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A STUDY OF SPARTEINE SULPHATE*

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OUTLINE

1. Introduction.
2. Pharmacology.
3. Therapeutics.
4. Methods and results of research.
5. Resume.
6. Conclusions.

INTRODUCTION

On account of the confusion and contradictions concerning clinical experiments and the results obtained from animal experimentation with the use of sparteine sulphate, the author was led to conduct a series of experiments upon animals, with the hope that it might be of benefit to the therapist who is still in doubt as to the true value of this drug. We find upon examination of the literature on the clinical use of sparteine, that a number of very careful clinicians have found it is a most reliable cardiac stimulant and diuretic. Wolferton¹ in his investigation found that it was superior to digitalis. He speaks of its diuretic effect and lays stress upon its reliability. Others claim that it causes a marked rise in blood pressure. Some² assert that the pharmacopeal dose is too small and if results are to be expected, large doses must be administered.

Julien³ found that the drug administered in doses of 0.02 to 0.03 gramme caused a rise in blood pressure and that the heart was strengthened, and that its action differed when administered to healthy and sick subjects. In healthy subjects he found that it quickened the action, while in pathological conditions it regulated it. Others tell us that they have found the drug unreliable and have ceased to use it. I have found upon inquiry clinicians who have used it in chronic heart diseases with good results. Others who have used it for its diuretic effect, claim that it produces marked diuresis in dropsical conditions of cardiac origin; some use it in shock and collapse. Petty⁴ found it to be a true heart tonic and a reliable diuretic in 0.130 gramme doses, especially in post-operative suppression of urine.

On the other hand we find the pharmacologist claiming only a depressing action for the drug. Cushny⁵ says the whole effect points to a paralysis of the motor nerve terminations and of the sympathetic ganglia and that it depresses the heart so that the contractions are weak. Pilcher and Solman⁷ in a series of experiments found that the drug was without effect upon the vasomotor center, except for the depression of the respiration which tends to produce asphyxial stimulation of the center.

Bastedo⁶ says it retards and weakens the heart by direct depression of the heart muscle and by stimulating the ganglia on the vagus nerve. McNider⁹ found in a series of experiments for its diuretic effect on the dog that large doses produced a diuresis, but failed to get results in other experiments and suggested that the samples might vary in potency.

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PHARMACOLOGY

Sparteine is obtained from the common broom plant, a native of Europe and Asia and naturalized in this country. Broom or scoparius contains besides this alkaloid, a neutral principle, scoparin, occurring in

Fig. 1(a).

Frog.—Suspension Method. Three drops applied every 3 minutes. Bottom line represents heart's action three minutes after 4th application. The lever moves upward in systole. (Contrast with tracing under digitalis.)

Fig 1(b).

Frog's Heart.—Showing the comparative effect of digitalis. Three drops applied every 3 minutes. The lever moves upward in systole.

pale yellow crystals and to which the diuretic effect is due when the infusion is administered. Sparteine was first discovered by Stenhouse in 1851 and occurs as a transparent oily liquid. The sulphate is the official salt. It belongs to the conium, lobeline, gelseminine group, a class of drugs that paralyzes both motor endings and ganglia, or rather the myoneural junction which is the term used for the true seat of action, which has been found to be between the end of the nerve and the contractile muscle substance. Green¹⁰ says that sparteine has a more toxic peripheral action and a less vigorous action on the central nervous system than the other members. Upon blood pressure it has a depressant effect due to its action upon the heart muscle.

THERAPEUTICS

Sparteine has been used as a heart tonic in chronic valvular diseases and in cardiac arrhythmia. It is recommended in dropsy of cardiac origin; in anuria and after surgical operations for suppression of urine.

Fig. 2.

Frog's Heart.—Perfusion Method. Heart first perfused with Ringer's solution. At point indicated on record 0.25 mgm. was injected with rubber tube leading to heart.

The average dose given in the Pharmacopeia is 0.012 gramme. This is said by some to be ridiculous. Some claim that in order to get the true effect, at least 0.130 gramme must be given every 2 to 6 hours. Others that from 0.300 to 0.650 gramme

Fig. 3.

