Review

PRACTICAL MANAGEMENT OF IRON OVERLOAD

The practical management of iron overload requires reliable estimation of body iron content and distribution as well as an understanding of how iron overload translates into clinical consequences. In this article, it will be seen that our ability to estimate the distribution of excess tissue iron, to predict its consequences and therefore to tailor treatment accordingly is surprisingly imprecise. Our understanding of how iron chelators best prevent these consequences is also limited. It will be seen that the safest and most effective ways of removing excess iron vary depending on the degree and rate of iron loading as well as the underlying condition being treated. Evidence of benefit in survival with chelation treatment takes many years to emerge and currently only exists for thalassaemia major patients treated with desferrioxamine. Long-term survival benefits have not been demonstrated in other iron-overloaded conditions or with other chelation regimens. In such circumstances, practical treatment protocols are necessarily based on inference rather than direct evidence.

ASSESSMENT OF IRON OVERLOAD

Estimation of the iron loading rate

The rate of iron loading will determine when chelation should start as well as the chelation regimen to be adopted. Excess loading may occur secondary to increased iron absorption or from repeated blood transfusions.

Iron loading from blood transfusion. This can be estimated from the total number of units of red cells given. A unit processed from 420 ml of donor blood contains approximately 200 mg of iron (0.47 mg/ml of whole donor blood). A more precise estimation of iron loading can be derived from the volume of blood transfused and the mean haematocrit of processed blood obtained from the transfusion centre. For the UK, assuming a mean haematocrit of 0.6 for SAG–M (saline adenine glucose–mannitol) blood, then the iron content is 0.7 mg per ml transfused.

Transfusion requirements vary with diagnosis. In thalassaemia major, the rate of iron loading is reasonably well defined provided a mean Hb value of 12 g/dl is achieved. The equivalent of 100–200 ml of pure red cells/kg/year (Modell, 1977) (i.e. 160–330 ml/kg of SAG–M blood/year) are transfused (equivalent to 116–232 mg of iron/kg body weight/year or 0.32–0.64 mg/kg/d) (Thalassaemia International Federation (TIF) Guidelines, 2000). The transfusion requirements and hence iron loading in unsplenectomized thalassaemia major patients are generally higher. However, hypertransfusion can also decrease splenic size (O’Brien et al. 1972) and the early introduction of a hypertransfusion regimen (Modell, 1977) may therefore reduce blood requirement.

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In healthy individuals, iron absorption is 1–1.5 mg/d and is balanced by iron loss from skin, gut, menstruation or pregnancy. Iron absorption is increased by anaemia, hypoxia, ineffective erythropoiesis and by the presence of HFE variant genes. In thalassaemia syndromes, iron absorption exceeds iron loss when erythron expansion exceeds five times that of healthy individuals (Cazzola et al. 1997). Thus, iron absorption in thalassaemia intermedia can be up to 5–10 times normal, or 0.1 mg/kg/d (Pippard et al., 1979; Gordeuk et al., 1987; Pootrakul et al., 1988). Splenectomy appears to increase the rate of GI hyperabsorption in thalassaemia intermedia (Fiorelli et al., 1990) and other conditions such as PK deficiency (Zanella et al., 1993) through mechanisms which remain speculative, such as hypoxia associated with microplumonary emboli (Chuan-sumrit et al., 1993). In thalassaemia major, hypertransfusion decreases hypoxia and expansion of the erythron, thereby decreasing GI absorption to 1–4 mg/d (Pippard & Weatherall, 1984). In individuals who are poorly transfused, absorption rises to 3–4 mg/d or more. This represents a supplementary 1–2 g of iron loading per year (equivalent to up to 3 months chelation treatment).

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levels of body iron is well established (Worwood, 1986) and the test is easy to perform compared with other tests for iron overload. However, the correlation between serum ferritin and body iron is not sufficiently precise to be of strong prognostic value. Serum ferritin will be disproportionately raised when inflammation or tissue damage is present. Conversely, serum ferritin will be falsely depressed when patients are scorbutic a frequent occurrence in iron overload owing to rapid oxidation of vitamin C (Chapman et al, 1982). Serum ferritin is also influenced by chelation treatment in a manner which is not a simple relationship with body iron. Thus, particularly for values above 3000 μg/l, serum ferritin levels fall faster with chelation than would be predicted from a diminution of body iron alone (Davis & Porter, 2000). A further problem is that the relationship between serum ferritin and body iron appears to be different for different haematological conditions, tending to be depressed relative to body iron in conditions in which iron overload is not predominantly secondary to blood transfusion. Thus, in thalassaemia intermedia, serum ferritin tends to underestimate the degree of iron overloading (unpublished observations).

With these caveats in mind, serum ferritin measured at regular intervals (at least 3 monthly with thalassaemia major) has some therapeutic and prognostic uses. A target ferritin of approximately 1000 μg/l is generally recommended standard practice in thalassaemia major (TIF Guidelines, 2000) and other forms of iron overload resulting from blood transfusion. However, the only study demonstrating a link between serum ferritin and prognosis showed that patients with values below 2500 μg/l on two thirds of occasions had less risk of cardiac complications than patients who failed this achievement (Olivieri et al. 1994).

The rate of fall in serum ferritin with chelation treatment is also a useful tool for giving information back to patients about their progress. Serum ferritin values below 3000 μg/l fall at a reasonably consistent rate with intravenous desferrioxamine therapy (130 μg/kg/month on 50 mg/kg/d) and this can be used to encourage patients and clinicians about realistic target values which can be achieved with such a regimen (Davis & Porter, 2000).

Finally, serum ferritin measurement can help to reduce the risk of desferrioxamine overdosing, particularly as the level of body iron falls with treatment. In thalassaemia major, if the mean daily desferrioxamine dose (mg/kg) divided by the serum ferritin (μg/l) exceeds 0.025 (this ratio is referred to as the Therapeutic Index) then the dose should be decreased (Porter et al, 1989b, 1998). The relationship between serum ferritin and body iron may differ in other conditions and this ratio is not applicable. This is particularly the case in sickle cell disorders in which the serum ferritin is disproportionately increased for weeks following vaso-occlusion (Brownell et al, 1986; Porter & Huehns, 1987).

Liver iron The liver is the major site of iron storage in iron overload, containing 70% or more of body iron stores (Modell & Berdoukas, 1981; Angelucci et al, 2000). Liver iron correlates closely with total body iron in transfusional iron overload and total body iron, and is approximately equivalent to 10.6 times the hepatic iron concentration (in μg/g of liver, dry weight) (Angelucci et al, 2000). The liver is also accessible for biopsy or for non-invasive measurement of iron content by Superconducting Quantum Interface Device (SQUID) or magnetic resonance imaging (MRI) and has therefore been the measurement most used for monitoring treatment and assessing prognosis.

