PATHOGENESIS OF CINCHOPHEN GASTRIC ULCER IN DOGS

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The mechanism of formation of cinchophen gastric ulcer in dogs is not yet completely understood. According to S. I. Filippovich [10], after administration of cinchophen to dogs, disturbances of higher nervous activity and of the conditioned-reflex phase of gastric secretion appear first. Other authors attach great importance in ulcer formation to changes in the efferent links of the reflex arc [2, 3], to an increase in the concentration of acetylcholine in the blood [6], to disturbances of the circulation in the stomach, to the peptic factor [7, 8], and to stimulation of the receptor apparatus of the gastric mucous membrane [4].

In this investigation the effect of administration of cinchophen on the level of the blood electrolytes was studied.

EXPERIMENTAL METHOD

Cinchophen was given to three healthy dogs in a dose of 0.2 g/kg body weight.

Blood for estimation of the electrolytes was taken from the fasting animals by puncture of a vein in the hind limb. To prevent the blood from clotting, heparin was first added to the tube at the rate of 2 drops for 8-10 ml blood. Plasma was obtained by centrifugation of the whole blood, and to obtain the erythrocytes the blood was centrifuged a second time after aspiration of the intermediate layer. The electrolytes were determined by means of the PPF-UNIIZ flame photometer, the blood and its constituents being diluted 20 times for the potassium estimation and a 100 times for the sodium estimation. To determine the background concentration of electrolytes, these were determined in the blood four times (over the period of 5 days) before administration of cinchophen.

EXPERIMENTAL RESULTS AND DISCUSSION

The changes in the potassium concentration following administration of cinchophen are shown in Fig. 1 (the changes in the potassium concentration in the plasma and erythrocytes were parallel with those in the potassium concentration in whole blood). On the first days of administration of cinchophen to the dogs, the blood potassium concentration rose sharply (there is no potassium in cinchophen). In dog No. 8, dying from cinchophen poisoning on the 8th day of its administration, for example, the potassium concentration rose from 5.2-6.0 (background) to 7.5-7.6 meq/liter (during the last two days); in dog No. 7, from 5.2-5.7 (background) to 7.2-7.6 meq/liter (at the height of the hyperkaliemia). However, in this dog, the blood potassium concentration began to fall on the 10th day of administration of cinchophen, and reached 6.5-6.6 meq/liter on the last days of the experiment. At necropsy a large ulcer was found in the pyloric portion of the stomach. The same picture was observed in dog No. 11 also. An increase in the potassium level from 5.5-6.5 (background) to 7.5-7.7 meq/liter was followed by a decrease to 4.9-5.3 meq/liter. This dog died from cinchophen poisoning on the 21st day of administration. As in dog No. 8, in dog No. 11, no ulcer was found at necropsy, but only hemorrhages in the gastric mucous membrane.

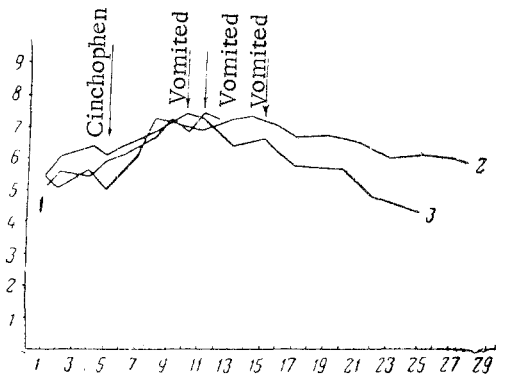

Fig. 1. Potassium concentration in whole blood of dogs poisoned with cinchophen (0.2 g/kg). 1) Dog No. 8, 2) dog No. 7, 3) dog No. 11. Along the axis of ordinates – potassium (in meq/liter), along the axis of abscissas – days of experiment.

What is the mechanism of the hyperkaliemia on the first days of cinchophen administration? One of the leading roles in the regulation of electrolyte metabolism is played by the adrenal cortex and, in particular, by its zona glomerulosa. The results of a histological investigation of the adrenals of dogs poisoned with cinchophen showed that the zona glomerulosa of the cortex

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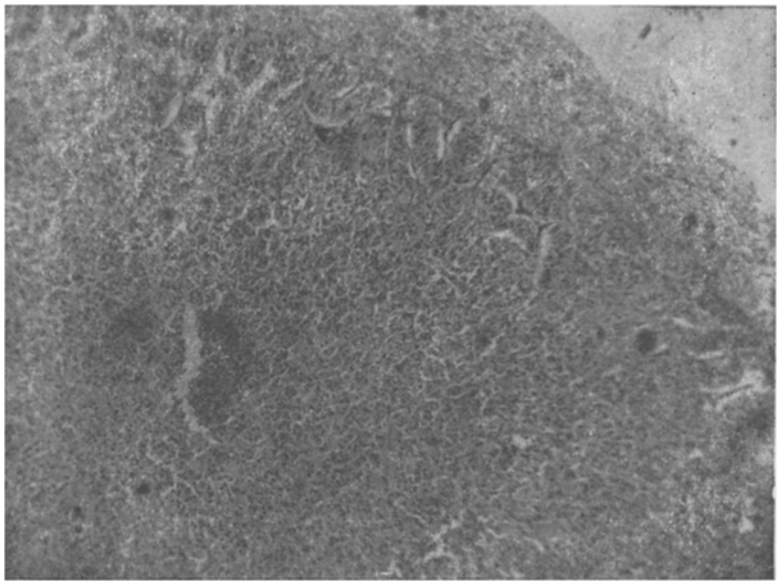

Fig. 2. Adrenal of dog No. 11. Photomicrograph. Hematoxylin-eosin. Magnification 7 x 10.