Turtle.—Suspension Method. Three drops applied every three minutes—(1) normal. (2 and 3) sparteine sulphate. (4) atropine after sparteine. (5) sparteine after atropine. Kymograph moves from left to right. Upper stroke represents diastole.

must be given to get the true effect. The confusion that exists as to the dose is very marked. It was these contradictory

statements that led to this investigation, which consists of almost all the methods used today in a similar research. It has been my aim in this series of experiments to show the action of sparteine sulphate upon animals from the lower to the higher. This will be followed as closely as possible by a clinical research.

METHODS AND RESULTS OF RESEARCH

Frogs, turtles, rabbits, and dogs were used in this investigation. The methods with results are given in order. The drug

sisted of connecting the apex of the heart to a lever which recorded the contractions upon revolving kymographs. The drug, sparteine sulphate, was applied in 0.1 per cent and 1 per cent solutions—3 drops every three minutes. At the end of three minutes the kymograph was allowed to revolve.

As seen by record No. 1, the rate of the heart was decreased, the diastole and systole being lengthened. The increase in amplitude noticed on the record was proved to be due to a weakened and relaxed heart muscle. The difference between the action of this drug and digitalis when applied to the frog's heart is very noticeable. The slowing of the heart under digitalis is followed by a strong systole which is absent with this drug. See Rec-

Fig. 4.

Turtle.—Heart first perfused with Ringer's solution. At star 0.25 mgm. sparteine was injected in rubber tube leading to heart.

Fig. 5.

Turtle.—Heart first perfused with atropine and then with sparteine sulphate.

was used dissolved in NaCl 0.75 per cent for frogs and turtles, and NaCl 0.9 per cent for the higher animals.

FROGS.

Suspension Method.—The animals were pithed (brain destroyed) and their hearts bared. Time was allowed for the animal to recover from the shock. The suspension method was used for obtaining records of the heart's action. This con-

Fig. 6.

Dog.—Showing toxic effects from third dose of 10 mgm. of sparteine sulphate. Approaching asphyxia.

Fig. 7.

Dog.—Showing the effect of 3 mgm. of sparteine sulphate upon blood pressure and urine flow. Base line represents zero blood pressure.

ord No. 1-B. In all, about twenty-four (24) frogs were used. The normal heart rate was taken and then at intervals of three minutes. The following chart will serve to show the action on the heart.

Sparteine sulphate 1-10% sol. Three drops applied to frog's heart every 3 minutes.

Experiment No.	1	2	3	5	6
Normal	10	9	10	8	11
After 3 min.	6	3	4	4	6
After 6 min.	4	3	4	4	6
After 9 min.	4	3	4	3	4
After 12 min.	4	3	4	3	4
After 15 min.	4	3	4	3	4

The drug did not seem to be toxic to the animal. Atropine first was applied to the hearts of several of the animals, the rate was slightly quickened,

but when sparteine was applied the heart decreased in rate.

A series of hearts were suspended in a glass chamber, the apex being attached to a rod at the bottom, the base being tied to a lever for recording its action on a revolving kymograph. The heart was first immersed in NaCl 0.75 per cent and then in a 0.1 per cent solution of the drug in NaCl 0.75 per cent. The heart was slowed immediately and in some instances ceased to beat at once, but recovered upon being removed from the solution.

Perfusion method.—In this series of experiments the frogs were pithed and a glass cannula

the drug being injected into the anterior lymph sack. They were carefully marked and placed under bell jars, and were all alive at the end of one hour. The frogs that were given the larger dose were pithed and the hearts bared; they were found to be very slow and dilated.

TURTLES.

The suspension method was also used with turtles and the drug applied every three minutes, 1.0 per cent and 0.1 per cent solutions were used. In each experiment the normal average was reduced from six in ten seconds to three in ten sec-

Fig. 8.

Showing the continued action after 4th injection. Toxic effect.

placed in the sinus venosus and the heart connected with a perfusion apparatus. The apex was connected with a lever for recording the action on a smoked drum. The heart was first perfused with Ringer's solution and while being perfused 0.015 gramme of sparteine sulphate was injected into the rubber tube leading to the cannula.

As seen by Record No. 2, the heart ceased to beat almost instantly, but recovered upon being perfused with Ringer's solution.