Liver iron concentration appears to have prognostic value in iron overload. The major study showing such a relationship was in 59 patients over 7 years of age, who had been treated with desferrioxamine for variable periods of time. It was found that all patients who died with cardiac complications had liver iron concentrations >15 mg/g dry weight (Brittenham et al, 1994). It was then argued (Olivieri & Brittenham, 1997) that patients with liver iron values in this range should be regarded as 'high risk'. However, as heart failure was the cause of death in all patients, it is likely that liver iron was not the primary determinant of cardiac-free survival but represented an association of risk. Furthermore, the duration of exposure to excess iron must also be taken into account as a prognostic determinant. Another important prognostic variable is probably the age and the levels of iron loading when this happens. Thalassaemia major patients currently alive in their late thirties and early forties began treatment in late childhood or adolescence at a time when liver iron values were considerably in excess of 15 mg/g dry weight (Barry et al, 1974). This shows that, provided iron levels can be subsequently reduced, a poor outcome does not inevitably result.

It has been suggested that realistic target levels of liver iron in treated patients should be less than 7 mg/g dry weight as heterozygotes with HH can reach such levels without significant pathology resulting (Olivieri & Brittenham, 1997). This analogy assumes that the distribution of iron between heart and liver is similar in heterozygotes with HH to patients with transfusional iron overload treated with chelators. This necessarily cannot take into account that such levels take a lifetime to accumulate in heterozygotes with HH but are reached in early childhood in transfusion-dependent patients. Furthermore, recent evidence suggests that levels of liver iron correlate poorly with cardiac iron in patients on chelation. Despite these caveats, a liver iron value above 7 mg/g dry weight, particularly in a young individual, is probably the best indicator currently available for initiating chelation treatment.

Liver iron concentrations are usually measured by chemical determination on a liver biopsy sample. Biopsy is an invasive procedure, but in experienced hands has a very low complication rate (Angelucci et al, 1995). Inadequate sample size (<1 mg dry weight) or uneven distribution of iron in the presence of cirrhosis (Villeneuve et al, 1996) may give misleading results. The measurement of liver iron can be performed on wet or dried samples and the conversion of one to the other varies according to the drying and measuring techniques used in the laboratory. An agreed international standardization of measurement and reporting would be helpful to practising clinicians. Liver iron can also be measured non-invasively by magnetic
indicators of heart iron content to mortality. This is partly because endomyocardial biopsy is impractical in routine clinical practice and is not a useful indicator of heart iron as a whole owing to very uneven iron distribution in the heart (Barosi et al. 1989). Post-mortem measurement of iron concentration in many organs (Modell & Berdoukas, 1981) showed than, even in patients dying of heart failure, heart iron was only a fraction of that in the liver. Furthermore, a simple relationship between heart iron concentration and heart failure is not consistent with the marked improvement in clinical heart failure left ventricular ejection fraction and cardiac dysrhythmias observed soon after commencing intravenous desferrioxamine (Davis & Porter, 2000). Recent development of cardiac T2* MRI measurement has provided an opportunity to study the relationship between this indirect parameter of heart iron and cardiac function as well as liver iron (Anderson et al. 2000a, b). Preliminary results suggest that patients with right or left ventricular ejection fraction below control values tend to have the lowest T2* values and, by implication, the highest myocardial iron. Interestingly, there was no correlation between liver iron as measured by biopsy or MRI and cardiac T2*. A cardiac MRI can measure right and left ventricular ejection fractions at the same time as T2* and, in principle, could be measured in any hospital with suitable MRI facilities. How this parameter can best be used in the monitoring and treatment of patients requires careful prospective study.

Heart iron and function. Although heart failure is the main cause of death in iron overload (Zurlo et al. 1989; Brittenham et al. 1994), little is known about the relationship of heart iron content to mortality. This partly because endomyocardial biopsy is impractical in routine clinical practice and is not a useful indicator of heart iron as a whole owing to very uneven iron distribution in the heart (Barosi et al. 1989). Post-mortem measurement of iron concentration in many organs (Modell & Berdoukas, 1981) showed than, even in patients dying of heart failure, heart iron was only a fraction of that in the liver. Furthermore, a simple relationship between heart iron concentration and heart failure is not consistent with the marked improvement in clinical heart failure left ventricular ejection fraction and cardiac dysrhythmias observed soon after commencing intravenous desferrioxamine (Davis & Porter, 2000). Recent development of cardiac T2* MRI measurement has provided an opportunity to study the relationship between this indirect parameter of heart iron and cardiac function as well as liver iron (Anderson et al. 2000a, b). Preliminary results suggest that patients with right or left ventricular ejection fraction below control values tend to have the lowest T2* values and, by implication, the highest myocardial iron. Interestingly, there was no correlation between liver iron as measured by biopsy or MRI and cardiac T2*. A cardiac MRI can measure right and left ventricular ejection fractions at the same time as T2* and, in principle, could be measured in any hospital with suitable MRI facilities. How this parameter can best be used in the monitoring and treatment of patients requires careful prospective study.

Urinary iron estimation. Different iron chelators induce different proportions of urinary iron relative to faecal excretion. Deferiprone excretes iron almost entirely in the urine (Collins et al. 1994), desferrioxamine excretes an approximately equal amount in the faeces (Pippard et al. 1982a), and the new oral chelator developed by Novartis, ICL670A (Sergejew et al. 2000), appears to excrete iron exclusively in the faeces in preclinical studies. Urine iron excretion with desferrioxamine increases in proportion to iron loading with transfusions (Modell & Beck, 1974), dose of chelation used (Sephton-Smith, 1962; Pippard et al. 1978a), ascorbate status (Pippard et al. 1982a) and in the transfusion cycle (Pippard et al. 1982a), being proportionally higher in the urine as the HB level falls. The proportion of urinary and faecal excretion iron excretion increases with the dose of desferrioxamine given (Pippard et al. 1982a). There is very considerable day to day variation in urinary iron excretion with the same dose of chelation, even in fully controlled trial conditions. Because of this day to day variability in urinary iron excretion and the variable proportion of faecal excretion, 24 h urinary iron measurement with desferrioxamine must be interpreted with caution.

INDICATIONS FOR TREATING IRON OVERLOAD

General principles

The decision of when to treat iron overload depends on linking a given level of iron overload to risk. As seen above, risk from iron overload is likely to depend not just on body or liver iron levels but also the duration of exposure to excess iron. Furthermore, not all tissues are equally susceptible to damage from a given level of excess iron; heart failure occurs at significantly lower levels of tissue iron than cirrhosis (Modell & Berdoukas, 1981). The most important reason for initiating treatment is to prevent heart failure, which is the major cause of death in transfusional iron overload (Zurlo et al. 1989). However, considerable other morbidity results from iron overload, particularly if it occurs in childhood, and the prevention of complications such as diabetes, hypogonadotrophic hypogonadism, poor growth, hypothyroidism and hypoparathyroidism are achievable goals with optimal chelation (De Sanctis et al. 1989; Zurlo et al. 1989).

