

Oral iron chelation is here

New oral chelation agents are challenging desferrioxamine

Iron overload is a potentially fatal disorder, damaging the heart, liver, and other organs. It may be due to repeated blood transfusions or increased gastrointestinal absorption of iron, or both—as occurs in the β thalassaemias. In patients given regular transfusions signs of organ damage (secondary haemochromatosis) become apparent when around 50-100 units of red blood cells have been given: at that time about 10-20 g of extra storage iron has been introduced into the body, six to 13 times the amount stored in normal people. Patients with primary haemochromatosis absorb excess iron from the diet. This amounts to far less iron than those having regular transfusions, but in time they still accumulate a lethal overload unless treated by venesection.

Patients with transfusional iron overload need treatment by chelation. Most such patients have a haemoglobinopathy.

Around 250 million people are heterozygotes with one of the haemoglobinopathies, and about 200 000 are born each year with potentially lethal homozygous thalassaemia or sickle cell anaemia. Most of the 100 000 with thalassaemia have one of the β variants,¹ and these patients can be maintained in good health by repeated transfusion and chelation from the first year of life. Even without chelation regular transfusion can prolong life to around 20 years—as opposed to death within three years of birth without treatment.

Many other conditions are—or should be—treated by chelation to prevent overload with iron from repeated transfusions. These include not only sickle cell anaemia but also aplastic anaemia, myelodysplasia/myelofibrosis, and, in some cases, chronic renal failure.² Desferrioxamine has been the mainstay of iron (and aluminium) chelation for the past 15 years. It is generally effective and non-toxic, but because of its high cost, the cumbersome subcutaneous method of administration, and toxic side effects only a small fraction of patients requiring chelation worldwide receive it. In India, for example, less than 5% of patients with β thalassaemia major could afford treatment with desferrioxamine.

What, then, about other chelators? Those such as EDTA and diethylenetriaminepenta-acetic acid, which are not selective for iron because of their carboxylic acid binding site, increase the excretion of zinc and magnesium, making them toxic. A new group of chelators, the α -ketoxyhydroxy-pyridines, has many advantages, including a high affinity for iron; a high selectivity for iron over other biologically important metals; stability in acidic and physiological conditions because of its heteroaromatic structure; ability to cross the cell membrane because of its neutral charge and the formation of neutral iron

complexes; and ability to remove iron from transferrin, ferritin, and haemosiderin.³ Several of this group of chelators have been shown to be effective in removing iron from mice, rats, rabbits, and monkeys, but only a few have been shown to be safe when given long term to animals. One of these, 1,2 dimethyl-3-hydroxypyrid-4-one (L1), has been shown in the past five years to be of comparable efficacy to desferrioxamine in increasing the urinary excretion of iron in patients with thalassaemia and myelodysplasia.⁴ The effectiveness of L1 in increasing iron excretion has been confirmed in centres around the world in trials of daily administration for up to 15 months.⁵⁻⁸

Pharmacokinetic studies have shown that orally administered L1 is absorbed from the stomach and enters the systemic circulation through the liver with a half life of 0.7-32 minutes, is metabolised in the liver to a glucuronide conjugate which is unable to bind iron, cleared through the kidneys with a half life of 47-134 minutes, and excreted almost completely in the urine in the form of mainly a glucuronide conjugate, unchanged L1, and L1 bound to iron.⁹ Variations among patients in the clearance and extent of metabolism of L1 have been noted. Removal of iron by L1 is thought to take place mainly from the serum and the liver.⁹ L1 does not increase faecal iron or absorption from the gut.

The amount of iron excreted by L1 depends on the dose and frequency of administration of the drug and the iron load of the patient. Single doses of L1 of 45-62 mg/kg in patients loaded with iron resulted in the urinary excretion of 10-70 mg iron (compared with less than 1 mg in normal people).⁹ Results so far indicate that doses of 50-100 mg of L1/kg/day seem to cause a rate of excretion of iron sufficient to reduce the iron load of patients and maintain in most cases serum ferritin concentrations of 1000-2000 μ g/l. Studies of intensive chelation have also been carried out and proved very effective; in one case 325 mg of iron was excreted in the urine after the oral administration of 16 g of L1 in divided doses.⁵ Overall, the results of iron removal by L1 are highly encouraging, and there is no reason to suspect that with safe doses this treatment will not be as effective as subcutaneous desferrioxamine.