One Hour Method.—A series of frogs were injected with 0.125 mgm., 0.250 mgm., 0.5 mgm., 1 mgm., 2 mgm., 3 mgms. of sparteine in solution,

Fig. 9(a).

Rabbit.—Showing the effect of 5 mgm. of sparteine sulphate upon blood pressure and urine flow when injected intravenously.

Fig. 9(b).

Showing the continued action from 5 mgm. of sparteine sulphate and from the injection of small doses repeated.

onds. As with the frog the amplitude was greater, but this was due to the muscle's relaxing or stretching. The heart was not paralyzed even when the organ was flooded with the drug, but gradually became smaller and only after several hours ceased to beat.

As seen by Record No. 3, a normal tracing was made (a Cushny myocardiograph being used). Sparteine was applied and resulted in a slowing of the heart, which became very irregular. Atropine sulphate was applied in 0.1 per cent solution. This removed this action so that the heart became regular again. Sparteine was again applied, but as

Fig. 10.

Dog.—Showing the effect upon blood pressure and urine flow of 2 mgm. of sparteine sulphate injected intravenously. Base line represents zero blood pressure.

noted by record, without effect, except to cause the heart to become smaller and weaker.

Perfusion Method.—This was also used with the turtle's heart. An apparatus of the Williams type was employed. The heart was first perfused with Ringer's solution. The normal out-flow in drops as well as the pressure was recorded with a water manometer. The apex was connected to a lever through a pulley for recording the action on a revolving drum. As shown by Record No. 4, upon injection of 0.250 mgm. into the perfusion liquid, the heart became smaller and weaker. The normal rate in outflow was 3 in 10 seconds, the water

otid artery for blood pressure tracing; a bladder cannula was inserted to record the flow in drops of urine; and the drug was injected in measured doses into an ear vein with a hypodermic syringe. A record was made of the heart, respiration, urine flow, and blood pressure, before and at five minute intervals after the injection.

The average dose injected was 5 mgm. with the following results: There was immediately upon injection of the drug, a fall in blood pressure; and the heart rate was reduced from 39 to 33 in ten seconds. The respiration was at first unaltered, but upon the second and third injections it became deep and labored at first, and then decreasing from 7 to 4 per ten seconds. The urine flow decreased from 3 in 10 seconds to 3 in 20 seconds. In several of the experiments the urine flow ceased altogether. The average record for several experiments in which the drug was injected in repeated doses, was blood pressure normal 100, heart 39, respiration 7, urine flow 3 in 10 seconds. After injection of drug, blood pressure 87, heart 25, respiration 3 and urine flow 0.

As seen by Record No. 9, there was first a fall and then a slight rise. During the rise there was a slight increase in the flow of urine, but this gradually decreased and after about one hour ceased altogether. The vagus is not tonically active in the rabbit, so that the fall in blood pressure as noted on the record is due either to a de-

Fig. 11.

Dog.—Showing the effect of 0.5 mgm. of sparteine sulphate upon blood pressure and urine flow. Base line represents zero blood pressure.

manometer registering 243, 3 minutes after injection, the outflow from the heart was one drop in 10 seconds, and the manometer registered 233. The heart recovered after perfusion with Ringer's solution. Atropine sulphate in 0.1 per cent solution was used first and followed with sparteine. As seen by Record No. 5, the heart ceased to beat almost immediately.

RABBITS.

The rabbits used were all healthy specimens of average weight. This experiment consisted of weighing the animal and using urethane anesthesia. The glass cannula was placed in the car-

Fig. 12.

Dog.—Showing the effect of 5 mgm. of atropine after sparteine sulphate. Signal line zero blood pressure, mercury manometer.

Fig. 13.

Showing the effect of sparteine after atropine. Signal line, zero blood pressure.

pressant action upon the heart muscle, a depressant action upon the accelerator mechanism, or to a dilator effect.

The following protocol will illustrate the method used in obtaining records of the experiments on rabbits and dogs. (Rate of heart and respiration is given in 10 seconds.)

Animal—Rabbit.

Weight—1.565 Kg.

Time—12:25 P. M. Urethane 50 c.c. 6 per cent sol. by stomach tube.

12:40 P. M.—Heart 39, respiration 7, blood pressure 100, urine flow 3 drops in 10 seconds.

