AN ORALLY ACTIVE IRON CHELATOR

IRON is essential for all organisms from bacteria to humans; but like excessive amounts of alcohol, which is so pleasant in moderation, a surfeit of iron is fatal. The lethal effects of iron overload can be immediate, as in an accidental or deliberate overdose of medicinal iron, or slow, as in congenital hemochromatosis and transfusional hemosiderosis. In the slowly developing conditions — the former due to hyperabsorption of iron in food and the latter to iatrogenic, as well as, in the case of thalassemia, hyperabsorptive factors — iron stores in the reticuloendothelial system are filled to the brim with nontoxic ferruginous granules. Spillage of iron into parenchyma and plasma is inevitable, and toxic effects due to oxidation of membranes follow. The excess iron saturates the binding sites of transferrin, the "delivery boy" of iron metabolism, allowing free iron to circulate and oxidize heart-muscle membranes[1] until the patient succumbs to heart failure and arrhythmia.

Thalassemia is one of the most common diseases in regions of the world where malaria has long been rampant. This inherited disorder of hemoglobin synthesis is fatal in infancy without transfusions but is fatal in adolescence even with them. The advent of treatment with subcutaneous deferoxamine has changed this gloomy prognosis. Recent studies demonstrate that over 90 percent of patients who comply with the difficult and expensive regimen of deferoxamine treatment survive without heart disease[2] and with minimal toxic effects if the dose is tailored to the iron burden.[3]

Deferoxamine has a very high and selective affinity for iron that is independent of the iron concentration.[4] The required dose is relatively low (about 40 to 50 mg per kilogram of body weight administered in an overnight subcutaneous infusion). Serious side effects are rare. But the drug is not active orally, and nightly subcutaneous self-administration is onerous, leading to a high frequency of noncompliance, a uniformly fatal "complication" of therapy.

There are only two alternatives to subcutaneous deferoxamine: allogeneic bone marrow transplantation for the 25 percent of patients with histocompatible donors, and an orally active iron chelator. The former has received attention recently because of a report from a center in Italy, where patients with good chelation had more than a 90 percent likelihood of indefinite thalassemia-free survival after bone marrow transplantation.[5] However, the investigators' method of stratifying patients is not readily reproducible, and experience with bone marrow transplantation in young patients with good chelation in the United Kingdom and the United States shows that the rate of disease-free survival is no higher than 75 percent and may be lower.[6,7] Nevertheless, bone marrow transplantation can solve the therapeutic problem once and for all and, until now, has been the only useful option if a patient cannot or will not use deferoxamine or if the blood supply is of uncertain safety and reliability.

In this issue of the *Journal*, Olivieri and her colleagues

feriprone has a checkered history. It was originally synthesized by Robert Hider and his colleagues at Essex University, and the early biologic assessments were performed at University College Hospital in London.[9] The drug was used in the clinic of another London hospital without sufficient studies of toxic effects in animals and without Hider's approval.

Deferiprone has a much lower therapeutic ratio than deferoxamine, for two reasons. First, deferiprone is considerably more toxic and regularly depresses the granulocyte count in both normal and iron-overloaded animals[10]; deferoxamine, in contrast, does not depress the marrow. In clinical studies, deferiprone has caused both agranulocytosis and arthralgia or arthritis; the frequency of these complications is not yet known. Second, though Olivieri and her colleagues clearly demonstrate that deferiprone can reduce iron stores to lower, if still elevated, levels in patients with severe overload, the drug has a concentration-dependent affinity for iron.[4] Three molecules of deferiprone are required to bind one molecule of iron, whereas deferoxamine binds iron tightly in a 1:1 ratio. For this reason, deferiprone must be present at very high concentrations (close to toxic levels) to be effective. It dissociates from iron when the concentration of iron in body fluids falls to the level achieved just a few hours after oral administration.[4] Hence, as demonstrated by Olivieri and her colleagues, deferiprone does not readily reduce excessive body iron stores below a certain level. It is therefore not clear that the drug will provide long-term protection from heart disease.

Not enough is known about the pharmacologic properties of deferiprone. Will the low levels of drug that remain in the plasma continue to chelate free iron and thereby protect heart-muscle membranes, or will the small but highly toxic pool of free iron remain or return to high levels between doses to do its damage? Over time, will the drug's ability to be absorbed prove to be a two-edged sword because it can also permeate the cell membranes of vital organs such as the kidney, with toxic effects? That has been the sad fate of an extremely active oral iron chelator called desferithiocin.[11] Finally, will adolescents really swallow enough pills to amount to 75 mg per kilogram in three divided doses every day? For an adolescent of average weight, this represents 1 to 2 g of the drug three times daily. Such a burdensome regimen is itself an open invitation to noncompliance and the development of heart disease. Ominously, 10 percent of the patients in the trial reported by Olivieri et al. did not comply with the regimen.

Given these concerns, clinical studies of deferiprone that last for several years and enroll at least 100 patients will be required before physicians can advise patients with thalassemia to dispense with nightly subcutaneous administration of deferoxamine and instead swallow a handful of capsules every eight hours. Patients who are unable or unwilling to use deferoxamine and for whom there are histocompatible donors available will have to weigh the unknown risks of defer-

Despite questions about the long-term efficacy and safety of deferiprone in the management of thalassemia, Olivieri and her coworkers are to be congratulated for rescuing the drug from a shaky start and for performing a careful initial study that moves the field forward. Whether deferiprone proves to be useful and safe will be known in the fullness of time. Whatever further studies of the drug reveal, it is comforting to know that the search for a better life for patients with thalassemia is in reliable hands.

Children's Hospital
Boston, MA 02115

DAVID G. NATHAN, M.D.

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