THE MODE OF ACTION OF DYSENTERY TOXIN

COMMUNICATION 4. EXPERIMENTAL THERAPY OF DYSENTERY TOXEMIA

I. P. Miagkaia

From the laboratory of receptor physiology (Head – Corresponding Member of the AN SSSR Prof. V. N. Chernigovskii) of the laboratory of pathological physiology (Head – Prof. V. S. Galkin) of the I. P. Pavlov Institute of Physiology of the AN SSSR (Director – Academician K. M. Bykov) and the Department of preliminary instruction in Internal Medicine (Head – Active Member of the AMN SSSR Prof. M. D. Tushinskii) of the Ist Leningrad Academician I. P. Pavlov Medical Institue

(Received November 26, 1956. Submitted by Active Member of the AMN SSSR V. N. Chernigovskii)

The antibacterial drugs in widespread use in the treatment of dysentery cannot be considered fully effective since in 22-25 % of cases in which they are used the disease acquires a chronic course [1]. For this reason attempts to speed up the processes of repair in the bowel are undertaken, by acting on the body as a whole. In this way, for instance, novocain [5, 6, 7, 8], and magnesium sulfate are used in the treatment of dysentery.

We thought it worth while to compare experimentally in dysentery toxemia the action of novocain and magnesium sulfate with that of the widely used sulfonamide drugs.

EXPERIMENTAL METHOD

We performed 39 experiments on cats. Dysentery toxemia was produced by giving two subcutaneous injections of Shiga dysentery toxin in a dose of 7-10 lethal mouse doses per 1 kg body weight with an interval of 24 hours between the injections. At the same time as the toxin injections and for 3 days afterwards, in 16 experiments novocain was injected intramuscularly (daily dose 0.01 g/kg) and in 12 experiments — magnesium sulfate (daily dose 0.015 g/kg). From 3-4 hours after the injection of toxin, oral administration of phthalyl sulfathiazole was commenced in 11 animals (daily dose 0.2 g/kg). During 4 days observations were made on the behavior of the animal, and its rectal temperature and weight were measured daily. On the fourth day of the toxemia the condition of the interoceptors of the small intestine was studied by a previously described method [4]. After the experiments the animals were autopsied.

The general pattern of the toxemia, the autopsy findings and the character of the interoceptive reactions of the animals receiving one or other form of therapy were compared with the results of preliminary experiments on untreated cats [4].

In untreated cats the injection of Shiga dysentery toxin caused the development of a severe illness, accompanied until the 4th day of the toxic effect by diarrhea and loss of weight amounting to 7 %. The temperature was raised, reaching its peak on the 3rd day. On the 4th day the temperature fell, often below normal. The temperature range was on the average 1.4° C. Areas of necrosis occurred in the mucosa of the alimentary tract in 5 out of 9 cats. In the 4 remaining cats changes in the stomach and bowel were moderate and took the form of hyperemia and edema of the mucosa with tiny hemorrhages and superficial ulcers. The intensity of the interoceptive intestinal reflexes of these animals was diminished when dysentery toxin was applied to the mucosa of a perfused intestinal loop, while that of healthy animals was unchanged.

EXPERIMENTAL RESULTS

In the 16 cats receiving novocain at the same time as toxin the condition was serious and differed little from the condition of animals not receiving novocain. By the 4th day of the toxemia all the cats had lost about 7 % of their weight. One of them had lost 23 % of its weight. The variation in temperature was on the average 1.2° C.

