

# EFFECT OF SOME NONSPECIFIC HYALURONIDASE INHIBITORS ON SPONTANEOUS BILE FORMATION

N. A. Brodyagin and G. E. Saburov

UDC 612.357.014.46:577.154.365.025.3

Intravenous injection of hyaluronidase inhibitors (heparin, pipolphen, and ascorbic acid) into dogs as a rule led to an increase in bile secretion and a decrease in the percentage of solid residue. The concentration of bile acids in the bile was lowered. No definite pattern could be detected with respect to the secretion of bilirubin and cholesterol.

The mechanisms of the intimate processes of bile formation have so far received little study. In the modern view bile formation includes the active secretion of the various components of bile by the liver cells (bilirubin, bile acids, bile pigments), the trans- and intercellular filtration of substances from the blood and bile through the capillary membranes (water, glucose, sodium, potassium, and chloride ions), and also the reabsorption of water and other substances from the bile capillaries and ducts and the gall bladder [3,5,6].

On the assumption that the hyaluronic acid-hyaluronidase system is concerned in the intimate mechanisms of bile formation, the effect of hyaluronidase inhibitors (heparin, pipolphen, and ascorbic acid) on the bile-secreting function of the liver was studied. The only property which these substances have in common is their ability to inhibit hyaluronidase [1].

## EXPERIMENTAL METHOD

The action of heparin, pipolphen, and ascorbic acid on spontaneous (fasting) bile formation was studied in long-term experiments on four dogs with Schwann fistulas of the gall bladder. After determination of the background level of bile secretion, the following substances were injected intravenously: in the experiments of series I heparin (500-1000 units/kg body weight), in series II pipolphen (2.5-5 mg/kg body weight), and in series III ascorbic acid (9-18 mg/kg body weight). The volume of bile was measured in hourly samples; bilirubin in the bile thus obtained was determined by the Van den Bergh method, bile acids by the Shire-Cooney method, and cholesterol by the method of Engel'gardt and Smirnova. Each experiment lasted 6 h.

## EXPERIMENTAL RESULTS

Intravenous injection of heparin in a dose of 500 units/kg body weight into the dog Chernyi led to a very slight decrease in bile formation during the first hour after injection of the inhibitor, on the average from 9.4 to 8.7 ml. The volume of bile secreted during the 5 h of the experiment fell by 13.1%, on the average from 37.6 to 32.3 ml ( $P < 0.05$ ).

Intravenous injection of heparin in a dose of 1000 units/kg body weight into the dog Lisenok caused an increase in bile formation by 24.2% in the first hour of the experiment, on the average from 9.5 to 11.8 ml ( $P < 0.01$ ), and during the 5 h of the experiment an increase of 7.7%, on the average from 49 to 53 ml. The solid residue in the dog Lisenok was increased by 39% compared with control days ( $P < 0.01$ ), and in the dog Chernyi it was increased by 15%. Secretion of bile acids by the dog Lisenok showed a mean decrease of 25%. Excretion of bilirubin and cholesterol with the bile was unchanged.

In response to injection of pipolphen (2.5 mg/kg body weight) into the dog Lisenok, fluctuations in the volume of bile compared with control dogs were very slight. In the dog Volk, after injection of the same doses of pipolphen, the mean volume of bile excreted was increased by 34.8%. Much larger doses of pipolphen were given to the dog Chernyi. Injection of this inhibitor in a dose of 5 mg/kg body weight caused an

---

Department of Normal Physiology, Tyumen Medical Institute (Presented by Academician V. N. Chernigovskii). Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 67, No. 2, pp. 21-23, February, 1969. Original article submitted March 4, 1968.

increase of 30% in bile secretion during the 5 h of the experiment compared with control days, on the average from 37.6 to 49 ml ( $P < 0.01$ ). In all three dogs, the intensity of bile secretion was increased in the first hour after injection of pipolphen, in the dog Volk, for example, by 92% and in the dog Lisenok by 56.8% ( $P < 0.01$ ). The solid residue in bile from the dog Lisenok fell by 17% ( $P < 0.01$ ), in the dog Volk by 20% ( $P < 0.05$ ), and in the dog Chernyi on the average by 31%. Excretion of bilirubin, bile acids, and cholesterol fluctuated slightly in all the experimental animals after administration of pipolphen.

No definite changes in the bile-secretory function of the liver could be detected in the three dogs after administration of ascorbic acid. The volume of bile excreted increased slightly both during the first hour after injection and during the 5 h of the experiment. These results are in agreement with those obtained by other workers [2,4]. An increase in bile secretion under the influence of ascorbic acid was found only in the dog Ral'f, amounting to 44.1%, on the average from 11.2 to 16.2 ml ( $P < 0.01$ ), and during the 5 h of the experiment by 33.1%, on the average from 49.5 to 65.9 ml ( $P < 0.01$ ). The excretion of bilirubin, bile acids, and cholesterol was not substantially changed after administration of ascorbic acid.

It can be concluded from these experiments with administration of hyaluronidase inhibitors that the hyaluronic acid-hyaluronidase system plays a definite role in the processes of filtration and reabsorption in the intimate mechanism of bile formation.

#### LITERATURE CITED

1. A. G. Ginetsinskii, *Physiological Mechanisms of Water and Salt Equilibrium* [in Russian], Moscow-Leningrad (1964), p. 344.
2. A. V. Gubar', *Byull. Éksperim. Biol. i Med.*, **12**, No. 5-6, 307 (1941).
3. A. S. Saratikov, *Bile Formation and Cholagogues* [in Russian], Tomsk (1962), p. 65.
4. Yu. N. Uspenskii, *Byull. Éksperim. Biol. i Med.*, **26**, No. 8, 102 (1948).
5. G. Bizard and J. Paris, *Rev. Internat. Hepat.*, **7**, 437 (1957).
6. J. Vanlerenberghe, *Presse Méd.*, **52**, 1237 (1957).