ORAL OR PARENTERAL IRON THERAPY IN
HAEMODIALYSIS PATIENTS?

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Summary

In 28 haemodialysis patients, in whom there was a high incidence of depleted
marrow iron stores, a significant rise in Hb and Hct, occasionally to a normal
level, was achieved as effectively with oral as with i.v. iron supplements. There
was a variable response to iron in individuals which could not be predicted from
the initial iron status. No patient in whom marrow iron stores were reassessed
after iron therapy developed increased marrow iron stores. Routine iron supple-
ments are recommended in haemodialysis patients with regular monitoring of
body iron stores.

Introduction

A number of factors, many still poorly understood, are responsible for the anaemia
associated with chronic renal failure4. In patients undergoing treatment by
intermittent haemodialysis a further contributory factor is introduced — that of
continued blood loss resulting from cannulation of fistulae2, blood sampling3,
and loss in the dialysate4. Since the introduction of a policy of minimal trans-
fusion by most haemodialysis units the importance of blood loss has become in-
creasingly recognised5 and subsequent studies have shown a high incidence of
depleted iron stores in patients being treated by haemodialysis6-8. Although
evidence concerning iron absorption in chronic renal failure has been conflicting
7,9,10 a significant improvement in anaemia has been demonstrated following
oral6,11,12 as well as parenteral iron therapy8,13-16.

We have compared the response of anaemia to oral and i.v. iron supplements
in a group of patients on haemodialysis in whom blood transfusion was restricted
to a minimum.

Patients and Methods

Twenty-eight patients were randomly allocated to one of two treatment groups.
TABLE I. Details of Haemodialysis Patients Treated with Iron

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Age (mean ± SEM)</th>
<th>Duration of haemodialysis (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow Fe 320 mg daily</td>
<td>14 (9M 5F)</td>
<td>35 ± 2.9</td>
<td>10.5 ± 7.1</td>
</tr>
<tr>
<td>Imferon 1 ml i.v. weekly</td>
<td>14 (11M 3F)</td>
<td>39 ± 3.3</td>
<td>23.5 ± 7.4</td>
</tr>
</tbody>
</table>

Details of the patients are shown in Table I. One group were given a slow release iron preparation (Slow Fe®) in a dose of 320 mg daily by mouth before breakfast, providing 100 mg of elemental iron daily. The other group were given iron dextran (Imferon®) 1 mL i.v. weekly, providing 50 mg of elemental iron, the Imferon being given during dialysis via the chamber of the venous return line. There was no significant difference in age between the two groups. The duration of haemodialysis prior to study was variable, 3 patients given oral iron and one patient given i.v. iron commencing haemodialysis at the time of onset of the study. Although the mean duration of dialysis was longer in patients given i.v. than in those given oral iron, this was not statistically significant. All patients were treated by haemodialysis for 8 hours twice weekly and a variety of dialysers were used (Travenol UF 11 coil, Gambro Lundia, Cordis-Dow HF and Meltec multipoint). The dietary protein intake was 70g daily providing 12–20 mg of elemental iron daily and all patients were treated with daily supplements of vitamin B₁ (1 mg) and B₂ (1 mg), nicotinamide (15 mg), ascorbic acid (200 mg), and folic acid (5 mg). Prior to this study blood was transfused only if indicated by severe symptomatic anaemia or to replace major acute blood loss and no patient had previously been treated with androgens or with iron.

The haemoglobin (Hb), haematocrit (Hct), plasma iron (Fe) and total iron binding capacity (TIBC) were measured before commencing iron therapy. All blood was taken immediately before dialysis. Marrow iron stores were assessed by examination of marrow obtained by sternal marrow aspiration. These studies were repeated after 12 months of treatment with iron but reassessment was made earlier in some patients if other aspects of treatment altered. Reassessment of marrow iron stores after treatment was made in only 7 patients treated by oral iron and 9 patients treated by i.v. iron. The Hb and Hct were measured on three occasions at approximately monthly intervals before and after iron therapy and the mean values used for comparison.

