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# Clinical and biochemical improvement following low-dose intravenous iron therapy in a patient with erythropoietic protoporphyria

Erythropoietic protoporphyria (EPP) affects porphyrin and iron metabolism and is most often due to dominant inheritance of a mutation in the ferrochelatase gene (*FECH*, EC 4.99.1.1) with penetrance dependant on the co-inheritance of a single nucleotide polymorphism, IVS3-48C, which reduces expression from the remaining wild-type gene (Gouya *et al*, 2002). This leads to inadequate iron insertion into protoporphyrin lX (PPIX), which can be metabolized only after its conversion to haem. Impaired ferrochelatase activity therefore causes PPIX accumulation at the sites of blocked haem synthesis. The exposure of PPIX to solar radiation generates reactive oxygen species and, by largely indiscriminate macromolecular damage, causes severe cutaneous reactions. EPP patients also have a subnormal iron status (Holme *et al*, 2007a; Delaby *et al*, 2009).

A 23-year-old Caucasian male, heterozygous both for a T→C substitution at nucleotide 557 of *FECH* and the IVS3-48C allelic variant, suffered life-long photosensitivity which had previously responded to oral iron therapy (Holme *et al*, 2007b). He consented to intravenous (IV) iron therapy offered because of incapacitating gastrointestinal symptoms.

Immediately prior to treatment (Fig 1, week 1) his free erythrocyte protoporphyrin concentration (FEP) was 32·1 μmol/l; during the previous 2 years this had fluctuated between 30 and 40 μmol/l, unrelated to the intermittent oral iron therapy. Serum ferritin concentration (SFn) was 63·8 μg/l and had not previously exceeded 50 μg/l. His serum erythropoietin concentration was normal at 10·7 mu/ml. Haemoglobin concentration (Hb) was typical at 126 g/l and remained without significant change throughout the study.

A proprietary iron hydroxide sucrose preparation (Venofer®; Synermed, (Pharmaceutical Products Ltd) Purley Surry, UK) was administered intravenously to augment iron stores in smaller doses and given at greater intervals than required by anaemic patients. A SFn target was set at 100–200 μg/l to provide adequate iron reserves without the risk of iron overload.

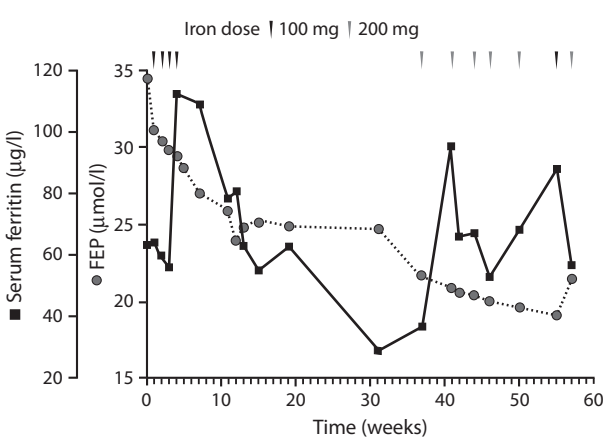


**Fig 1.** Change in free erythrocyte protoporphyrin (FEP) and serum ferritin concentration after treatment with intravenous iron. Iron doses were either 100 mg (dark arrows) or 200 mg (lighter arrows).

**Table I.** Symptoms recorded by the patient before regular iron therapy was taken, after oral iron and after intravenous iron.

| Symptoms | Before iron given | After oral iron therapy | After intravenous iron therapy |
|---|---|---|---|
| Solar sensitivity | Rapid burning | Some burning | Improved |
| | Ulceration | Improved | Absent |
| | Scarring | Improved | Absent |
| | Oedema | Improved | Absent |
| | Up to 3 d in bed | Improved | No need for bed rest |
| Wind sensitivity | Exposed areas painful | No change | Improved |
| | Hands feel cold | No change | No change |
| | Sweating palms | No change | Improved |
| | Tachycardia | No change | Absent |
| | Oedema | Improved | Absent |
| Nail changes | Discolouration | Improved | Normal |
| | Brittle | Brittle | Improved |
| | Lateral ridges | Improved | Normal |
| | Lifting | Improved | Normal |
| Cutaneous abnormalities | Pale; never tans | Improved | Now tans without discomfort |
| | Translucency | Substantial improvement | Now normal |
| | Fragile; easy bruising | Improved | Improved |
| | Tactile epidermolysis | Improved | Absent |
| | Scarring on exposed areas | No change | Absent |
| Other symptoms | Fatigue | Substantial improvement | Now normal |
| | Stamina | Substantial improvement | Improved but still suboptimal |
| | Poor mental concentration | Substantial improvement | Now normal |
| | Poor musculature | Improved | Substantial improvement |
| Body fat | | 10% | 6% |

