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Abstract

The effect of desferrioxamine on several hematological parameters was studied in growing rats. Animals given desferrioxamine intramuscularly (150 mg/kg daily) had increased urinary iron after one week, and decreased hemoglobin after 2 weeks. The difference in hemoglobin concentration between the treated and control groups was significant after 4 weeks of treatment with desferrioxamine, but the difference in the numbers of erythrocytes was not significant. The anemia was of hypochromic type. Desferrioxamine at this dosage did not retard growth. These findings support our previously reported concept of "iron-losing anemia".

KEYWORDS: desferrioxamine, iron excretion, iron deficiency anemia.

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EXPERIMENTAL ANEMIA INDUCED BY EXCESS IRON EXCRETION

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Abstract. The effect of desferrioxamine on several hematological parameters was studied in growing rats. Animals given desferrioxamine intramuscularly (150mg/kg daily) had increased urinary iron after one week, and decreased hemoglobin after 2 weeks. The difference in hemoglobin concentration between the treated and control groups was significant after 4 weeks of treatment with desferrioxamine, but the difference in the numbers of erythrocytes was not significant. The anemia was of hypochromic type. Desferrioxamine at this dosage did not retard growth. These findings support our previously reported concept of "iron-losing anemia".

Key words: desferrioxamine, iron excretion, iron deficiency anemia.

The exact mechanism of iron absorption in the intestinal mucosa is not understood. We previously (3) examined the relationship of mucosal iron content and *in vitro* intestinal iron absorption in biopsy specimens and showed that the quantity of iron localized in mucosal tissue was related to the rate of iron absorption. We also described patients who had iron deficiency anemia and who passed excessive amounts of iron in their gastric juice (4). Hence we proposed a new clinical entity of "iron-losing anemia" for these cases. These earlier studies revealed that both excretion and absorption rates were closely related to the amount of iron localized inside and outside the mucosa. These findings led us to suggest that absorption and excretion are facets of one phenomenon and we proposed (5) the concept of "mucosal equilibrium" for iron metabolism in gastro-intestinal tract. Furthermore, we developed an iron excretion test with an "iron excretion index" to investigate urinary iron loss (6). In the study, a high excretion index was consistently observed in "iron-losing anemia".

The present paper further reports an iron-losing state produced experimentally by desferrioxamine treatment.

MATERIALS AND METHODS

A total of 20 growing, male Wistar-strain, albino rats, each weighing 50-60 g, were used. The rats were divided into four groups. Desferrioxamine was in-

jected intramuscularly daily for 5 weeks at a dose of 50 mg/kg (Group I), 100 mg/kg (Group II) or 150 mg/kg (Group III). Animals in Group IV were injected with an equal volume of the saline vehicle used in experimental groups.

Body weight, erythrocyte count, hemoglobin concentration and total urinary iron excreted per day were determined weekly for each rat during the period of treatment. Blood was collected from a tail vein. The rats kept in metabolic cages (Tokiwakagaku products, T-241, Japan) were fed on a regular diet containing iron. Urine and feces fell separately through double stainless steel screens to the bottom of the alumite cages where the urine was collected. These cages allowed satisfactory urinary collection with negligible iron contamination. Urinary iron was estimated using the method described by Losowsky (7), and total urinary iron per day was calculated.

RESULTS

Effect on body weight. No significant differences were found in body weight between the four groups, although growth appeared slightly slower in Group III. Fig. 1 shows the growth of Group III animals.

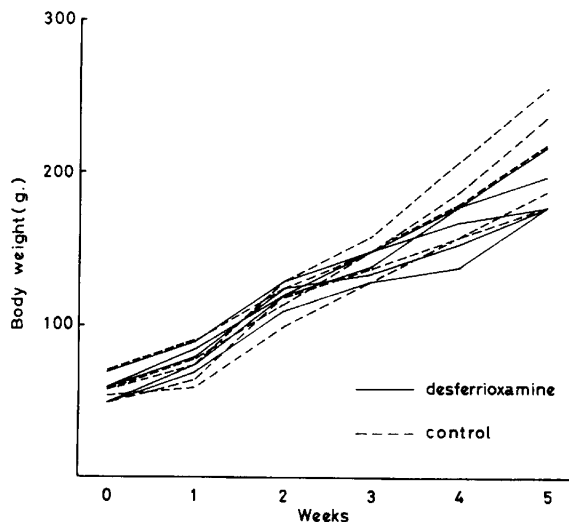


Fig. 1. The effect of desferrioxamine on the body weight of Group III rats.

Erythrocyte count. The counts in Groups I, II, III and IV did not differ significantly. Fig. 2 shows the erythrocyte counts in Group III rats.

Effect on hemoglobin concentration. No significant difference was observed between Group I and the control group. Group II showed a lower mean hemoglobin concentration than the control group, but the difference was not significant. In

Group III, the mean hemoglobin concentration was slightly lower after 2 weeks of injection than in the control group, and at 5 weeks the difference between the two groups was significant (Fig. 3). The anemia in Group III was thus hypochromic.