The Hb and Hct were measured on a Coulter-S counter. Marrow was stained for iron by standard techniques using Prussian blue, and iron stores were graded by one of us (AP) as low, normal or high. The normal range of plasma Fe was 14–22 μmol/L for males and 10–28 μmol/L for females, and the normal range of plasma TIBC was 45–72 μmol/L.

Statistical analysis of all data was made using non-parametric tests.
**TABLE II.** Haemoglobin (Hb), Haematocrit (Hct), Plasma Iron (Fe) and Total Iron Binding Capacity (TIBC) Before and After Treatment with Iron (Figures are mean ± SEM)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Slow Fe 320 mg oral daily</th>
<th>Imferon 1 ml i.v. weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hb(g/dl)</td>
<td>Hct(%)</td>
</tr>
<tr>
<td>Before iron therapy</td>
<td>6.8 ± 0.3</td>
<td>20.9 ± 0.92</td>
</tr>
<tr>
<td>After 12 months iron therapy</td>
<td>8.4 ± 0.68</td>
<td>25.8 ± 2.02</td>
</tr>
<tr>
<td>Significance of change</td>
<td>p &lt; 0.02</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

**TABLE III.** Number of Patients (as a Proportion of the Total Number of Patients) in Whom the Plasma Iron was Less than Normal and There was < 20% Saturation of TIBC Before Treatment with Iron

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Slow Fe 320 mg daily</th>
<th>Imferon 1 ml i.v. weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma iron less than normal</td>
<td>11/14</td>
<td>8/14</td>
</tr>
<tr>
<td>&lt; 20% saturation of TIBC</td>
<td>9/14</td>
<td>8/14</td>
</tr>
</tbody>
</table>
Results

Before treatment with iron the Hb, Hct, plasma Fe and TIBC did not differ significantly in the two groups (Table II). The majority of patients in both groups had a normal plasma TIBC but a low plasma Fe and percentage saturation of TIBC with iron (Table III) and low marrow iron stores (Figure 1). However in 25% of

![Graph showing number of patients with low and high iron stores before treatment](image)

Figure 1. Marrow iron stores in haemodialysis patients before treatment with iron

patients the iron stores were normal and in two patients they were high. Both plasma Fe and percentage saturation were poorly correlated with marrow iron stores; iron status as defined by marrow iron stores would have been wrongly classified in 10 patients using plasma iron alone.

After both oral and i.v. iron therapy there was a significant rise in Hb and Hct (Table II and Figure 2) and there was no significant difference between the responses in the two groups. In individual patients the response to iron therapy was variable. In four patients given oral iron (one of whom required blood transfusion during the period of study), and in three given i.v. iron there was no rise in Hb. In addition two further patients treated by i.v. iron, in whom there was only a small rise in Hb with iron, required blood transfusion for symptomatic anaemia. No other patient required blood transfusion over the period of iron therapy. At the other extreme one patient in each group, neither of whom had polycystic kidney disease, attained a normal Hb in response to iron therapy (Figure 2). The response to iron could not be related to the type of renal disease apart from the fact that a rise in Hb occurred in all patients with polycystic kidney disease; however, even in these patients, the response was variable (Figure 2). No relationship was observed between the change in Hb in response to iron therapy and the duration of haemodialysis, the initial plasma Fe or marrow iron stores. There was a highly significant correlation between the Hb after iron therapy and the Hb before iron therapy ($r=0.67; p<0.001$) and there was no relationship between the change in Hb and the initial Hb.
There was no significant change in either plasma Fe or TIBC after iron therapy in either group (Table II). In the two patients in whom the Hb rose to normal there was a marked increase in plasma Fe to a level well above the upper limit of normal. A similar response was observed in one patient treated by i.v. iron in whom the Hb failed to rise and who required blood transfusion. Of eleven patients showing a rise in Hb in response to iron in whom marrow iron stores were reassessed, seven showed no change in iron status (initial iron stores low in six, normal in one), in one with initially high iron stores these became normal, and in three the iron stores fell from normal to low. Marrow iron stores were reassessed in five patients in whom the Hb did not rise; in four patients there was no change (initial iron stores low in three, high in one) and in one patient who required blood transfusion the iron stores rose from low to normal.
Discussion

The high incidence of iron deficiency in these patients confirms previous findings in haemodialysis patients subjected to a minimal transfusion policy and not treated with iron supplements. In this and in previous studies plasma Fe and percentage saturation correlated poorly with marrow iron stores. These measurements therefore cannot be used as an accurate indication of iron stores in haemodialysis patients.