Thalassaemia major

The point at which blood transfusions have deposited enough iron to cause irreversible tissue damage has not been assessed in prospective trials. Current practice is based on balancing the known risks of excessive early treatment with the perceived risks of delayed treatment. Current practice is to start desferrioxamine when ferritin values reach 1000 µg/l or when 10–20 transfusions have been given. It is clear that the risk of overdosing is greatest in young children, particularly from effects on growth (Piga et al. 1988; Olivieri et al. 1992a) and audiometric disturbances (Olivieri et al. 1986). If treatment is commenced before the age of 3 years then this should be given with great caution. Liver iron concentrations above 7 mg/d dry weight should be regarded as an indication for treatment, although arguably lower levels of liver iron (e.g. above 3·5 mg/g dry weight) also require treatment (Olivieri & Brittenham, 1997).

Thalassaemia intermedia

As already discussed, the rate of iron loading is highly variable and the relationship between serum ferritin and body iron can be different from thalassaemia major (Fiorelli et al. 1990). Treatment typically needs to begin later in life than thalassaemia major. An estimation of liver iron is advisable before starting treatment to see whether this has exceeded 7 mg/g dry weight, as serum ferritin tends to underestimate parenchymal iron loading in this condition. In general, the rates of iron loading will be less than in thalassaemia major and the regime must be modified accordingly. Many patients with thalassaemia intermedia begin on a hypertransfusion regimen similar to thalassaemia major at some point in their lives and a chelation regime

similar to that given in thalassaemia major will need to commence at this point.

Other anaemias associated with excess iron absorption
As with thalassaemia intermedia, the rate of iron overloading is highly variable and difficult to predict. Ineffective erythropoiesis and the co-inheritance of HFE mutations may increase the risk of iron loading (Cotter et al, 1999) as, unlike thalassaemia intermedia, conditions such as pyruvate kinase deficiency and inherited sideroblastic anaemia commonly affect Northern Europeans and co-inheritance of a HFE mutation will occur in about 1 in 10 such patients. Liver biopsy for measurement of tissue iron levels and for assessment of fibrosis is advisable before starting treatment. It is probable that the measurement of cardiac iron will be an additionally useful variable. In congenital dyserythropoietic anaemia, iron overload is generally a function of age and the degree of ineffective erythropoiesis, although the rate of loading is variable (variability independent of HFE) and some patients never require chelation therapy (Wickramasinghe et al, 1999).

Sickle cell disorders
Iron overload is not seen in sickle cell disease without blood transfusions. Although there are no large studies of the effects of transfusional iron loading in HbSS, it is likely to carry similar risks to other disorders. Typically, transfusion begins later in life than in transfusion-dependent anaemias and is often given sporadically, except in the prevention of recurrent stroke. Manual exchange transfusion decreases the risk of iron loading and can even reverse iron loading (Porter & Huehns, 1987) and should be encouraged. However, when exchange is not possible on a regular basis because of poor venous access or because sufficient numbers of trained staff are not available, then top-up transfusion is frequently given, inevitably leading to iron overload. In steady state, there is a reasonable correlation between serum ferritin and the number of units of blood transfused (Porter & Huehns, 1987) or liver iron (Brittenham et al, 1993). However, the measurement of iron overload in sickle cell disease using serum ferritin is seriously flawed, as the serum ferritin remains disproportionately raised for weeks after a vaso-occlusive episode (Brownell et al, 1986; Porter & Huehns, 1987). Liver iron (and ideally heart iron with MRI) should be measured before treatment and at regular intervals thereafter. Decisions about when to start treatment will depend on practical as well as theoretical considerations. Regular use of desferrioxamine infusion can be very difficult for sickle patients, particularly in adolescence and beyond, and Portacaths have a high thrombosis and infection rate in sickle cell disorders (personal observations).

Other forms of transfusional iron overload
The age at which regular transfusion begins is critical to the iron removal strategy to be adopted. Inherited anaemias which may be transfusion dependent and require chelation treatment include Fanconi anaemia and Diamond–Blackfan anaemias (Ambruso et al, 1982). The decision to start chelation in such conditions will be based on similar principles to thalassaemia major. In transfusional-dependent anaemias of adult onset, such as acquired aplastic anaemia, myelolipobrosis, osteopenosis or iron overload resulting from transfusion with repeated courses of high-dose chemotherapy, the decision to remove accumulated iron must be weighed against the prognosis of the underlying condition on a case by case basis.

Genetic haemochromatosis
Until the recent identification of the genes responsible for genetic haemochromatosis, the most effective way of identifying this condition was using a transferrin saturation of > 50% on two samples, the second of which being a fasting value (Worwood, 1999). Serum ferritin is usually elevated but has been shown to be less reliable as a screen than fasting transferrin saturation. Historically, confirmation of the diagnosis has been achieved by liver biopsy and measurement of liver iron with an ‘hepatic iron index’ > 2 (hepatic iron index = mmol iron per g dry wt divided by the patients age). However, it is now possible to make an early genetic diagnosis based on homozygosity for C262Y or compound heterozygotes for C282Y/H63D. This then raises the question as to the role of liver biopsy in deciding when to commence phlebotomy, particularly in younger patients. Detection of fibrosis is often given as a reason for biopsy but it has been shown that, in absence of hepatomegaly, a raised alanine transaminase (ALT) or a serum ferritin >1000 μg/l, fibrosis is very unlikely and biopsy may not be necessary (Guyader et al, 1998). Therefore, in younger patients, identified using genetic screening and without the above risk factors, liver biopsy may not be mandatory. Treatment is generally indicated in men with serum ferritin levels of > 300 μg/l and in women with serum ferritin levels of > 200 μg/l, regardless of the presence or absence of symptoms. In cases in which transferrin saturation or serum ferritin are raised but genetic screening for HFE mutations does not show homozygous C282Y or C282Y/H63D, liver biopsy can be of value in determining the extent of iron loading or of other liver pathology.

TREATMENT OF IRON OVERLOAD
Phlebotomy
Phlebotomy is the most efficient and least toxic way to remove excess iron. As 1 pint of blood contains 200 mg of iron and can be performed 1–2 times a week in patients who do not have compromised erythropoiesis.

Genetic haemochromatosis. This should be treated by phlebotomy (Barton et al, 1998), as a unit of blood can generally be removed once or twice per week, resulting in iron removal of between 1 and 2 g of iron per month, considerably in excess of that achieved with iron chelation therapy. Phlebotomy is continued until the serum ferritin and transferrin saturation indicate that iron stores have just reached the iron deficient range (ferritin < 20 μg/l and transferrin saturation < 16%). Thereafter 1 unit of
blood is venesected every 3–4 months to prevent the reaccumulation of iron, generally maintaining serum ferritin < 50 µg/l.

Post bone marrow transplant (BMT). Patients who have received successful BMT for β-thalassaemia major must be venesected repeatedly until normal (or low normal) levels of iron stores are obtained (Angelucci et al. 1998). This can be achieved with phlebotomy, the frequency of which will be determined empirically by what can be tolerated without clinically relevant falls in Hb values. Baseline Hb values are affected by the genotype of the donor (i.e. whether thalassaemia trait) and it is unrealistic to expect to achieve the same Hb levels as those seen with patients venesected for genetic haemochromatosis.

