*Ann Clin Biochem* 1981; **18**: 215–217

# Changes in serum ferritin levels after intravenous iron

R W BLUNDEN, J V LLOYD, Z RUDZKI, AND R J KIMBER

*From the Division of Haematology, Institute of Medical and Veterinary Science, Frome Road, Adelaide, South Australia, 5000*

SUMMARY The effect of intravenous iron dextran on serum ferritin levels was observed in two patients with iron deficiency anaemia. Serum ferritin levels rose sharply and reached peak levels seven to nine days after infusion when at least 90% of the infused iron had been removed from the plasma. A linear relation was shown for each patient between the logarithm of the serum ferritin levels and the logarithm of the calculated cellular non-haem iron levels.

Most patients with iron deficiency are treated with oral iron but parenteral administration is indicated in some patients with malabsorption or where the rate of absorption from oral preparations cannot keep pace with continued blood loss. Intramuscular iron therapy is often used but requires multiple injections and can be painful for the recipient. Intravenous iron can be administered as a single infusion but the recommended safety precautions must be observed.

Although the effects of oral iron[1] and intramuscular iron[2] on serum ferritin levels have been well studied, data on the effects of intravenous iron on serum ferritin levels are limited. We have recently followed the changes in serum ferritin levels in two patients with proven iron deficiency anaemia after a single dose of intravenous iron.

## Patients

CASE 1

A 68-year-old woman had recurrent iron deficiency anaemia confirmed by low values for Hb, MCHC, MCV, and serum iron, on several occasions over the previous 10 years. No stainable iron had been detected on smears of marrow aspirate. There had been a number of documented rises in Hb levels with reticulocytosis in response to iron administration. Faecal blood loss studies had shown a small but persistent gastrointestinal blood loss, but all barium contrast studies and endoscopies of the gastrointestinal tract were normal. At the time of this study her Hb was 6·8 g/dl and serum ferritin $<5\ \mu g/l$.

The patient refused oral iron because of gastrointestinal side effects, and therefore 40 ml of iron dextran (Imferon®, Fisons) was infused intravenously with 500 ml of normal saline, a total dose of 2 g of elemental iron.

CASE 2

A 76-year-old man with anaemia (Hb 8·9 g/dl) had severe atrophic gastritis demonstrated by gastroscopy. MCV, serum iron, transferrin, and ferritin levels were consistent with iron deficiency. There was no history of chronic blood loss, and faecal blood loss studies were normal. He had been transfused to a Hb level of 11·0 g/dl three days before iron therapy was given. Since oral iron would be poorly absorbed because of gastritis, 20 ml of iron dextran (Imferon®, Fisons) was infused intravenously with 500 ml of normal saline, a total dose of 1 g of elemental iron.

## Material and methods

Serum ferritin was estimated by a two-site immunoradiometric assay,[3] and serum iron as recommended by the International Committee for Standardisation in Haematology,[4] incubating for 2 hours with chromagen solution to ensure complete measurement of Imferon® iron. Haematological measurements were made on a Model S Coulter Counter. Red cell mass, total blood volume, and plasma volume were determined using patient's red cells labelled with $^{51}Cr$.[5]

Total plasma iron was calculated from the serum iron level and the plasma volume. Iron utilised for Hb synthesis was calculated from the formula:

$$\text{Iron (mg)} = \frac{\text{change in Hb}}{100} \times \text{Blood volume (ml)} \times 3{\cdot}4$$

Cellular non-haem iron (CNHI) was calculated to be the amount of iron removed from the plasma less that required for the observed Hb synthesis. Iron stores before infusion were assumed to be zero for the purpose of these calculations. The levels of CNHI in case 1 were calculated for only the first 11

days of the study. After this time calculations were considered unreliable since faecal blood loss rates were not available for the period of the study.