The results in this study confirm the value of iron supplement in haemodialysis patients. The significant improvement in anaemia observed in the majority of patients was comparable to that reported in previous studies using both oral and parenteral iron. In addition this study shows that a significant rise in Hb can be achieved as effectively with oral as with i.v. iron, an observation not previously reported. In the past there has been conflicting evidence about iron absorption in chronic renal failure but more recent studies indicate that iron absorption in chronic renal failure is normal and is regulated by the state of iron balance. The satisfactory response to oral iron observed in this study and in previous studies confirms that significant iron absorption occurs in patients with chronic renal failure, particularly if iron stores are depleted.

It is likely that the improvement in anaemia in response to iron is mainly due to correction of iron deficiency. However, in contrast to some previous observations, we found a marked variation in the response irrespective of iron status. In addition we were not able to identify any factor which was clearly associated with a poor response although we cannot exclude more severe blood loss in these patients as an explanation since blood loss was not recorded accurately. The failure to predict the response of anaemia to iron therapy from the initial iron status may reflect both the limitations of the methods used to assess iron status and marked variation in blood loss. However it seems likely that other factors must be involved in determining the response to iron in addition to iron status. We have found a close correlation between the Hb before and the Hb after iron therapy. In addition there was no relationship between the degree of change in Hb and the initial Hb as might be expected in uncomplicated iron deficiency. Thus the degree of anaemia in individual patients appears to be set at a predetermined level, not necessarily related to the type of renal disease, which can be influenced equally at any one level by iron therapy.

Iron stores were not repleted in these patients after iron therapy. This may indicate that the dosage of iron used was insufficient to replenish depleted iron stores as well as to replace continuing losses. However no patient developed increased iron stores during therapy although the marked rise in plasma iron in some patients indicates that they may be at risk of this in the future. Increased iron stores as indicated by plasma ferritin have been found after treatment with i.v. iron for a longer period. There is therefore a need to monitor iron status regularly in patients receiving iron supplements, both to ensure that sufficient iron is given and to prevent iron overload.

In conclusion the findings in this study indicate that a significant improvement in the anaemia in patients with chronic renal failure undergoing long term haemo-
dialysis can be achieved as effectively with oral as with i.v. iron supplementation and blood transfusion requirements can be kept at a low rate. Since the response to iron cannot be predicted from the initial iron status, iron supplements should be given to all haemodialysis patients and the iron status should be monitored regularly. As the theoretical risk of inducing iron overload may be greater with i.v. than with oral iron the use of oral iron supplements may be safer on a long-term basis.

References

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Open Discussion

BAKER (London) There is a tendency for haemoglobin to rise with time on dialysis. Are you really justified in talking about a 'response' to iron treatment when you have not got an untreated control group?

WINNEY Obviously a third control group would have been of value but we were limited by the number of patients available for study. However before this study the haemoglobin in these patients had been either stable or falling since the onset of dialysis. There was also no relationship between the response to iron therapy and the duration of haemodialysis. It is therefore very unlikely that the improvement in anaemia was unrelated to iron therapy.

DZURIK (Bratislava) Did all your patients on oral iron therapy respond? It is not our experience; have you not found decreased absorption in some of them?

WINNEY Improvement in anaemia did not occur in all patients given oral iron.
We did not study iron absorption in these patients but other investigators have found iron absorption to be normal in haemodialysis patients.

VAN YPSELESE (Leuven) In your patients receiving oral iron there are different types of response. Is the type of response related to the intake of antacids, a factor known to modify intestinal iron absorption?

WINNEY The majority of patients studied took antacids but there was not a marked variation in the dosage. We therefore do not think that this was a factor modifying response to oral iron.