Studies on Some Actions of Sulphated Polysaccharides on Arteriosclerosis (IV)

ORAL ADMINISTRATION OF DEXTRAN SULPHATE

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As the dextran sulphate which we synthesized has a low molecular weight, the intestinal absorption of this dextran sulphate was considered. The clearing activity and clotting time were measured after oral administration of this preparation. And it was confirmed that this preparation is absorbed from the intestine in both man and dog. The improvement of lipid metabolism in aged human subjects was observed by the oral administration of this preparation.

IT WAS reported that dextran sulphate preparation of low molecular weight and low S-content induced clearing activity in the plasma after the intravenous administration and the clearing effect was exceeded that of heparin (1). As this preparation was a polymer with an extremely short chain length, the possibility of intestinal absorption was expected.

In this paper, the clearing activity and anticoagulant activity after the oral administration of this preparation were reported.

EXPERIMENTAL METHODS

1) Animal experiments:

Seven to 10 kg of dogs in the fasting state were received orally enterocoated tablets of the dextran sulphate which was synthesized by us. The blood samples were drawn from femoral veins. Clearing activity and clotting time were measured as reported previously (1).

2) Human experiments:

For the measurement of clearing activity, four young men were studied and plasma was taken at two hours intervals after the oral administration of these tablets. In order to investigate the influence on lipid metabolism, ten aged human subjects running in age from sixty to seventy years were given orally these tablets for four weeks and serum lipids were measured at two weeks intervals (1) (2).

Fig. 1. Effect on Clotting time in dogs.

RESULTS

1) Effects of oral administration of dextran sulphate on clotting time in dogs.

Enterocoated preparation of dextran sulphate of high S-content (18.8%) and low molecular weight was used in this experiment. During 6 or 8 hours after administration clotting time was measured. It was shown in Fig. 1 that the clotting time was prolonged two hours later to thrice of the initial level and the prolongation was continued for more than 6 hours by 75 mg of this preparation per kg body weight, but no changes were observed by 10, 20 and 30 mg per kg.

2) Clearing activity induced in the plasma after oral administration in dogs.

The preparation was given orally to dogs

in various amounts which did not prolong clotting time. Clearing activity was measured at two hours intervals after giving the preparation. As shown in Fig. 2, the high level of clearing activity was maintained for ten hours by the administration of 10 and 20 mg per kg, while by 5 mg per kg the lower effect and by 30 mg per kg no constant effect were observed. This indicates that the tablets of the dextran sulphate was absorbed continuously from the intestine and the amount of 10 to 20 mg per kg is the most suitable dose for the production of clearing activity.

3) Clearing activity induced by oral administration of the dextran sulphate preparation of different S-content in dogs.

Clearing activity induced by the sulphated dextran in the midst (12.1%) was compared

Fig. 2. Clearing Activity induced with oral administration of various amount of dextran sulphate.

Fig. 3. Clearing activity induced with the dextran sulfate of different S-content in dogs.

with that of the highly sulphated preparation which was used in the experiment 1) and 2). The data on Fig. 3 indicates that the preparation of middle S-content has the similar activity to the preparation of high S-content in the production of clearing factor, but it is doubtful that the dextran sulphate of middle S-content can induce the same clearing activity in plasma of human body as dog.

4) Clearing activity induced in human plasma after oral administration.

Twenty-four mg of dextran sulphate per kg (S-content=18.1%) was given orally to four young men. The clearing activity in

Fig. 4. Clearing activity induced with oral administration of dextran sulphate in human body.

Fig. 5. Oral administration of dextran sulphate in patients.

each subject was shown in Fig. 4. All subjects maintained the effective clearing activity for 6 hours.

5) Clinical investigations.

Ten aged patients who have arteriosclerosis were treated with the preparation in the dosage of 15 mg per kg daily. Four weeks later, the fall of total cholesterol was observed in eight patients of the ten. The same tendency was observed in the fall of free cholesterol and c/p. (Fig. 5, 6 and 7).

Fig. 6. Oral administration of dextran sulphate in patients.

Fig. 7. Oral administration of dextran sulphate in patients.

DISCUSSION

Heparin and heparinoid substances had been considered effective only when injected

intravenously or intramusclely (3), the buccal absorption of these substances had been attempted (4). Loomis (5) reported that no significant destruction of heparin was observed in the intestine of dogs. In another report (6), he attributed the difficulty of intestinal absorption of the ionized sulfonic acid groups and the acidity of glucuronic acid carboxyl groups, and noticed that partially desulphated or slightly methylated heparin was absorbed in the near physiological pH. As dextran sulphate has no carboxyl group, it is considered to be more stable in the intestine. The molecular weight of the dextran sulphate preparation which we synthesized is far below that of heparin and near the lowest limit of molecular weight of hitherto known polymers. Dextran sulphate is expected to be more absorbable than heparin. This thinking was confirmed in both the experiments of dogs and human subjects.

SUMMARY

The dextran sulphate of low molecular weight which we synthesized was confirmed to be absorbed from the intestine in both dog and human body. Continuous and the most effective clearing activity was obtained without prolongation of clotting time by the oral administration of 10~20mg of the preparation per kg body weight. The improvement of lipid metabolism in aged human subjects was observed by the oral administration of the preparation.

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