Chelation Therapy for Iron Overload

Gregory Szewczyk Literature Seminar February 13, 1997

A variety of inorganic materials regulate chemical processes within the body, and any change in their homeostatic concentration results in chemical imbalances that can be highly toxic.[1] The quintessentially toxic metals lead, mercury and arsenic are readily absorbed into the body and cause damage to the kidneys, liver and central nervous system.[2] The current treatment for metal intoxication is to administer chelating agents that complex the metal, and can be rapidly eliminated from the body.[2-5]

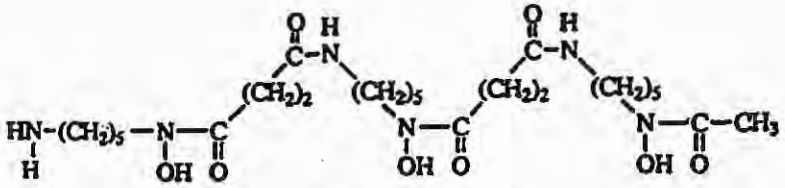
Iron is a metal that the body relies heavily upon for normal function. Approximately 4.2g are harbored within the body, the majority of which is bound to hemoglobin. Large increases in physiological iron content initiate the formation of hydroxyl radicals which attack the lipids in the body via the Fenton reaction.[6] The peroxy radical can then attack adjacent lipids propagating the reaction damaging tissue and organs.

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^- + \bullet OH$$

$$Lipid\text{-}H + \bullet OH \rightarrow H_2O + Lipid\bullet$$

$$Lipid\bullet + O_2 \rightarrow Lipid\text{-}O_2\bullet$$

Iron overload is not a trivial problem. In recent years there has been a two to three fold increase in the number of acute iron toxicity incidents among children aged six or younger who accidentally consume iron containing pills.[7] The two most prominent causes of iron overload are hemochromatosis and b-thalassemia (Cooley's anemia).[8] Both are genetic disorders which ultimately result in too much iron being stored within the body. Hemochromotosis generally affects 3-8 people out of 1000, and causes the body to store excessive amounts of iron (40-70 mg/kg body weight). In b-thalassemia there is unbalanced hemoglobin synthesis due to decreased synthesis of b-polypeptide chains. Blood transfusions are required to replace defective hemoglobin, but excessive iron storage quickly results in toxic levels.

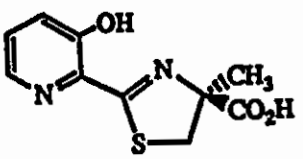


Deferoxamine B

Figure 1

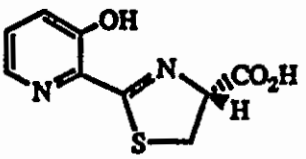
Currently, the only clinically approved treatment for iron overload is subcutaneous injection with deferoxamine B (Figure 1). Deferoxamine B is a trihydroxamate siderophore[9] that is isolated from *Streptomyces pilosus*. Recently a versatile organic synthesis has been published.[10] Mössbauer spectroscopy indicates that a complex is formed between Fe(III) and deferoxamine B while Fe(II) remains preferentially uncoordinated.[11] At physiological pH (7.4) a 1:1 hexadentate complex is formed ($K_f = 10^{30.5}$) with a spectrophotometric absorbance maximum at 425 nm. Lowering the pH causes the spectrum to shift to longer wavelengths indicating that the complex formed is now less than hexadentate.[12] The autoxidation of Fe(II) to Fe(III) produces hydroxyl radicals, and is accelerated in the presence of deferoxamine B.[13] Though deferoxamine had an extremely large LD_{50} (250mg/kg) optimal Fe(III) binding occurs when administered continuously in low doses.[14] A 10 year study of desferrioxamine treatment of patients with thalassemia shows that there is a general decrease of hepatic iron. Cardiac as well as other organ dysfunctions are mitigated indicating only small amounts of bodily damage could be attributed to deferoxamine promoted autoxidation.[15]