In other groups of patients, such as those who are in sustained remission following BMT or chemotherapy for haematological malignancy but have received multiple blood transfusions, phlebotomy may be advisable to normalize iron loading. Assessment of iron overload using serum ferritin alone can be unreliable, so that independent confirmation of excess iron loading should be sought. This may simply be a reliable documentation of the transfusion of many units of blood. It is not unusual for a patient undergoing induction, consolidation and BMT to have received in excess of 60–100 units of blood (Bradley et al., 1997). Transferrin saturation in excess of 50% supports a suspicion of iron overload. Non-invasive estimation of liver iron stores using SQUID or MRI can be helpful if available.

Sideroblastic anaemia. Iron overload often complicates sideroblastic anaemia. Co-inheritance of an HFE variant such as C282Y of H63D may increase the risk of iron loading. Phlebotomy should be considered as a therapeutic option as some patients have surprisingly shown an improvement in Hb levels following normalization of tissue iron with phlebotomy (Cotter et al., 1999). The rate of phlebotomy that can be tolerated is highly variable and needs to be determined empirically.

Porphyria cutanea tarda. This disorder, characterized by a photosensitive dermatosis and hepatic siderosis, is associated with a number of risk factors including co-inheritance of an HFE mutation, high alcohol ingestion, hepatitis C infection (Bulaj et al., 2000) and thalassaemia trait (Adjarov et al., 1984). Treatment is effective with phlebotomy or desferrioxamine (Rocchi et al., 1991). Provided there is adequate erythropoietic reserve, phlebotomy is generally simpler to perform.

**Principles and objectives of chelation therapy**

The goals of chelation can be summarized firstly as the achievement of safe tissue iron concentrations by promoting negative iron balance and secondly as the detoxification of iron until this goal has been achieved. Only a small proportion of body iron is available for chelation at any point in time and some of this iron is required for a variety of essential metabolic functions. Chelatable iron is that which becomes available from the continuous catabolism of red cell haemoglobin amounting to 20–30 mg/d as well as iron that is made available within cells from the continuous breakdown of ferritin within lysosomes. It follows that large intermittent doses of chelator will be less efficient and potentially more toxic than lower doses given more continuously. Because iron is needed for essential metabolic functions, the dose schedule used for any chelator involves a balance between the risks of excess iron and those of excess chelator (Porter, 1997). The efficiency of currently used chelator regimens is remarkably low; 90% of administered subcutaneous desferrioxamine is excreted without binding iron (Porter et al., 2000) with 96% of deferiprone having the same fate (Al-Refai et al., 1995b). As discussed, a ‘safe’ level of tissue iron varies with age diagnosis and rate of iron loading and probably also on iron distribution within the body. An assessment of organ function in addition to tissue iron levels will influence chelation management (TIF Guidelines, 2000).

Detoxification of iron requires stable binding of the six co-ordination sites of iron by a chelator, with the prevention of redox cycling and oxidative damage. In general, *hexadentate chelators*, having six binding sites, have a more stable co-ordination chemistry than bidentate chelators, which have only two active co-ordination sites and therefore require three chelator molecules for each iron atom. This is particularly important at low concentrations of chelators when bidentate compounds tend to dissociate. Rapid improvement in cardiac function with continuous intravenous desferrioxamine is probably a result of chelation of relatively small toxic iron pools within the plasma compartment, such as plasma non-transferrin-bound iron (Porter et al., 1996), or within the heart, such as the chelatable labile intercellular pool (Zanminelli et al., 1997).

The reader is referred to other publications (Porter, 1996) for a detailed discussion of the principles of chelation therapy.

**Subcutaneous desferrioxamine infusion**

*Mechanism of action and pharmacology*. Desferrioxamine is a siderophore (a naturally occurring iron-carrier) and is produced and purified from the microbe *Streptomyces pilosus*. One molecule of chelator binds one atom of iron forming the highly stable hexadentate iron complex ferrioxamine at physiological pH values. Owing to its size, desferrioxamine is poorly absorbed from the gut. Desferrioxamine is metabolized in the liver into iron-binding metabolites which are more plentiful when the therapeutic index is high and there is greater excess of iron-free chelator (Porter et al., 1998). Urine iron is derived from that released after the breakdown of red cells in macrophages, whereas faecal iron is derived from iron chelated within the liver (Hershko & Rachmilewitz, 1979; Pippard et al., 1982b). Desferrioxamine has a short plasma half-life (initial half-life, 0–3 h) (Lee et al., 1993), being eliminated rapidly in urine and bile. Once an infusion of desferrioxamine stops, iron chelation will cease soon thereafter. Because at any moment only a small proportion of body iron is available for chelation, the longer the duration of infusion, the more efficient the chelation process. This may be particularly important in patients with severe iron overload (Davis & Porter, 2000).

**Evidence of efficacy**. There is now overwhelming evidence for the efficacy of desferrioxamine on long-term survival. © 2001 Blackwell Science Ltd, British Journal of Haematology 115: 239–252
Evidence for improvement in survival with desferrioxamine treatment is persuasive. Desferrioxamine was initially evaluated intramuscularly and early studies showed that liver iron and fibrosis could be stabilized over a period of 8 years in children (Barry et al., 1974). It was then found that 24 h i.v. desferrioxamine infusions induced more urinary iron than the same dose given as an intramuscular bolus (Propper et al., 1976). Later it was shown that 24 h subcutaneous desferrioxamine was nearly as effective as intravenous desferrioxamine at inducing urinary iron excretion (Hussain et al., 1976; Propper et al., 1977). Iron balance could be achieved in transfusion-dependant thalassaemia with only a 12-h infusion at a dose of 30 mg/kg, measuring urinary iron only (Pippard et al., 1978, 1982a). In principle, iron balance can be achieved at even lower desferrioxamine doses when given daily, if faecal excretion and increased excretion with ascorbate (Pippard et al., 1982a) are taken into account.

Evidence for the efficacy in preventing (Wolfe et al., 1985; Zurlo et al., 1989: Brittenham et al., 1994; Olivieri et al., 1994) and reversing (Marcus et al., 1984; Davis & Porter, 2000) the long-term cardiac complications is persuasive. Evidence for improvement in survival with desferrioxamine is now incontrovertible (Zurlo et al., 1989; Brittenham et al., 1994; Olivieri et al., 1994; Gabutti & Piga, 1996).