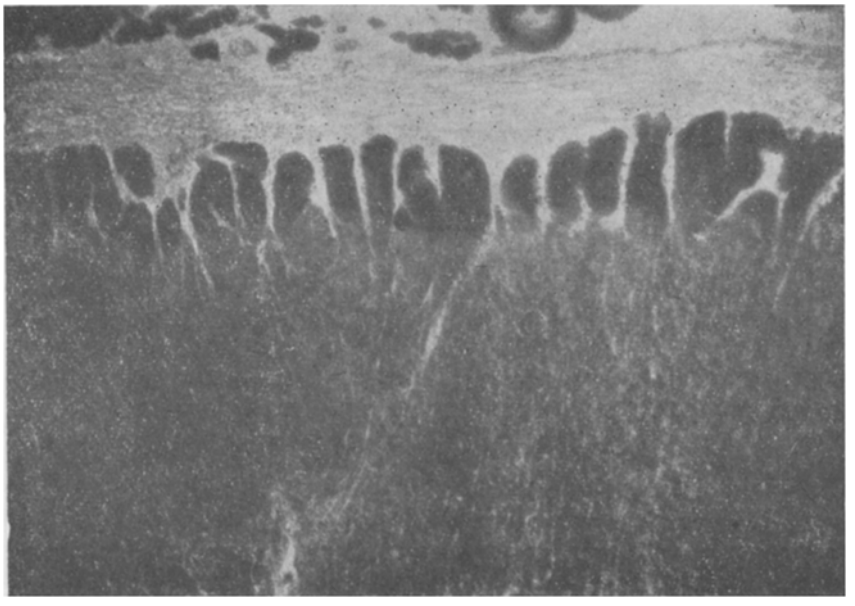

Fig. 3. Adrenal of dog No. 8. Photomicrograph. Sudan Black. Magnification 7 x 10.

is widened and consists of narrow loops of glomeruli. The cells of this zone are elongated and the cytoplasm of these cells shows vacuolation and granular degeneration. The zona fasciculata is fairly wide, its cells are small and tightly packed without a clearly defined fascicular structure, pycnosis and a foamy structure of the cytoplasm of the cells can be seen, and the intercellular spaces are widened and distended with lymph. Blood cells have escaped from the dilated capillaries into the intercellular spaces (Fig. 2). Staining for lipids (Sudan III, Sudan Black) revealed an uneven distribution of sudanophilic substances in the adrenal cortex. Large amounts were seen in the zona glomerulosa and much less in the zona fasciculata, which stained irregularly; in some places the staining was strong, in others weak, and in some places no sudanophilic substances whatever were present (Fig. 3).

Consequently, the morphological picture showed the presence of a lesion and depression of the functional activity of the zona glomerulosa with some increase in the level of function of the zona fasciculata. A decrease in

the output of mineralocorticoids by the zona glomerulosa of the adrenal cortex was evidently the cause of the hyperkaliemia of the dogs receiving cinchophen. But in that case, what caused the subsequent fall in the blood potassium level observed in dogs Nos. 7 and 11? In the author's opinion, the reason here was the frequent vomiting occurring in dog No. 7 on the 10th day and in dog No. 11 on the 5th day of cinchophen administration. The gastric juice of dogs contains a high concentration of potassium (7.2-22 meq/liter [1]), so that a considerable loss of gastric contents as a result of vomiting must undoubtedly lead to hypokaliemia. Another important factor in the loss of potassium was the diarrhea appearing in the dogs following administration of cinchophen. What is not understood is why the sodium concentration in the blood of these animals did not fall. A possible explanation of this may be that dogs are animals losing very little sodium after adrenalectomy (and after lesions of the zona glomerulosa of the adrenal cortex [9]).

The disturbance of potassium metabolism and depression of the mineralocorticoid function of the adrenal cortex demonstrated by these experiments in cinchophen ulcer helped to explain the increase in gastric secretion and also the increase in the total and free acidity of the gastric juice [5, 11] of dogs receiving cinchophen. Groza and co-workers [20] showed that changes in the volume of gastric secretion ran parallel to changes in the blood potassium concentration. The importance of calcium ions in the process of secretion of hydrochloric acid by the gastric mucous membrane has been stressed by many investigators [13, 14, 24, and others]. On the other hand, the activity of the gastric glands is also considerably dependent on the balance of mineralocorticoids, which depress the acid-forming function of the stomach [14, 18, 19, 21, 22], and the glucocorticoids, which stimulate this function [15, 16, 17, 23, 25, and others]. A local injury to the zona glomerulosa of the adrenal cortex by cinchophen, with a simultaneous increase in the output of glucocorticoids (a non-specific reaction to administration of a toxic substance) disturbed the balance between the two groups of hormones concerned in the regulation of gastric secretion, the end result of which (together with other factors) is autodigestion of the stomach wall.

Certain clinical signs (hypovolemia, arterial hypotension, an increase in the blood urea concentration, and also the disturbances of mineral metabolism described above) suggest a decrease in the output of mineralocorticoids in peptic ulcer, which Bojanowica [12] regards as a special form of partial adrenal insufficiency. For this reason the facts described in this paper indicate a certain similarity in the pathogenesis of experimental cinchophen ulcer and of peptic ulcer in man.

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