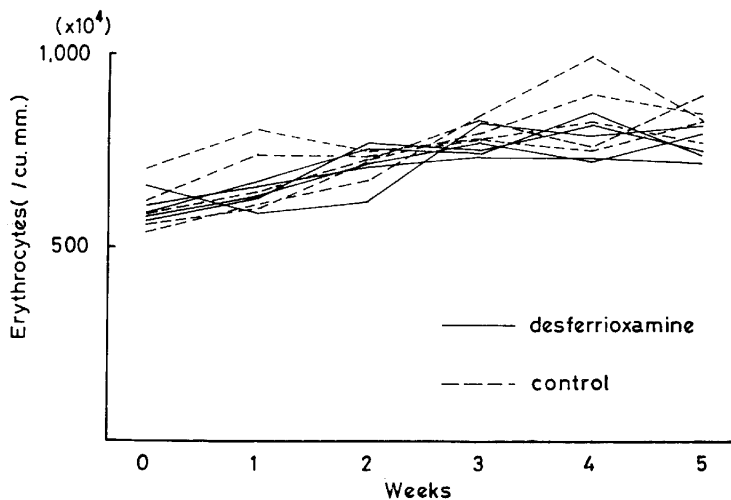


Fig. 2. Effect of desferrioxamine on erythrocyte counts in Group III rats.

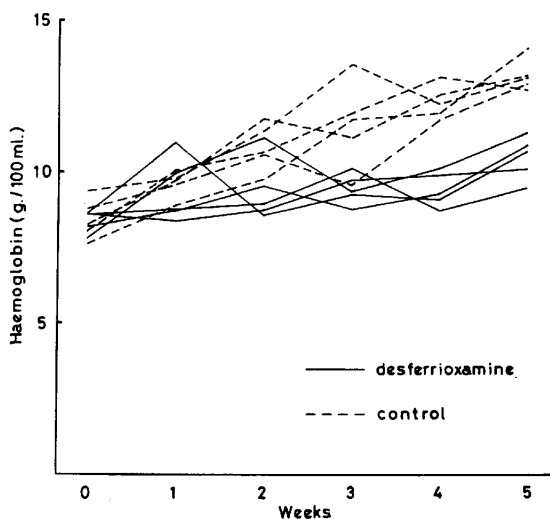


Fig. 3. The effect of desferrioxamine on hemoglobin concentration in Group III rats.

Effect on total urinary iron per day. The difference between Group I and the control group was not significant. Group II rats showed increased urinary iron

excretion after 3 weeks of the injection as compared with control rats. Group III showed increased urinary iron excretion after one week as compared to the control group, and after 2 weeks, the difference between the two groups increased and was significant. This increase preceded the decrease in hemoglobin concentration (Fig. 4).

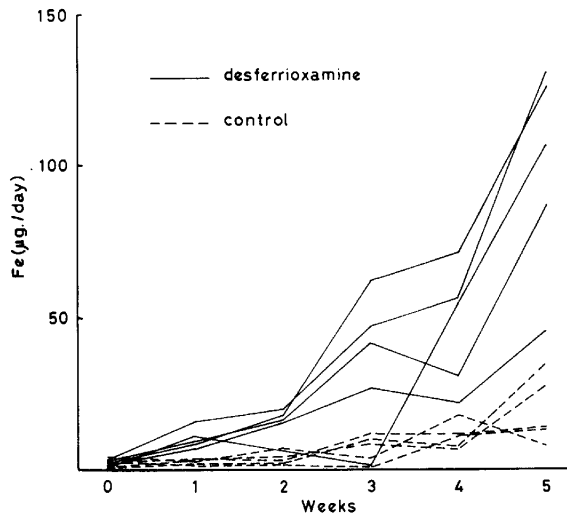


Fig. 4. The effect of desferrioxamine on total urinary iron per day in Group III rats.

DISCUSSION

Since the hypothesis of mucosal block (2), many theories have been proposed to explain the mechanism of iron absorption from intestinal mucosa. Crosby (1) proposed that the absorption capacity of the mucosal cell is determined by its iron content and that this iron is subsequently lost by epithelial sloughing. This concept is similar in some aspects to our proposal of "mucosal equilibrium" (5).

In idiopathic hypochromic anemia, intensive observation of iron metabolism has been made only in advanced stages, and few studies have dealt with etiologic aspects. We found (4) a higher iron content than normal controls in the gastric juice of some subjects already treated for iron deficiency anemia. These findings suggested (4) that in some idiopathic hypochromic anemias, increased iron excretion to the gastro-intestinal tract may be the cause of the hypochromic state, termed "iron-losing anemia". As the excretion of iron into gastric juice is related to the excretion of iron into urine (4), we used (6) an iron excretion test in which urinary and serum iron levels were estimated after intravenous injection of iron. Some patients with idiopathic iron deficiency anemia were apt to relapse

and had a significantly higher "iron excretion index", suggestive "iron-losing anemia".

In the present study we tried to induce anemia experimentally by causing excess excretion of iron. After one week of desferrioxamine injection, the urinary excretion of iron increased compared with the control group. The hemoglobin concentration was lower after 2 weeks. At 4 weeks of treatment, the hemoglobin concentration was significantly lower with a hypochromic blood picture.

There is no previous paper which has reported the administration of high dose desferrioxamine for a long time to induce iron deficiency anemia. Desferrioxamine is a powerful iron chelating agent which can remove iron even in iron deficient states (8, 9), and it was possible to induce an iron deficient state by small but continued iron excretion in this experiment. The anemia induced by excessive excretion of iron in the present study could be a model for the "iron-losing anemia".

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