## Results

After intravenous iron, serum iron rose to extremely high levels (8000 and 4750 μmol/l) immediately after infusion, as the Imferon® was distributed throughout the plasma (Fig. 1). Hb levels rose rapidly in case 1 by 3·6 g/dl over 25 days. The Hb response in case 2 was much slower, probably related to the transfusion a few days before infusion. Serum ferritin reached peak levels at approximately day 7 in case 1 and at day 9 in case 2, at which time it can be calculated that over 90% of the infused iron had been removed from the plasma. Serum ferritin levels then steadily declined.

### RELATION BETWEEN SERUM FERRITIN LEVELS AND CNHI (Fig. 2)

*From infusion to peak serum ferritin levels*

In both cases there was a straight-line relation between log serum ferritin and log CNHI ($r = 0{\cdot}995$), with no significant difference in the slope of the regression lines. The regression line for case 1 was positioned 0·225 unit ($\log_{10}$ scale) to the right of that for case 2.

*After peak serum ferritin levels (case 2 only)*

A drop in serum ferritin levels from 225 to 160 μg/l was observed with no apparent decrease in CNHI. This was followed by a linear log/log relation between serum ferritin levels and CNHI as iron was removed from the tissues for Hb synthesis ($r = 0{\cdot}986$). The slope of this line was not significantly different from that for prepeak levels but was positioned 0·1 unit ($\log_{10}$ scale) below this line.

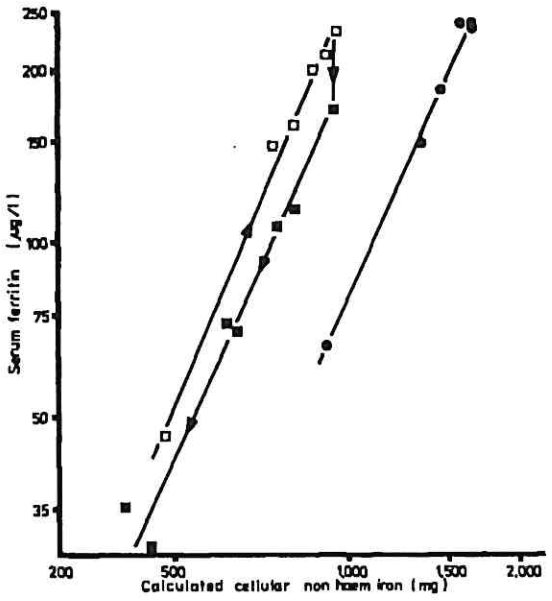


Fig. 2 *Relation between serum ferritin levels and calculated non-haem iron levels for case 1 (●) and case 2 (□ before and ■ after peak serum ferritin levels) (log/log scale).*

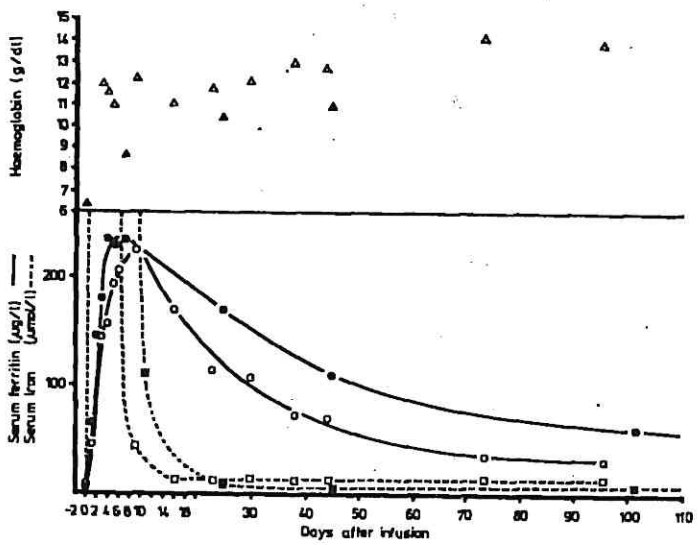


Fig. 1 *Changes in serum ferritin, serum iron, and haemoglobin levels after infusion of intravenous iron as iron dextran (Imferon®) for case 1 (closed symbols) and case 2 (open symbols).*

## Discussion

The close correlation between storage iron and serum ferritin levels has been demonstrated by a number of techniques.[6 7] In particular, low serum ferritin levels very reliably indicate low iron stores.[8]

Treatment of iron deficiency with oral iron supplements produces a slow rise in serum ferritin levels, which continues over a period of months,[1] while intramuscular iron produces an increase over a period of three or four weeks.[2] The present study shows that a single dose of intravenous iron causes a rapid increase in the level of serum ferritin, which reaches a peak approximately one week after infusion.