An initial course of 400 mg of IV iron (100 mg on each occasion) given over 5 weeks increased the SFn predictably (Walters *et al*, 1973) to 113 μg/l (Fig 1) but this fell to 26 μg/l after 8 months without treatment. The possibility of urinary iron loss was noted in the product literature and on only the first day after an iron infusion, mild haemosiderinuria was detected and an iron loss of 8·5 mg/24 h determined. There was no overt evidence of significant intravascular haemolysis (falling Hb, red cell fragmentation, reticulocytosis, hyperbilirubinaemia or fall in serum haptoglobin concentration). Except immediately after an iron infusion his serum iron concentration varied between 10·2 and 33·1 μmol/l (reference range 8–32 μmol/l), as was found prior to treatment and unrelated to any other parameter.

A striking improvement in his general health (Table I) was evident within the first 2 months of treatment. His tolerance to solar radiation increased, he became asymptomatic and developed a suntan without discomfort. There was a visible and sustained increase in musculature. There had been no exposure to anabolic steroids. No adverse effects were experienced.

Unexpectedly, the FEP fell immediately during the first course of treatment (Fig 1) and closely followed a linear time-dependence ($r^2 = 0{\cdot}96$), indicating stable, intracellular retention of PPIX and a non-random age-dependent loss of PP1X-containing red cells. As the red cell lifespan cannot be prolonged and there is no haem synthesis in post-reticulocyte stage red cells, the slope (−0·08 μmol/d) of the decay is the net effect of the decreasing number of residual PPIX-rich red cells and their replacement by new red cells with lower, but still significant, PPIX concentrations. This was confirmed by fluorescent flow cytometry of a random whole blood sample, taken between courses of treatment, which indicated the presence of two discrete red cell populations with different, but elevated PPIX (data not shown). From these data the maximum red cell lifespan of 120 d would imply that a minimum FEP of 22 μmol/l could be achieved in this patient with this schedule of iron treatment.

At 90 d from the beginning of treatment the FEP became stable but resumed a linear (−0·03 μmol/d; $r^2 = 0{\cdot}852$) decay after iron therapy was reintroduced. These findings confirm the link between the iron therapy and the fall in FEP. A median FEP of 21·4 μmol/l has been maintained for over 5 years with intermittent doses of 200 mg of iron up to three times yearly with neither symptoms of EPP appearing nor evidence of iron overload (SFn 150–240 μg/l). Liver function has remained normal throughout.

Only small, controlled doses of iron are required to give this patient a significantly improved quality of life. Enhanced iron stores, haemoglobin, myoglobin and a significant urinary loss account for all the iron administered.

The iron deficit in EPP patients has been attributed to defective iron absorption (Holme *et al*, 2007a). This is supported by the findings in the current patient in whom the over-

all iron administered indicated a requirement of 1·5–2 mg daily i.e. approximating to that needed to compensate for the insensible iron loss and for the augmentation of iron stores in an adult male.

The evidence for the value of iron therapy in EPP is contradictory, with a report of benefit in one patient (Gordeuk *et al*, 1968) whilst others reported an unexplained exacerbation of symptoms developing up to several weeks after the beginning of treatment (Milligan *et al*, 1988). There is anecdotal evidence of benefit from hypertransfusion of red cells and haematin infusions, both of which would increase iron availability, but no definitive evidence of these inducing a symptomatic relapse. *In vitro* studies have shown (Crooks *et al*, 2010) that iron availability determines the stability of early ferrochelatase and we suggest that this mechanism may decrease FEP and alleviate symptoms in EPP. The effect of iron status on the expression of genes relevant in EPP merits exploration.

For EPP patients considered for iron therapy on the basis of intractable symptoms or evidence of low iron status (Holme *et al*, 2007a), it is suggested that small doses of intravenous iron may be administered safely and an early fall in FEP used as an indicator of response. Doses of 1 mg iron/kg IV intermittently to patients with a SFn <100 μg/l are likely to be effective and it is unnecessary to achieve an FEP <25 μmol/l to obtain a symptomless remission.

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## Authorship and disclosures

DPB was responsible for all clinical aspects and wrote the paper. EMM collected and analysed the data and assisted in writing the paper. Neither author has a gainful financial interest in this work.

## Conflicts of interest

The authors report no conflict of interest.

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