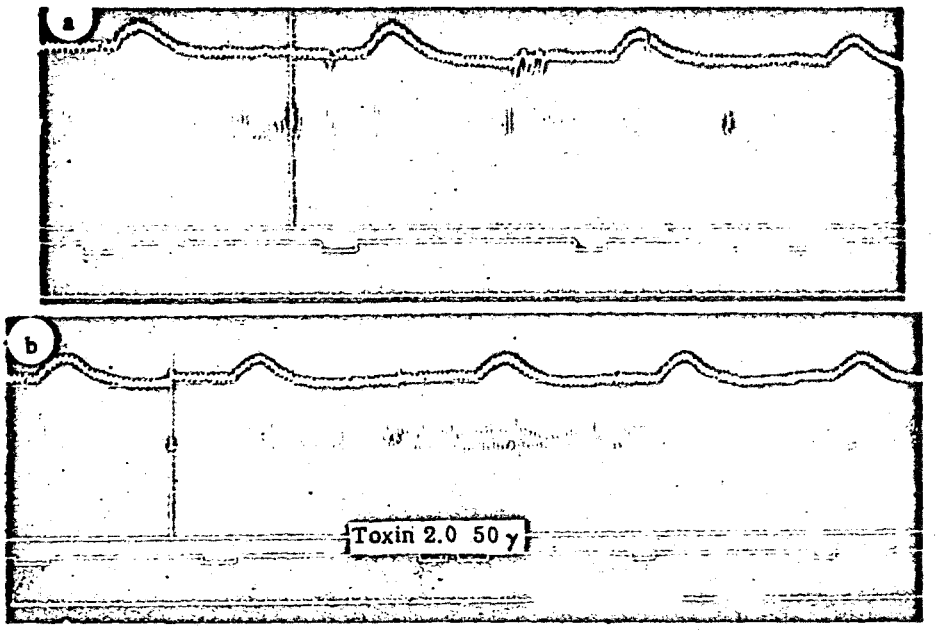

Fig. 1. Experiment dated April 20, 1956. Cat 4150 g in weight. Explanation in text.
Interpretation (from above downward): arterial pressure, original level of arterial pressure, respiration, zero line of manometer, record of stimuli, time record at 5-second intervals. Quantity of nicotine expressed in γ.

As shown at autopsy, the use of novocain not only did not prevent the development of lesions in the alimentary tract but, on the contrary, in some cases it led to the development of more severe morphological changes. In 11 animals of this series areas of necrosis were found in the mucosa of the alimentary tract, often larger than in the control series, and only in 5 animals were moderately severe lesions found in the intestine (hyperemia and edema of the mucosa, superficial ulceration, hemorrhages).

Interoception in the intestine of 12 of these animals was studied; the 4 remaining cats, being in such a serious state, died while preparations were being made for the experiments. In 11 experiments in this series the introduction of toxin into the lumen of a perfused loop of bowel was not accompanied by change in the pressor reactions of the arterial blood pressure in response to injection of nicotine into the vessel [Fig. 1]. In only one experiment was absence of reflex reactions of the arterial blood pressure to nicotine observed.

It was thus shown that the use of novocain does not change the intensity of the reflexes to nicotine. The character of the interoceptive reactions of the bowel in these cats was in no way different from the same reactions in animals not receiving novocain. The "removal of pathological interoception" with novocain, recommended by I. V. Sepp [7] is not followed by improvement in the condition of the experimental animals.

The development of lesions in the mucosa of the bowel with unchanged intensity of reflexes after application of toxin to the mucosa of the bowel of these animals shows that changes in the interoceptive reflexes are more likely to be the result than the cause of the pathological process.

The results obtained do not agree with the successful use of novocain in clinical practice described above.

In a second series (of 12 experiments) magnesium sulfate was used. Eleven of these cats were characterized by a good general condition. These animals differed little outwardly from healthy ones and took their food well. As a rule they did not develop diarrhea but they all lost weight (on the average 6%) and their temperature variation was 0.9° C.

The exception in this series of experiments was the development of a severe hemorrhagic enterocolitis in one cat which died on the 3rd day after injection of the toxin.

The interoceptive function of the bowel was studied in 11 animals. Application of dysentery toxin to the mucosa of a perfused portion of bowel in 7 animals did not produce any change in the intensity of the interoceptive reflexes to nicotine. At autopsy of these cats slight changes were found in the alimentary tract, consisting of hyperemia and edema of the mucosa, mainly of the distal portion of the small bowel and the whole of the large bowel.