Iron injected intravenously is totally present in the plasma after infusion, and its rate of removal can be readily monitored. Henderson and Hillman[9] have shown that the iron dextran complex is first cleared into the reticuloendothelial system, where ionic iron is liberated and stored as ferritin and haemosiderin. Some iron dextran still remains in cells months after infusion.

With Imferon® there is no urinary iron loss,[10] and therefore calculations can be made of the total amount of cellular iron (ferritin, haemosiderin, and iron dextran) not present as Hb (CNHI) if blood loss (and therefore iron loss) rates are known for each patient. Estimates of dietary intake of iron are not critical because of the rapidity of the initial changes.

The relation between log serum ferritin levels and log CNHI levels is linear for both patients (Fig. 2), and the slopes of the two regression lines are not significantly different, indicating a similar response in both patients. The positional difference of the two lines suggests that, in linear terms, case 1 required 1·7 times the amount of CNHI required by case 2 to stimulate an equivalent level of serum ferritin.

Calculations of CNHI for case 2 after peak serum ferritin levels were reached once again show a similar relation with serum ferritin (Fig. 2). After an unexplained drop with no apparent change in CNHI, serum ferritin levels fell as iron was removed from the storage compartment to newly formed haemoglobin. This line is parallel to that for prepeak levels, but a positional difference indicates that serum ferritin levels were consistently 20% lower than prepeak levels for the same amount of CNHI.

The main findings of the present study are that serum ferritin levels reach a peak seven to nine days after an intravenous infusion of iron dextran, and that the changes in serum ferritin levels reflect the changes in calculated cellular non haem iron levels.

We thank Dr Norris Carter, senior visiting physician, Royal Adelaide Hospital, for allowing us to study case 2.

### References

1 Bentley DP, Jacobs A. Accumulation of storage iron in patients treated for iron deficiency anaemia. *Br Med J* 1975; **2**: 64–6.
2 Birgegard G, Hogman C, Killander A, Levander H, Simmonson B, Wide L. Serum ferritin and erythrocyte 2, 3-DPG during quantitated phlebotomy and iron treatment. *Scand J Haematol* 1977; **19**: 327–33.
3 Miles LEM, Lipschitz DA, Bieber CP, Cook JD. Measurement of serum ferritin by a 2-site immunoradiometric assay. *Anal Biochem* 1974; **61**: 209–24.
4 International Committee for Standardization in Haematology. Recommendations for measurement of serum iron in human blood. *Br J Haematol* 1978; **38**: 291–4.
5 Mollison PL, Veall N. The use of the isotope $^{51}Cr$ as a label for red cells. *Br J Haematol* 1955; **1**: 62–74.
6 Walters GO, Miller FM, Worwood M. Serum ferritin concentration and iron stores in normal subjects. *J Clin Pathol* 1973; **26**: 770–2.
7 Bezwoda WR, Bothwell TH, Torrence JD, MacPhail AP, Charlton RW, Kay G, Levin J. The relationship between marrow iron stores, plasma ferritin concentrations and iron absorption. *Scand J Haematol* 1979; **22**: 113–20.
8 Lipschitz DA, Cook JD, Finch CA. A clinical evaluation of serum ferritin as an index of iron stores. *N Engl J Med* 1974; **290**: 1213–6.
9 Henderson PA, Hillman RS. Characteristics of iron dextran utilization in man. *Blood* 1969; **34**: 357–75.
10 Will G, Groden BM. The treatment of iron deficiency anaemia by iron dextran infusion: A radioisotope study. *Br J Haematol* 1968; **14**: 61–71.

*Accepted for publication 26 February 1981*