Major toxic side effects of L1 in animals during the administration of subacute doses of 200 mg/kg/day for up to 12 months include a lowering of the white cell count, hypocellularity of the bone marrow affecting mainly progenitors of white cells, enlargement of the adrenals, and hypersalivation.³ Histopathological examination of rats treated with acute intragastric doses of L1 of greater than 2 g/kg have

shown congestion in various organs, suggesting death from congestive heart failure. L1 and its iron complex are not mutagenic and do not increase the growth of yersinia in vitro.³

Toxic side effects observed during multicentre clinical trials with L1 in over 200 patients known to have mainly thalassaemia and other volunteers in the United Kingdom, India, Switzerland, Canada, the Netherlands, Italy, and Czechoslovakia include transient episodes of agranulocytosis in two patients; musculoskeletal and joint pains in 19 patients; one fatal incident with a patient who developed a lupus-like syndrome; gastric intolerance in 12; and an increased requirement for transfusions of red cells in a patient who had not had a splenectomy.^{3,6,10} A more detailed report on the efficacy and toxicity of L1 and other chelators in humans is given elsewhere.¹¹

The prospect of identifying the few people who may be susceptible to L1 requires further attention. Such screening has been suggested for other drugs—for example, screening for the production of sulphoxide in patients treated with penicillamine. Other measures might include withdrawing L1 during acute inflammation and infection—both of which activate neutrophils and monocytes¹²—and introducing protocols of low doses given often. Toxicity long term and not efficacy is the major issue that needs to be addressed with L1 now and possibly other related oral chelators in the near future. Formal long term studies of toxicity in animals and clinical trials will possibly be required before all patients switch from desferrioxamine to L1 or some other oral chelator. Such studies, however, are expensive and may never be supported by pharmaceutical companies because of the

classification of L1 and related chelators in the “orphan drugs” category.

The potentially life saving benefits of treatment with L1 in patients loaded with iron who are not adequately treated with desferrioxamine may outweigh the risks of its possible toxicity, and its introduction in such patients may now be appropriate.

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Camelford revisited

Still not the last word

The Cornish town of Camelford is again in the news. In July 1988, 20 tonnes of concentrated aluminium sulphate was accidentally discharged into a local reservoir. Drinking water was heavily polluted for up to three days, not only by the primary contaminants but also by copper, zinc, and lead dissolved from domestic plumbing. The acute effects on the town's inhabitants included gastrointestinal disturbances and oral ulceration.

In response to persistent public concern, in January 1989 the government appointed an independent group of experts to advise on the possible long term consequences of the episode. The advisory group, chaired by Dame Barbara Clayton, reported in July 1989.¹ While conceding uncertainties, it concluded that long term toxic effects were unlikely on the basis of current knowledge. It did, however, support the collection of further information—for example, on outcomes of pregnancy—as well as making recommendations about the handling of any similar incidents in future.

Despite the advisory group's reassuring conclusion public anxiety was not allayed. Furthermore, new information emerged which suggested that people living in Camelford at the time of the accident had persistent symptoms and clinicopathological abnormalities. In particular, there were reports of raised serum aluminium concentrations several months after the incident, of sensitivity to aluminium in some people, of a high prevalence of perceived difficulties with memory, and of abnormalities on neuropsychological testing. The advisory group was therefore reconvened to examine the

fresh evidence, and its second report was published two weeks ago.²

Like the first, the report is carefully considered and clearly reasoned, and it again concludes that long term toxicity is unlikely. The limitations of the new data are discussed. For example, much of the information derives from self selected and highly unrepresentative samples or is inadequately controlled. The advisory group accepts that the accident has led to real mental and physical suffering but suggests that the excess of reported symptoms may be attributable to anxiety and heightened awareness rather than a direct toxic effect. There are specific recommendations for further research but not for the large scale epidemiological survey that some have advocated. This conclusion is unlikely to satisfy those who believe that the community has been seriously poisoned.

The task of the advisory group was always going to be difficult. In some ways its situation is similar to that which clinicians face when presented with an anxious patient whose symptoms seem after routine investigation to signify nothing sinister. How far should one go in trying to exclude improbable diagnoses before offering reassurance? Prolonged investigation may throw up spurious abnormalities that increase the patient's conviction of major pathology. On the other hand, just occasionally there will indeed be serious underlying disease.

Epidemiological investigation of the alleged health effects is far from straightforward. There is no reliable way of measuring exposure to the contaminated water retrospectively.