing of heart. Synchronous with this the excursions of the lung volume are rapidly reduced to zero. The whole is immediately abolished by atropine.

tion but still amply high enough to allow of a sufficient amount of blood reaching the medullary centers. The respiratory failure must be attributed to failure of the center.

Intestinal volume. When sufficient eseridine was given to cause the sudden fall of blood pressure and slowing of the heart described above, the intestinal volume was observed to undergo a sudden increase, synchronous with the fall of blood pressure. This was usually short lasting and thereafter the volume tracing followed that of the blood pressure, almost exactly. With smaller doses, no change was observed.

Lung volume. This was recorded in the usual manner, a cannula being thrust through the chest wall and connected to a slack tambour, while the animal was given artificial respiration from a pump. No change was observed during the first slow rise of blood pressure following the injection of eseridine. When sufficient of the drug was given to cause the blood pressure to fall suddenly, the lung volume underwent a synchronous diminution, even to abolition of the excursions of the lever. On administration of atropine, the lung volume rapidly increased again, synchronously with the changes in blood pressure and heart rate.

Vagus. After the administration of large amounts of eseridine, the blood pressure becomes very low and the rate of the heart greatly reduced. At this time, stimulation of the vagus in the neck is not followed by any further reduction in either the blood pressure or the heart rate. This was also observed with physostigmine (3) and, from this fact and from the observation that at this time nicotine produces no slowing of the heart, the deduction was made that the vagus ganglion cells were paralysed. This was supported by the observation that the similar cells in the intestine of the rabbit are paralysed by physostigmine.

If the vagus is stimulated in the neck after the administration of small amounts of eseridine, 2.5 mgm. per kilogram, the blood pressure drops as in the normal. Instead of rising again immediately the stimulation is ended, the blood pressure now remains depressed for a prolonged period of time. It seems that, in some manner, the sensitivity of the heart muscle to vagus stimulation has become greatly increased. The nature of this increase is obscure and is being investigated more fully. The results of these experiments will form the subject of a further communication.

SUMMARY

Apart from the obscure results of the experiments described in the last section, there can be little doubt but that the activity of eseridine, as exemplified by its action on the intact dog, can be shortly described as stimulation of the parasympathetic nerve mechanism. The production of slowing of the heart rate, diminution of blood pressure and of lung volume, increase of intestinal

volume, narrowing of the pupil, increase of bronchial secretion is entirely typical of such stimulation. These changes are all abolished by atropine as would be expected under such circumstances.

In the rabbit and toad heart, however, there is no evidence of any action of the drug on the vagus mechanism. The only effect produced by eseridine on these organs is a slowing and weakening of the beat by direct action on the muscle.

In the rabbit intestine, on the other hand, the production of increased movement and enhanced tone, abolished by atropine, prove the action of eseridine in this case also to be exerted on the parasympathetic mechanism.

In every part of this investigation, a close parallelism between the action of eseridine and that of physostigmine has been demonstrated. The two drugs act on the same mechanism and in the same manner in each instance but the activity of the former is only about one-tenth of that of the latter.

CONCLUSIONS

1. The M.L.D. for the rabbit, dog and toad has been determined to be about ten times as large as that of physostigmine.

2. Eseridine has been shown to possess the same action, but only about one-tenth as great as physostigmine on the isolated heart of the toad and rabbit, the isolated intestine of the rabbit and on the intact dog.

3. Eseridine possesses an obscure power of prolonging the effect of stimulation of the vagus on the heart of the dog.

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