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More pieces to the iron chelation puzzle

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Regular blood transfusions are life-saving treatment for patients with severe anemias, including those with beta thalassemia, sickle cell disease, myelodysplastic syndromes, and other conditions. But, the treatment is a double-edged sword – each unit of transfused blood contains 200 mg of iron and because the body has no mechanism to excrete excess iron, chronic iron overload often results, causing damage to the liver, heart, endocrine organs, and other tissues. Iron chelation therapy, thus, has played a vital role in the management of these patients since the introduction of the parenterally administered chelator deferoxamine (DFO) more than 40 years ago.

In this issue, Evans, et al. report on in vitro kinetic studies of the interaction of DFO with deferiprone (DFP), in removing non-transferrin bound iron from plasma of thalassemic patients. DFP is an oral agent first used in humans in the late 1980s and DFO/DFP combination therapy has been under clinical study for most of the two decades since. However, controversy still exists over how the agents interact in removing iron and how they can be administered together most effectively.

The study by Evans, et al. strengthens the evidence for the "shuttle theory," wherein DFP acts as the shuttle for removing iron and loading it onto DFO, which serves as the ultimate iron "sink" for excretion. Earlier studies supporting the shuttle effect were more indirect, showing excretion and retention of radioactive iron, 7 days after administration of the agents in rats in vivo or 24 hours after application to cultured heart cells[1]. By measuring the formation of ferroxamine (FO) in real time, the current study demonstrates the shuttling phenomenon more directly.

As noted by the authors of the current study, the shuttle theory provides a rationale for simultaneous administration of the two drugs. However, proponents of sequential or alternating administration suggest that other mechanisms, such as access to different iron compartments, could cause the agents to be additively or synergistically effective with alternating administration, but these remain theoretical[2].

The need for optimizing chelation regimens—including DFO/DFP combinations—is a pressing one. Despite the dramatic improvements in survival and quality of life of patients with beta thalassemia and other transfusion-dependent anemias that have occurred during the DFO era, cardiotoxicity continues to be the leading cause of death in these patients[3]. Relatively poor compliance with DFO regimens has been partially to blame: Because it has a short plasma half-

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life and is not orally active, DFO is given as an overnight subcutaneous infusion 5 to 7 nights per week, a regimen that can be difficult to maintain.

The development of DFP itself resulted from a search for oral agents in hope of improving compliance. In addition, the DFP-iron chelate carries no net charge and therefore has the potential to penetrate membranes and remove iron directly from cells, unlike the DFO- iron chelate which has a net positive charge. In cultured heart muscle, DFP has been shown to have rapid access to intracellular iron pools, whereas DFO does not[1]. Extensive clinical testing of DFP has shown the compound to be the most effective of the three clinically available iron chelators in preventing cardiac toxicity[4]. But side effects– including frequent gastrointestinal symptoms and idiosyncratic side effects such as erosive arthritis and severe agranulocytosis– has limited its use as a single agent, particularly in the United States where it is approved for compassionate use only.

Combination DFO/DFP therapy has been pursued as a way to limit the disadvantages of the agents as monotherapies as well as take advantage of possible additive or synergistic effects between the two. Clinical studies of the combination have taken two general approaches. In the sequential approach, DFO infusions are typically administered overnight for 2-3 days at its usual dose and oral DFP is taken on the other 5 days each week. When compared with DFO alone, the results have been mixed, with one trial showing no difference between the two regimens[5], while others have suggested the combination is more effective to be more effective in improving cardiac function, reducing serum ferritin, and increasing urinary iron excretion than DFO[6] or DFP[2] alone.

In protocols representing the “simultaneous” approach, DFP is usually taken on its usual daily schedule and overnight infusions of DFO occur over a variable number of nights per week. Studies using these protocols have for the most part also shown greater improvement in cardiac function with the combination than with single agents[7,8]. From the study by Evans, et al., it appears that maximal effect of the combination may be achieved with more directly simultaneous administration—a mixture of the two drugs given at the same time.

Overall results of the clinical studies of DFO/DFP combination therapy have led groups such as the International Committee on Chelation (ICOC) to recommend the DFO/DFP combination as first line therapy to prevent transfusion-related iron overload[9]. Other groups, such as the Italian Society of Hematology, for example, recommend DFO/DFP combination therapy as rescue therapy for patients who develop severe iron overload, defined as serum ferritin > 3,000 ng/ml, liver iron content higher than 45 mg/g or overt iron-related cardiomyopathy (e.g. left ventricular ejection fraction <55%, arrhythmias, cardiac failure)10.

Data like those provided by Evans, et al., promise to aid in refining dosing regimens that are even more effective at treating and preventing iron overload and cardiotoxicity. Additional studies examining the chelators’ interaction at the cellular level as well as their possible differential access to iron storage compartments within the body will further inform these efforts. How much these new regimens will contribute to the changing landscape of iron chelation therapy is not clear. The role of the other currently available oral chelator, deferasirox, also continues to be defined and head to head comparisons of deferasirox and DFO are ongoing, leading some to speculate that if deferasirox is successfully used in the type of patients who tended to be noncompliant with DFO in the past, it may prevent the need for rescue therapy altogether[11].

Regardless, most researchers agree that the iron chelation therapy is entering a new era which includes new approaches to combination therapy as well as a greater emphasis on individualized therapy[9]. Kinetic studies such as those conducted by Evans, et al. will continue

to be important in establishing a rational approach to evaluating and optimizing iron chelation protocols in the new era.

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