Compliance with treatment is the key to survival. Patients who comply have 100% survival at the age of 25 years, whereas survival is only 32% in those who comply poorly (Brittenham et al., 1994). Patients who administer subcutaneous desferrioxamine infusions more than 250 times a year (about five times a week) have 95% survival at 30 years of age, whereas survival at 30 years of age is only 12% in those who fail to achieve this target (Gabutti & Piga, 1996). Recently reported relatively poor results from the UK database with only 50% survival at 35 years probably reflect poor compliance in patients not attending thalassaemia centres (Modell et al., 2000). The results contrast with those of a single UK centre (University College London Hospital, UCLH) in which actuarial survival in 103 patients at 40 years was 80% (Davis et al., 2001).

A variety of endocrine complications of transfusional iron overload are also becoming less common in optimally treated cohorts of patients (De Sanctis et al., 1989). Subcutaneous desferrioxamine infusions, beginning before the age of 10 years, significantly reduce gonadal dysfunction, with improvement in pubertal status and growth (Bronspeigel-Weinroth et al., 1990). There is continuing improvement in fertility, although secondary amenorrhoea is still common (Chatterjee et al., 1993). The onset of glucose intolerance is delayed and glucose intolerance may be improved by the timely use of desferrioxamine (Fosburg & Nathan, 1990).

Recommended dose and frequency. Accumulated experience has shown that, on a regime of 40 mg/kg (range 30–50 mg/kg) given as 8–10 h infusions on a minimum of five nights a week, iron balance is achieved in hypertransfused patients with thalassaemia major and, by inference, other patients who are completely transfusion dependent. This will maintain iron levels below those regarded as toxic (Olivieri & Brittenham, 1997). However, the dose of desferrioxamine should be adjusted according to body iron load, age and diagnosis. A dose of 40 mg/kg is usually adequate in transfusion-dependent patients who comply with treatment five nights a week, although a mean daily dose of up to 50 mg/kg may be necessary and more frequently if unacceptable levels of iron loading have already accumulated. Doses above 40 mg/kg are not recommended until growth is complete because of the risk of growth retardation with doses above this (Piga et al., 1988). In patients under 5 years of age, doses in excess of 35 mg/kg/d may be inadvisable. In severe iron overload, although doses above 50–60 mg/kg have been given, these are not recommended by the manufacturers and increase the risk of unwanted effects. Recently, it has been shown that urinary iron excretion similar to that achieved with 10 h infusions can be achieved by twice daily 'bolus' s.c. injections of desferrioxamine infusion (Jensen et al., 1996; Borgna-Pignatti & Cohen, 1997; Franchini et al., 2000). However, the effects on faecal excretion and long-term iron balance are not known. These 'boluses' generally have to be given over about 10 min to minimize the discomfort of administration. In patients already established on s.c. infusions, this approach has not been a popular alternative in our clinic. However, this may offer an alternative to the use of infusion pumps when these are not available or in older patients (e.g. with myelofibrosis) in whom training in the use of infusion pumps proves impractical.

Downward adjustment of the dose can be made as ferritin falls by reference to the therapeutic index in thalassaemia major (Porter et al., 1989a). If liver iron quantification is available, a scheme for dose adjustment has been suggested (Olivieri & Brittenham, 1997). However, liver iron determinations are unlikely to be available more frequently than yearly, even in centres performing these measurements routinely, and ferritin measurements are therefore still helpful in dose adjustment. These schemes will reduce the risk of toxicity from excess chelator, but it is not a substitute for careful clinical monitoring.

In patients with less than total transfusion requirement, clearly required dosing and frequency may be less. An effort should be made in such cases to estimate the rate of iron loading and iron excretion. Subcutaneous infusions of standard doses of desferrioxamine two to three times weekly will generally achieve negative iron balance in thalassaemia intermedia and other haemolytic conditions requiring intermittent transfusions, but this should be worked out on an individual basis. In sickle cell disease, chelation is not necessary unless patients receive frequent ‘top up’ rather than exchange transfusions. Iron balance with desferrioxamine and the proportions of faecal and urinary iron excretion appear similar to those seen in thalassaemia syndromes (Collins et al., 1994). Ferritin should not be used as a criterion for starting treatment and estimation of liver iron is recommended for initiation and monitoring of treatment.

Vitamin C increases desferrioxamine-induced urinary iron excretion by increasing the availability of chelatable iron.
Monitoring and encouraging compliance. Compliance is affected by many factors, both practical and psychological. It is becoming clear that results from dedicated thalassaemia centres are better than for isolated clinicians. Compliance requires a sustained and secure relationship between the doctor, patient or parents with regular discussion and support. In an appropriately funded centre, the input of haemoglobinopathy specialist nurses and psychologists is invaluable to maximize compliance at different stages in a patient’s life. Continuity of care is critical to success, particularly in adolescence and early adult life. Input from an experienced psychologist, counsellor or trained nurse can help to identify when ‘life events’ have contributed to a period of poor compliance.

There is no perfect way to measure compliance, particularly if the patient wishes to mislead clinicians about chelation use. One approach is to give patients a calendar in which each infusion of desferrioxamine is noted down during the treatment. Poor compliance should be suspected when the serum ferritin rises in the absence of inflammatory disease or when liver iron increases. The return of used vials, the use of prescriptions and the logging of infusion times with CADD pumps have all been used to monitor compliance.

Prevention and management of chelation-related complications. Toxic effects resulting from desferrioxamine overdosing are now rare provided recommended dosing schedules are not exceeded and doses are reduced at low levels of iron loading. Toxicities resulting from excess dosing include: high frequency sensory neural loss with tinnitus and deafness in severe cases (Olivieri et al, 1986; Porter et al, 1989a); retinal toxicity with night blindness, impaired colour vision, visual fields and visual acuity (Davies et al, 1989a); retinal toxicity with night blindness, impaired colour vision, visual fields and visual acuity (Davies et al, 1989a); retinal toxicity with night blindness, impaired colour vision, visual fields and visual acuity (Davies et al, 1989a); retinal toxicity with night blindness, impaired colour vision, visual fields and visual acuity (Davies et al, 1989a); retinal toxicity with night blindness, impaired colour vision, visual fields and visual acuity (Davies et al, 1989a); retinal toxicity with night blindness, impaired colour vision, visual fields and visual acuity (Davies et al, 1989a). At very high doses of 10 mg/kg/h or more, occasional cases of renal impairment (Koren et al, 1991) and interstitial pneumonitis have been reported (Freedman et al, 1990).

High frequency sensorineural loss and retinal damage are generally reversible provided they are identified early (Olivieri et al, 1986; Porter et al, 1989a). Therefore, regular screening is advised particularly if intensive chelation treatment is being contemplated. In patients developing complications, desferrioxamine should be temporarily stopped and reintroduced at lower doses when investigations show resolution. There may also be an increased risk of retinal toxicity in patients with diabetes (Arden et al, 1984).