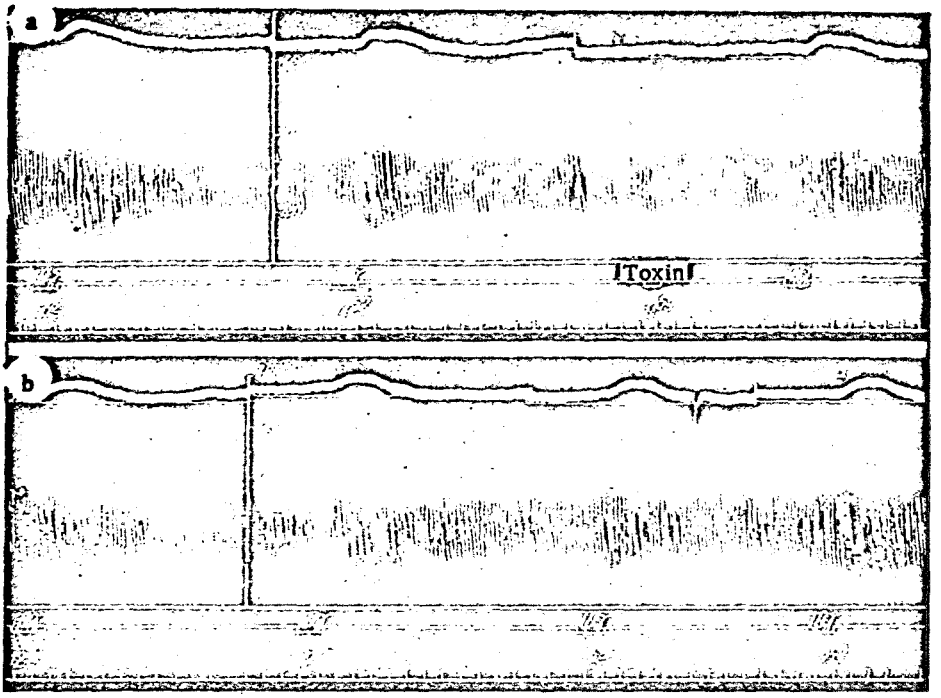

Fig. 2. Experiment dated June 7, 1956. Cat weighing 3400 g. Explanation in text.
Interpretation as in Fig. 1.

Fig. 2 is an illustration of this experiment. The intensity of reflex increase of arterial pressure (10 mm of mercury on injection of 10 γ of nicotine) does not change in the course of 41 minutes after stimulation of the intestinal mucosa with toxin.

In 3 experiments the introduction of dysentery toxin into the lumen of the perfused loop of bowel led to a twofold increase in the intensity of the reflexes to nicotine compared with the original.

In Fig. 3 are shown kymograms of one of these experiments. Application of dysentery toxin to the mucosa of a perfused loop of bowel caused, in response to injection of 100 γ of nicotine, a rise of 6 to 18 mm of mercury in the arterial blood pressure. The intensity of the reflexes was restored after 50 minutes.

In two of the three animals the morphological changes consisted of edema of the mucosa of the alimentary tract and hemorrhages in the pyloric part of the stomach or the beginning of the duodenum. The third animal developed edema of the mucosa only.

In only one experiment did the introduction of dysentery toxin into the lumen of the bowel lead to suppression of the reflexes to 100 γ of nicotine for a period of 43 minutes. Only in this case was there formed a small (0.2 x x 0.6 cm) localized area of necrosis in the mucosa of the duodenum.

In control experiments in which magnesium sulfate was not given, severe toxemia developed in the 4th day as a result of the action of the dysentery toxin. Introduction of toxin into the lumen of the perfused intestinal loop led to a persistent lowering of the reflexes to nicotine. These animals showed severe hemorrhagic areas of necrosis in the stomach and duodenum and edema of the mucosa of the large bowel.

These experiments showed that in experimental conditions the parenteral administration of magnesium sulfate considerably weakens the action of dysentery toxin.

