MECHANISM OF ABSORPTION OF TWO INTRAMUSCULAR IRON PREPARATIONS

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The mechanism of absorption from an intramuscular depot of an iron-sorbitol-citrate and an iron-dextran complex has been studied in anaesthetised cats in which the lymph vessels were cannulated. The results are discussed in relation to the molecular size of the two iron complexes.

IN a recent study from this laboratory (Lindvall and Andersson 1961) the properties of an iron-sorbitol-citrate complex for intramuscular injection were described. This complex was rapidly absorbed from the injection site in rabbits. In the following experiments the mechanism of absorption from the intramuscular injection site in cats was studied and the iron-sorbitol-citrate preparation compared with an iron-dextran complex.

METHODS

The iron-sorbitol-citrate complex, Jectofer, and the iron-dextran complex, Imferon, both contained 50 mg. of elementary iron per ml. and the pH of the solutions were 7·5 and 5·8 respectively. They will be referred to as iron-sorbitol and iron-dextran.

Cats, 3·0–5·0 kg., were anaesthetised with pentobarbitone sodium (35 mg./kg.). After laparotomy the thoracic duct was cannulated 5–10 mm. above the entry of the intestinal lymphatics with polyethylene tubing. The iron preparations were injected deep in the gluteal region in doses corresponding to 3 mg. Fe/kg. The injected leg was mechanically exercised throughout the observation period and the flow of lymph was continuously collected in test tubes. Arterial blood samples (7 ml.) were taken 6–8 times during an experiment and after each sample, the same volume of Ringer's solution was given intravenously. Control experiments showed that the sampling of blood did not affect the analytical values if the sampling was not repeated more than eight times at 15 min. intervals.

The analytical procedures for the determination of iron in serum, unsaturated iron-binding capacity (UIBC) and lymph iron were those described by Lindvall and Andersson (1961). The analytical values for iron in serum include plasma-bound iron and circulating iron preparation. The sum of iron in serum and UIBC does thus not represent true total iron binding capacity and is therefore denoted "TIBC." Paper electrophoresis of lymph collected during the experiments, as well as controls consisting of lymph mixed with iron-sorbitol preparation, was carried out on Whatman No. 1 paper in veronal buffer of pH 8·6. The paper strips were stained for iron with acid potassium ferrocyanide and scanned by a EEL densitometer.

RESULTS

In preliminary experiments the iron concentration of the serum was studied after intramuscular injection of iron-sorbitol into normal cats

with or without the lymph vessels from the injected leg being ligated. It was observed that the iron in serum rose in both instances but the rate of rise with ligated lymph vessels was slower. Thus at least part of the dose was absorbed directly into the blood stream.

In subsequent experiments the lymph flow was collected and blood samples taken at regular intervals during 2 hr. after the injection of the iron-sorbitol or the iron-dextran preparations. In these experiments,

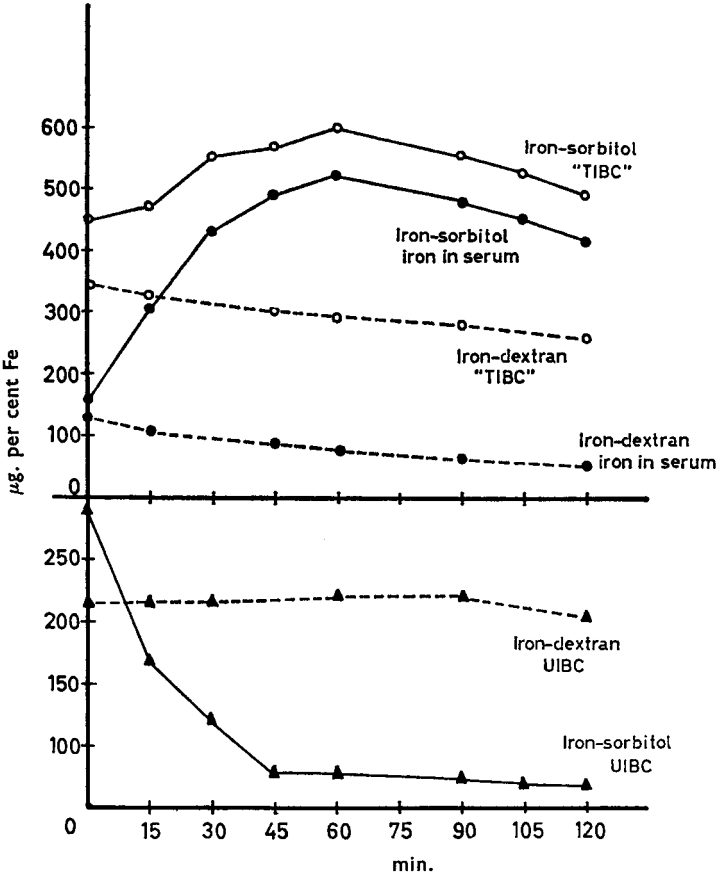

FIG. 1. Cats 3·0 and 3·2 kg., cannula in the thoracic duct. Iron-sorbitol (———) and iron-dextran (– – – –) respectively were injected i.m. at zero time. Dose 3 mg. Fe/kg. UIBC = unsaturated iron binding capacity "TIBC" = sum of iron in serum and UIBC.

where the lymph from the injection site was prevented from entering the blood, analysis showed that with iron-sorbitol a large elevation of the values for iron in serum occurred with a simultaneous decrease in unsaturated iron-binding capacity. With iron-dextran no such changes were noted, indicating that it was not absorbed by the blood. A typical experiment is illustrated in Fig. 1.