Interpretation of poor growth requires considerable skill and experience because both iron overload and excessive treatment can retard growth. Risk factors include a young age of starting treatment (< 3 years) and doses in excess of 40 mg/kg/d (De Virgillis et al, 1988; Piga et al, 1988). Growth velocity resumes rapidly when the dose is reduced to < 40 mg/kg/d and does not respond to hormonal treatment. Skeletal changes include rickets-like bony lesions and genu valgum in association with metaphyseal changes, particularly in the vertebrae, giving a disproportionately short trunk (De Virgillis et al, 1988; Olivieri et al, 1992a; Gabutti & Piga, 1996). Radiographic features include iron, but if given in excessive doses may increase the toxicity of iron (Nienhuis, 1981). It is recommended not to give more than 2–3 mg/kg/d as supplements; these should be taken at the time of the desferrioxamine infusion so that liberated iron is rapidly chelated. It is advisable not to start vitamin C supplementation until desferrioxamine treatment has been ongoing for several weeks.

Achieving acceptable compliance. Practical measures may be used to maximize compliance. Local mild reactions are quite common with skin itching, erythema, induration and mild to moderate discomfort at the site of subcutaneous infusions. Persistent local reactions may be reduced by varying the site of injection, lowering the strength (this should never be above 10%) or by adding 5–10 mg of hydrocortisone to the infusion mixture in severe cases. The choice of needles is important to success and various options may need to be explored with the patients or parents to find a preference. Butterfly needles (25 gauge) suit many patients: they must be inserted at an angle of about 45° to the skin surface and care should be taken to teach patients to avoid intradermal injection, which can lead to skin ulceration. The needle tip should be inserted well into the subcutaneous tissues and the tip should move freely when the needle is waggled. Other patients prefer needles which are inserted vertically (such as ‘Thallaset’ needles). These have a very narrow gauge and preattached tape for easy adhesion to the skin. The siting of the needle insertion is also important: the optimal position is generally in the abdomen, although the deltoid and thigh can be used if necessary; the optimal position is generally in the abdomen, although the deltoid and thigh can be used if necessary; the optimal position is generally in the abdomen, although the deltoid and thigh can be used if necessary; the optimal position is generally in the abdomen, although the deltoid and thigh can be used if necessary. EMLA (Astra-Zaneca) cream applied at least 30 min before insertion of the needle is helpful to some patients, especially children.

Historically, the most widely used battery-operated syringe drivers (e.g. Graseby) deliver 10–30 ml. These are suited to subcutaneous infusions for 8–12 h daily. However, they are intermittently noisy and larger than ideal for daytime use. Recently, small silent infusors (Cronoject) have been introduced as delivery systems, both intravenously and subcutaneously; the more advanced of these have devices record the time and frequency of use, thus helping in monitoring compliance.
vertebral demineralization and flatness of vertebral bodies. Growing patients should have annual radiological assessment of the thoracolumbar–sacral spine as well as the forearm and knees, and the dose of desferrioxamine should be reduced if significant changes are noted, as they are irreversible (De Sanctis et al. 1996). The risk factors are the same as for growth retardation.

Care should be taken to prevent sudden intravenous boluses of desferrioxamine as this may lead to nausea, vomiting, hypotension with acute collapse or even transient aphasia (Dickerhoff, 1987). Care should also be taken with desferrioxamine in combination with psychotropic drugs, as desferrioxamine potentiated the action of phenothiazine derivatives leading to reversible coma in two non-iron-overloaded patients (Blake et al., 1985).

Severe allergy to desferrioxamine is a rare event and independent of dose. This can present with true anaphylaxis or, occasionally, with less obvious features such as fevers, muscle aches or arthralgia during infusions. It can be effectively treated by careful desensitization, carried out under close medical supervision (Miller et al., 1981; Bosquet et al., 1983). Desensitization is usually successful, but may need to be repeated more than once. If it is unsuccessful, an alternative chelator such as deferiprone should be considered. Occasionally, severe local reactions with local erythema at the site of the subcutaneous infusion can respond to desensitization.

There is an increased risk of *Yersinia infection* in iron overload and this increases further with desferrioxamine use because ferrioxamine can be used by *Yersinia* as a source of iron for growth (Robins-Browne & Pricp, 1985; Gallant et al., 1986). Any patient taking desferrioxamine who presents with diarrhoea, abdominal pain or fever should stop treatment until *yersinia* infection can be reasonably excluded. *Yersinia* can be diagnosed using special culture media from blood or stool or by serological tests, but the pick-up rate is low and treatment should be initiated on clinical suspicion. Ciprofloxacin is the current treatment of choice. Desferrioxamine can generally be restarted after about 2 weeks of treatment. Rarely, is infection recurrent. Other infections such as *Klebsiella* may also be exacerbated by continued desferrioxamine. It is sensible to stop desferrioxamine in anyone with an unexplained fever until the cause has been identified.

Intravenous desferrioxamine for high-risk cases

In patients with consistently high levels of iron overload or those who develop cardiac or other serious complications, 24 h continuous chelation therapy should be considered. Historically, high doses of i.v. desferrioxamine were given in high-risk cases, with resulting toxicity (Davies et al. 1983; Marcus et al., 1984), and often as intermittent infusions (Cohen et al., 1987). In principle, continuous infusion will provide better protection from non-transferrin plasma iron (Porter et al. 1996) and recent findings provide evidence of the long-term benefit of continuous desferrioxamine at relatively modest doses (Davis & Porter, 2000). An actuarial survival of 61% at 13 years was found in high-risk patients (n = 25) with life-threatening cardiac dysrhythmias (n = 6), left ventricular dysfunction (n = 6), gross iron overload (n = 10) and poor tolerability of subcutaneous desferrioxamine (n = 3). Using continuous infusion of desferrioxamine through the Portacath, cardiac dysrhythmias were reversed in 6/6 patients; resting left ventricular ejection fraction improved in 7/9 patients from 36 ± 6% to 49 ± 8% (P = 0.002), with reversal of biventricular heart failure in 4/4 patients. The principal catheter-related complications were infection (1-15/1000 catheter days) and thromboembolism (0.48/1000 patient days), similar to other patient groups. Desferrioxamine toxicity was observed in only one patient, in whom the recommended therapeutic index was transiently exceeded. Portacaths stayed in situ a median of 21 months, which was generally long enough to observe a significant fall in serum ferritin and improvement in cardiac performance. The rate of fall in ferritin was initially rapid (approximately 1000 g/l/month) for values above 4000 μg/l and slower at 130 μg/l/month below this value. Preliminary results in a further prospective study also show significant improvement in cardiac T2* within 6 months of commencing this regimen (Anderson et al., 2000a).

Doses in excess of 50–60 mg/kg appear not to be necessary to achieve reversal of heart failure or dysrhythmias and continuous chelation appears to be the key to this success. Attention to detail of Portacath management is important to successful outcome. Patients had Portacaths accessed with repositioning of the needle once weekly by trained staff on daycare. The regular repositioning of the needle appeared to be helpful in reducing local infection at the exit site of the port. Owing to the finding of thrombosis and the prothrombotic tendency of thalassaemia patients, concomitant use of warfarin with a view to running an International Normalized Ratio (INR) value between 2 and 3 is now standard practice in our unit.

Compliance is generally much improved using this regimen often continuing after the Portacath was removed.