12:45 P. M.

Sparteine sulphate 5 mgm. in ear vein.

12:50—Heart 33, respiration 7, blood pressure 923, urine flow 3 in 20 seconds.

1:00 P. M. Heart 35, respiration 5, blood pressure 99, urine flow 3 in 10 seconds.

1:15 P. M. Sparteine sulphate in vein.

1:20 P. M. Heart 33, respiration 6, blood pressure 105, urine flow 3 in 20 seconds.

1:45 P. M. Heart 33, respiration 4, blood pressure 100, urine flow 0.

1:50 P. M. Heart 32, respiration 4, blood pressure 112, urine flow 1 in 30 seconds.

2:05 P. M. Heart 25, respiration 3, blood pressure 87, urine flow 1 in 30 seconds.

DOGS.

The animals used in this research varied in size, age and sex. They were carefully weighed and morphine-ether anesthesia was used. A cannula was placed in the carotid for blood pressure tracing. The drug was injected in measured quantities into the femoral vein through a glass cannula inserted for this purpose. In most of the experiments the kidney was placed in a copper oncometer with a rubber bag filled with water which led to a water manometer for registering the volume. In a majority of the experiments a glass bladder cannula was inserted for registering the urine flow. It is customary to insert the cannula in the left ureter. I have found that the failure to obtain results in some instances is due to the small opening in the tube becoming stopped up, or the kidney being damaged by being placed in the oncometer. With the cannula in the bladder, the flow is obtained from both kidneys.

Varying amounts as well as different makes of the drug were used in this experiment as well as all of the others. The smallest amount given was 0.5 mgm. per Kg., the largest 10 mgm. per Kg. A record of the heart, respiration, blood pressure, oncometer, and urine flow was carefully recorded.

As seen by figures No. 7 and No. 10, there occurred with each injection a sudden rise in blood pressure followed immediately by a fall. It was noted that the rise after the second and third injections were not so high as with the first.

In all of these experiments the blood pressure did not return to normal until large doses had been administered. With the administration of small and large doses it was noted that the respiration was depressed and that the heart was more or less irregular, the respiration finally ceasing before the heart. There was also a decrease in kidney volume; and after a slight increase in urine flow, which occurred at the initial rise and fall, there was a decided decrease. In some of the experiments the urine ceased to flow altogether.

In every experiment upon dogs the drug proved fatal. In one experiment the first injection of 5 mgm. per Kg. proved fatal. Artificial respiration through the trachea failed to relieve this condition.

There was with one animal a rise of blood pressure without the fall, as seen in figure 11. This occurred with the first injection of 0.5 mgm. per Kg. With this animal there was a slight increase in kidney volume and urine flow, but this did not

last. The heart and respiration were decreased in rate with each successive dose.

The following experiments were carried out upon several of the animals: Atropine in 5 mgm. doses was injected after sparteine, and as seen by figure 12, there was a decided fall in pressure. In others, sparteine was injected after atropine, and as seen by figure 13 there was a gradual rise in blood pressure. This always proved fatal.

RESUME.

1. Sparteine is not toxic to the frog. The heart is slowed and weakened by a depressant action upon the heart muscle and by a stimulation of the vagus endings.

2. Sparteine slows the turtle's heart by stimulation of the vagus endings and by a depression of the heart muscles.

3. Sparteine slows the heart of the rabbit. It slows the respiration, decreases the flow or urine, and causes a fall in blood pressure.

4. Sparteine causes a preliminary rise of blood pressure in the dog, followed by a fall. The fall was not so marked when small doses were given. The kidney oncometer shows a decrease in volume in a majority of the experiments. There is a slight increase in urine flow with the rise and the first fall.

The experiments did not prove conclusively the cause of the rise in blood pressure, but the results obtained with the kidney oncometer tend to show that it is due to a vaso-constrictor action. The fall is due to stimulation of the vagus. This is proven by first injection of atropine and afterward by sparteine. Atropine seems to increase the toxicity of sparteine.

CONCLUSIONS

Sparteine is not a cardiac stimulant. It is a depressant to both the heart and respiration. Death is due to failure of the respiration, aided by the action of the drug upon the heart muscle.

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