Fig. 2. shows the result from analysis of the lymph from the same animals as are represented in Fig. 1. The iron content of the lymph starts to rise almost immediately with iron-sorbitol while for iron-dextran there seems to be a certain delay in the absorption of iron. In some experiments the absorption of iron-dextran into the lymph, once started, proceeded with practically the same rate as that of iron-sorbitol, while in others, the iron-dextran was absorbed much more slowly. This was not related to the flow of lymph. Consequently iron-sorbitol absorption in the lymph

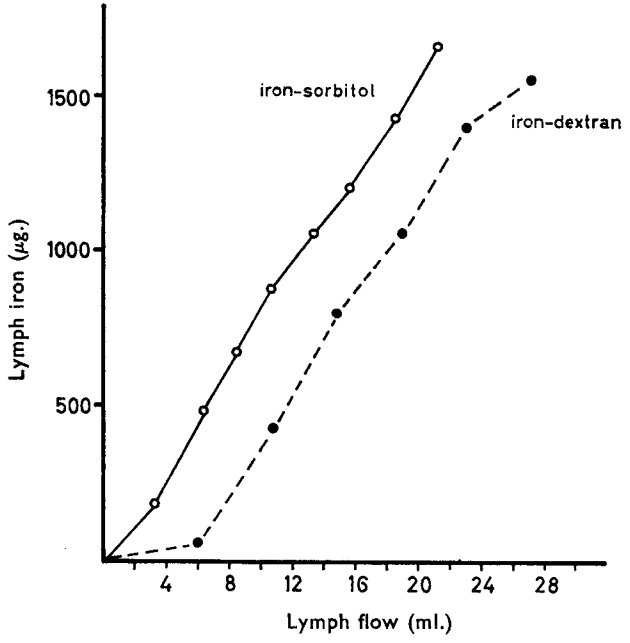

FIG. 2. Same cats as in Fig. 1. Iron in lymph after i.m. injection of iron-sorbitol (———) and iron-dextran (– – – –).

ranged from 10–16 per cent of the dose whereas iron-dextran absorption was more variable and ranged from 1–15 per cent during the same 2 hr. period.

Because of the complexity of the electrophoretic staining pattern of iron-sorbitol, no definite conclusions can be drawn about the iron component of the lymph except that the fastest moving fraction of iron-sorbitol with the lowest molecular weight (Lindvall and Andersson 1961), seen in control studies where the preparation was mixed with normal lymph, seems to be missing.

DISCUSSION

Molecular size is of predominant importance in the absorption of a compound from an intramuscular depot since it determines the route and to some extent also the rate of absorption. This has been shown for toxins and snake venoms by Barnes and Trueta (1941) who found that venoms

of molecular weight 5,000 were absorbed directly by the blood stream, while toxins and venoms with molecular weights above 20,000 were taken up and transported by the lymphatics. Everett and others (1954) demonstrated that the lymphatics play an insignificant role in the absorption from a subcutaneous site of inorganic iron, whereas protein-bound iron was absorbed almost exclusively by this route. Beresford, Golberg and Smith (1957) presented evidence that the iron-dextran complex is absorbed lymphatically after intramuscular injection. Though no direct data on the molecular weight have been given, Beresford and others state that the molecular dimensions of the iron-dextran complex are such as to make the absorption by the lymph the most important contribution.

The iron-sorbitol complex used in this study has been found to be composed of several fractions with different molecular weights. Our colleague, F. R. Eriksson tells us they all, however, fall below 5000.

The rapid decline in unsaturated iron-binding capacity (UIBC in Fig. 1) after iron-sorbitol injection indicates that at least one fraction immediately reacts with the transferrin. Since the total iron-binding capacity is increased, additional amounts of iron—not reacting with transferrin—must have entered the blood. Because of the rapid elimination of iron-sorbitol from the bloodstream (Lindvall and Andersson 1961) it is not possible to estimate directly the amount of iron-sorbitol absorbed by the blood. Indirectly, however, a rough estimate may be made by subtracting from the total dose those quantities of iron retained in the muscle (20 per cent) and those recovered in the lymph (16 per cent). If allowance is made for some iron being retained in the lymph nodes, 50–60 per cent of the injected dose of iron-sorbitol seems to have been absorbed by the blood in the 2 hr. experimental period.

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