Continuous desferrioxamine infusion should thus be considered in patients at high risk, namely those with ferritin values persistently > 2500 μg/l (Olivieri et al., 1994); liver iron > 15 mg/g dry weight (Brittenham et al., 1994); significant cardiac disease such as significant cardiac dysrhythmias (Davis & Porter, 2000) or evidence of falling ventricular function (Davis & Porter, 2000). This regimen should also be considered for those with the inability to use subcutaneous desferrioxamine regularly, or with persistent poor compliance, female patients who plan pregnancy, patients planning a bone marrow transplant and those with active hepatitis C. Before inserting a Portacath, or after this is removed, continuous subcutaneous desferrioxamine using disposable infusors should also be considered, as excellent results can be obtained. Experience of Portacath use in sickle cell patients has been less good, with a higher incidence of thrombosis and infections, and we do not generally recommend this approach.

Oral chelation therapy with deferiprone

Mechanism of action and pharmacology. Three deferiprone (L1) molecules are required to bind one iron atom (bidentate
chelation). Each molecule is neutrally charged, has about a third of the molecular weight of desferrioxamine and is more lipid soluble. These properties allow rapid GI absorption and access to intracellular iron pools (Porter, 1996).

The drug appears in the plasma 5–10 min after oral ingestion with high plasma concentrations in excess of 300 µmol/l at a dose of 50 mg/kg (Kontoghiorghes et al., 1990; Al-Refaie et al., 1995b). The plasma half-life is short (1–52 h) (Al-Refaie et al., 1995b) and there is rapid inactivation by glucuronidation in the liver. The major form in the urine is the iron-free glucuronide (Kontoghiorghes et al., 1990). Unlike desferrioxamine, there is no effective iron excretion in the faeces. The iron–chelate complex of bidentate chelators are less stable than hexadentate chelators such as desferrioxamine and there is in vitro and animal data to support this concern. There has been little clinical investigation which addresses this question, although it is possible that the arthritis associated with deferiprone, particularly in heavily iron-loaded patients, results from instability of the iron–chelate complex. The effect of ascorbate on iron excretion with deferiprone is not clear but is potentially harmful and is not recommended.

**Evidence of efficacy.** Evidence of efficacy is based on the effects on iron excretion, serum ferritin and liver iron concentration. There are as yet insufficient data to draw conclusions about the long-term effects on morbidity and mortality. Daily doses between 90 and 200 mg/kg were initially reported to induce sufficient urinary iron excretion for negative iron balance in heavily overloaded patients (Kontoghiorghes et al., 1987). Later it was found that 75 mg/kg/d but not 50 mg/kg/d promoted negative urinary iron balance in poorly chelated patients and that urinary iron correlated with serum ferritin (Olivieri et al., 1990).

Balance studies showed the effect on faecal excretion is not clinically significant (Olivieri et al., 1990; Collins et al., 1994) and that total iron excretion at 75 mg/kg/d in three divided doses is about 60% of that seen with a 12-h infusion of desferrioxamine at 50 mg/kg (Collins et al., 1994).

Falls in serum ferritin have been most apparent in untreated or inadequately treated patients beginning with values above 5000 µg/l (Al-Refaie et al., 1992). In India, where many patients have no chelation treatment, the serum ferritin fell from initially very high levels by an average of more than 3500 µg/l over a 20-month period (Agarwal et al., 1992). There was also a significant but less dramatic fall in serum ferritin in poorly chelated patients from Canada over 3 years from 3975 to 2546 µg/l at a dose of 75 mg/kg/d (Olivieri et al., 1995). In patients with pretreatment values below 2500 µg/l there was no significant change, a finding confirmed in other studies (Hoffbrand et al., 1998; Cohen et al., 2000). An analysis of changes in serum ferritin for patients with pretreatment values of approximately 1000 µg/l or less would be helpful.

The effects of deferiprone on liver iron were not reported until 1995 when a 3-year follow-up was reported in 21 patients (Olivieri et al., 1995). The findings tend to parallel those with serum ferritin in that decrements occur mainly in patients with high pretreatment values. In a more recent follow up in the same patients over a mean of 4-6 years, hepatic iron was above 15 mg/g dry weight in 7 out of 18 patients (39%) (Olivieri et al., 1998), with a trend to reduction only in patients with the highest pretreatment values. In other studies in which only single biopsies were performed (Hoffbrand et al., 1998), hepatic iron was greater than 15 mg/g dry weight in 10 out of 17 patients (58%) after a 2–4 year follow up and below 7 mg/g dry weight in only two patients. In a 7–8 year follow up of seven patients, there was an ‘unexplained resurgence’ of serum ferritin after 4–5 years, associated with a concomitant increase in liver iron in three cases (Tondury et al., 1998). There is considerable variability between different studies concerning the effectiveness at reducing liver iron to acceptable levels (Longo et al., 1998; Del Vecchio et al., 2000), which could reflect variable rates of metabolism such as glucuronidation of deferiprone in different populations. It seems clear, however, that liver iron does not equilibrate at acceptable levels in a sizeable proportion of patients receiving 75 mg/kg/d, the only dose at which prospective toxicity data are available.

In conditions in which the rate of iron loading is slower than in thalassaemia major, it would be anticipated that liver iron should equilibrate at more acceptable levels at doses of 75 mg/kg or less. Indeed, in a case report of a patient with thalassaemia intermedia, liver iron was reduced from 14·6 to 1·9 mg/g dry weight after 9 months of deferiprone (Olivieri et al., 1992b). Controlled prospective studies on these and other iron-loaded patients, such as transfused patients, sickle cell disease would be helpful in deciding the balance of risk and benefit in such patients.

The effect on cardiac function, cardiac dysrhythmias and cardiac iron are uncertain, although anecdotal evidence using T2-weighted spin echo magnetic resonance imaging (Olivieri et al., 1992b) suggests that cardiac iron can be reduced. In a large study, 5 out of 51 patients treated with deferiprone died after a mean of 18 months treatment, four with congestive heart failure (Hoffbrand et al., 1998). Because of the absence of a control group and the heterogeneity of the patients, it is not possible to interpret the significance of these deaths with confidence.

**Indications, dose and frequency.** There is still uncertainty about the long-term efficacy of this drug (Pippard & Weatherall, 2000a). Thus, while some are wary of recommending deferiprone, even as second line-therapy (Pippard & Weatherall, 2000b), others are enthusiastic about extending its use (Wonke et al., 1998; Kontoghiorghes et al., 2000). This uncertainty is also reflected by the recent licensing of the drug by the European Medicines Evaluation Agency (EMEA) in Europe but not by the Federal Drug Administration (FDA) in the USA. In 1993 the FDA recommended that two prospective randomized studies be performed before licensing could be considered. The first of these, the safety study, has been completed and published for 187 patients (Cohen et al., 2000) and has been discussed. Unfortunately, the second, a randomized trial comparing the efficacy of desferrioxamine and deferiprone, was never completed because of disagreements between some of the investigators and the participating pharmaceutical company, Apotex. Because of remaining uncertainties, it
seems advisable that all reasonable avenues for giving desferrioxamine should be exhaustively explored before considering deferiprone.