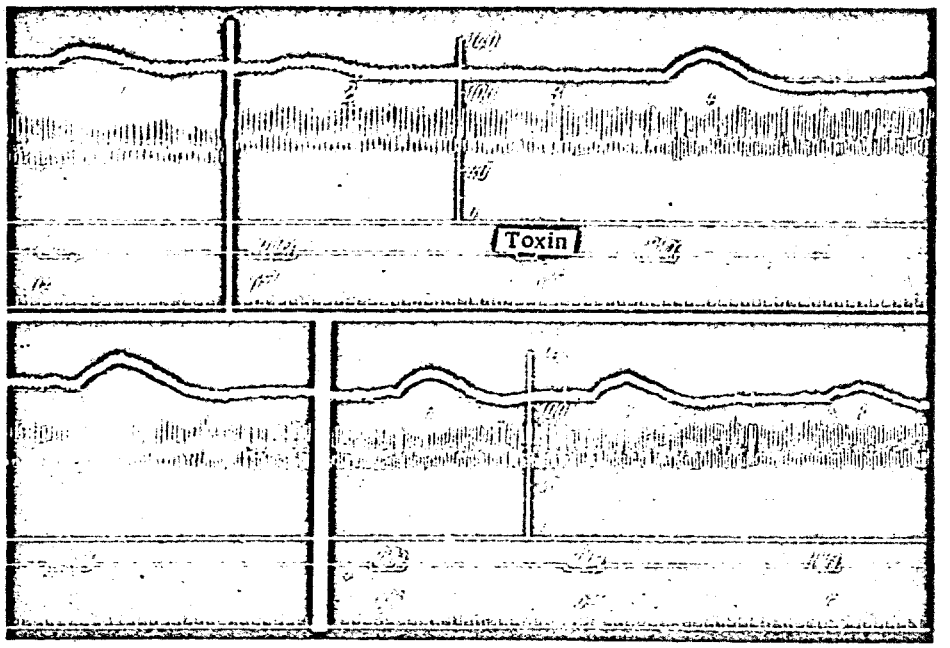

Fig. 3. Experiment dated May 18, 1956. Cat weighing 3050 g. Explanation in text.
Interpretation as in Fig. 1.

Our results shed no light on the mechanism of this positive effect. It is difficult to connect it with the narcotic effect of magnesium sulfate since the doses used were much too small.

The positive results from the use of magnesium sulfate in experimental dysentery toxemia and its good therapeutic results in acute and chronic dysentery [2, 3] give grounds for further study of this drug and also for its use in the therapy of dysentery.

The most severe toxic effects developed when sulfonamide drugs were given (11 experiments). On the 4th day of the illness the condition of these animals was far more serious than the controls. However, their loss of weight was rather less — 6 %, possibly on account of the greater edema of the tissues. The variation in the temperature, like the control group, was 1.4° C. Two cats in this series died on the 3rd day and one on the 4th day of toxemia. The morbid anatomical picture was completely in keeping with the severity of the disease. In 10 animals were found severe changes in the alimentary tract, including areas of necrosis in the pyloric part of the stomach. In only one cat was the degree of involvement of the bowel moderate (hyperemia, edema, small hemorrhages).

Study of the interoceptive function of the intestine of these animals (8 experiments) showed a marked lowering of the pressor reactions to injection of nicotine into a vessel after application of dysentery toxin to the mucosa of the perfused loop of bowel (3 experiments). In 2 experiments a diminution of intensity of the pressor reactions of the arterial blood pressure was also observed, but against a background of unstable reflexes, and in 2 experiments there was a small rise in the intensity of the reflexes to nicotine (from 10 to 14 mm of mercury). In one experiment no changes in the reflexes could be obtained.

The results obtained show that sulfonamide drugs have no antitoxic action in poisoning due to Shiga dysentery toxin in cats.

On the contrary, their use greatly aggravates the course of the poisoning.

In respect of diminution of the toxic effects, the results of these experiments are not in agreement with the successful clinical application of the sulfonamide drugs. It must be remembered, however, that in our ex-

periments phthalyl sulfathiazole was used not in infection but in toxemia, the severity of which probably caused the appearance of toxic properties of the sulphonamides.

SUMMARY

Intramuscular injection of novocain in dysentery intoxication does not improve the general condition of the animals. Magnesium sulfate used in the same conditions relieves the course of this disease. Sulfanilamide preparations have no antitoxic effect in dysentery intoxication.

LITERATURE CITED

[1] P. A. Alisov, Terap. Arkh. 5, 95-96 (1956).

[2] A. Ia. Gasul', Sovet. Med. 8, 16-17 (1948).

[3] A. Ia. Gasul', Sovet. Med. 3, 13-14 (1951).

[4] L. P. Miagkaia, Biull. Eksptl. Biol. i Med. 43, 5, 77-82 (1957).*

[5] B. Ia. Padalka, Dysentery; Etiology, Clinical Features and Therapy.** pp 131-149 (1955).

[6] N. A. Ponomarev, Klin. Med. 22, No. 9, 78 (1944).

[7] L. V. Sepp, Voenno-Med. Zhur. No. 3, 34-37 (1954).

[8] F. F. Iurchak, Vrachebnoe Delo, No. 6, 533-538 (1953).

* Original Russian pagination. See C. B. translation.
** In Russian.