The dose of deferiprone for which prospective observations about side-effects are available is 75 mg/kg/d in three divided doses (Cohen et al. 2000). It is not known whether higher doses increase the risk of unwanted effects. It is advisable that treatment is monitored with weekly blood counts so that treatment can be stopped rapidly if the white count begins to fall significantly. A liver biopsy to assess liver iron and liver fibrosis is also advisable before starting treatment and at intervals thereafter. Because of fluctuations in liver function, liver function tests should also be monitored regularly.

Some clinicians have investigated the combined use of desferrioxamine with deferiprone, either concomitantly (Wonke et al. 1998) or sequentially (Aydinok et al. 1999), the former study being associated with a fall in serum ferritin and the latter with a small fall in liver iron in 6/7 patients over a 6-month period. Combined treatment has the potential advantage of decreasing exposure to both drugs and increasing the iron excretion obtained with deferiprone alone. Reported patient numbers are too small to comment on the possible toxic effects of combined chelation. However, mixed ligand therapy could, in principle, increase both the efficacy and the toxicity of chelation therapy because the low-molecular-weight deferiprone could ‘shuttle’ iron or other metals onto a desferrioxamine ‘sink’. Until these issues have been investigated further, it is difficult to make general recommendations except to say that sequential treatment (i.e. desferrioxamine followed by deferiprone) has theoretically less risk of unforeseen effects of metal shuttling than concomitant treatment (i.e. both drugs at the same time).

Prevention and management of chelation-related complications. The most serious adverse effect is agranulocytosis [absolute neutrophil count (ANC) < 0·5 x 10^9/l]. This was initially reported in 3–4% of patients treated with deferiprone, with mild neutropenia in an additional 4% (Al-Refaie et al. 1992, 1995a). The mechanism is unclear because, although agranulocytosis appears unpredictable in humans given at 75 mg/kg/d, the effect in laboratory animals was dose and time dependent (Porter et al. 1989b, 1991; Hoyes et al. 1993). In a more recent prospective multicentre study, agranulocytosis occurred in 0·6% per 100 patient years at a dose of 75 mg/kg (rounded down to the nearest half tablet of 250 mg) in three divided doses in which patients had weekly blood counts and deferiprone was discontinued if the ANC was <1·5 x 10^9/l (Cohen et al. 2000). Milder forms of neutropenia (ANC 0·5–1·5 x 10^9/l) were observed in 5–4/100 patient years more frequently in non-splenectomized patients. It is therefore recommended that the ANC be monitored every week or more frequently if there are signs of infection. Treatment should be stopped at the first signs of falling neutrophil counts. Neutropenia and agranulocytosis generally resolve within 4–124 d of discontinuation of treatment (Hoffbrand et al. 1989; Hoffbrand, 1994; Cohen et al. 2000). Growth factors have been used in severe or protracted neutropenia, although their value is uncertain. In patients with agranulocytosis, reintroduction of deferiprone leads to a rapid fall in the neutrophil count in some patients, and is therefore contraindicated. In patients with milder forms of neutropenia, reintroduction should only be considered under conditions of very careful monitoring. It may be wise to avoid deferiprone in patients in whom stem cell or progenitor function is compromised, such as those with Diamond–Blackfan anaemia.

Painful swelling of the joints, particularly the knees, has been seen in 6–39% of patients treated with deferiprone (Agarwal et al. 1992; Al-Refaie et al. 1992). This complication is more common in patients with higher ferritin values (Agarwal et al. 1992; Cohen et al. 2000) and usually, but not always, resolves after stopping therapy. Other unwanted effects are nausea (8%), mild zinc deficiency (14%) and fluctuation in liver function tests (44%) (Al-Refaie et al. 1995a). In the prospective study (Cohen et al. 2000), the ALT value was significantly higher than the baseline value at 3 months and 6 months, but those with values twice baseline levels did not increase significantly either in the hepatitis C-positive or -negative group. Unwanted effects caused treatment to be stopped in 13–30% of patients in various studies (Al-Refaie et al. 1992, 1995a; Hoffbrand et al. 1998). Isolated initial reports with deferiprone, such as a fatal systemic lupus erythematosus (Mehta et al. 1991), increased antinuclear antibodies and rheumatoid factors (Mehta et al. 1993), and a fatal varicella infection, have not been confirmed in more recent studies. Progression of audiometric disturbances has been described in five out of nine patients who were switched from desferrioxamine to deferiprone (Chiodo et al. 1997). In the same study, however, seven patients without audiometric disturbance who were switched to deferiprone developed no new abnormalities. Deferiprone is teratogenic in animals and should not be given to patients attempting to conceive. Until more is known, contraception must be used by potentially fertile sexually active women and men taking deferiprone.

One study has described progression of hepatic fibrosis during treatment with deferiprone (Olivieri et al. 1998). In another study, hepatic fibrosis was found in 7 out of 11 patients on long-term deferiprone, and the fibrosis was greater in the hepatitis C-positive group than the hepatitis C-negative group (Tondury et al. 1998). Other reports have failed to find progression of fibrosis which could not be explained by concomitant hepatitis C infection (Hoffbrand et al. 1998; Piga et al. 1998; Wanlass et al. 2000). Assessment of fibrosis does not lend itself to ease of quantification and is also subject to sampling effects. Furthermore, the presence of hepatitis C confounds the interpretation of results. Although there is no proof of progression of fibrosis on deferiprone treatment, it seems advisable to recommend serial liver biopsies for patients on long-term treatment.

CONCLUSIONS AND FUTURE PERSPECTIVES

From the above, it can be seen that the management of iron
overload has to be tailored to the disease and individual in question, but the treatments and diagnostic tools currently available have a number of limitations. Because iron chelators were historically viewed as ‘orphan drugs’, much of the information gleaned about both desferrioxamine and deferiprone was necessarily obtained from relatively small, clinician-led, observational studies. The paucity of large controlled prospective studies, which are inevitably prohibitively expensive if not financed by a large pharmaceutical company or a major governmental research body, allowed the emergence of a diverse range of views about the safety and efficacy of available treatments. In this article an attempt has been made to base recommendations about practical management on evidence, recognizing that this is not always possible.

Despite these limitations, life expectancy in iron-overloaded patients continues to improve. Encouragingly there are a number of new oral chelators in preclinical and clinical trials which are being supported by pharmaceutical companies. It is hoped and anticipated that, with the clinical trials which are being supported by pharmaceutical companies. It is hoped and anticipated that, with the emergence of new techniques for monitoring iron overload, the accumulated experience of clinicians and the future backing of the pharmaceutical industry, the practical management of iron overload will continue to improve.

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**Keywords:** iron overload, chelation, thalassaemia, desferrioxamine deferiprone.