Improvements in therapy are required because deferoxamine B is not orally active and it has a relatively low plasma half-life. Attaching biocompatible polymers such as dextran has shown to increase plasma half-life 10-fold, and to raise the LD_{50} to approximately 4000mg/kg.[16] In order to circumvent the lack of oral efficacy derivatives have been synthesized that can remove iron more efficiently. Adding catecholate moieties to the amino terminus of deferoxamine B has demonstrated that the iron binding ability of deferoxamine B can be increased.[17]



DFT

Figure 2



NDFT

Figure 3

The need for an orally active chelating agent has caused scientists to turn to another siderophore: desferrithiocin (Figure 2).[18] Desferrithiocin is isolated from *Streptomyces antibioticus* and shown itself to be not only orally active, but a better iron chelator ($K_f = 10^{31}$) than desferrioxamine B.[19] Animals exposed to the drug suffered from nephrotoxicity which was ameliorated with lower dosage.[20] Nordesferrithiocin (Figure 3), a derivative that replaces the methyl group of desferrithiocin with a hydrogen atom shows a much lower toxicity while remaining orally active and having only a slightly reduced Fe(III) formation constant ($K_f = 10^{29}$).[21]

References

1. Kaim, Wolfgang; Schwederski, Brigitte *Bioinorganic Chemistry*: *Inorganic Elements in the Chemistry of Life*; John Wiley and Sons: Sussex, England, 1994.

2. Correia, Maria; Becker, Charles E., *Basic and Clinical Pharmacology*; Katzung, Bertram G., Eds.; Appleton and Lange: Norwalk, Connecticut, 1995.

3. Jones, Mark M., "New Developments in Therapeutic Chelating Agents as Antidotes for Metal Poisoning," *Toxicology,* **1991**, *21*, 209-233.

4. Bell, Colin F. *Principles and Applications of Metal Chelation*; Oxford University Press, 1977.

5. Bertini, I; Gray, H.B.; Lippard, S. J.; Valentine, J. S. In *Bioinorganic Chemistry*; University Science Books: Mill Valley, California, 1994.

6. Hallaway, Philip E.; Eaton, John W.; Panter, S. Scott; Hedlund, Bo E., "Modulation of Deferoxamine Toxicity and Clearance by Covalent Attachment to Biocompatible Polymers,"*Proc. Natl. Acad. Sci. USA*, **1989**, *86*, 10108-10112.

7. Berkovitch, Matitahu; Matsui, Doreen; Lamm, Steven H.; Rosa, Franz; Koren, Gideon, "Recent Increases in Numbers and Risk of Fatalities in Young Children Ingesting Iron Preparations," *Vet. Hum. Toxicol.*, **1994**, *36*, 53-55.

8. Linker, Charles A. In Current Medical Diagnosis and Treatment, Tierney, Lawrence Jr.; Eds.; Appleton and Lange: Stamford, Connecticut, 1996.

9. Raymond, K. N.; Muler, G.; Matzanke, B., "Complexation of Iron by Siderophores: A Review of their Solution and Structural Chemistry and Biological Function," *Top. Curr. Chem.*, **1984**, *123*, 49-101.

10. Bergeron, Raymond J.; McManis, James S.; Phanstiel, Otto; Vinson, J. R. Timothy, "A Versatile Synthesis of Deferrioxamine B," *J. Org. Chem.*, **1995**, *60*, 109-114.

11. Bock, Jay L.; Lang, George, "Mossbauer Spectroscopy of Iron Chelated by Deferoxamine," *Biochim. Biophys. Acta,* **1972**, *264*, 245-251.

12. Birus, Mladen; Bradic, Zdravko; Kujundziz, Nikola; Pribanic, Marijan, "Iron(III) Complexation by Desferrioxamine B in Acidic Aqueous Solutions. The Formation of Binuclear Complex Diferrioxamine B,"*Inorg. Chim. Acta,* **1983**, *78*, 87-92.

13. Klebanoff, Seymour J.; Waltersdorph, Ann M.; Michel, Bryce R.; Rosen, Henry, "Oxygen-based Free Radical Generation by Ferrous Ions and Deferoxamine," *J. Biol. Chem.*, **1989**, *264*, 19765-19771.

14. Propper, Richard D.; Shurin, Susan B.; Nathan, David G. *Symposium on the Development of Iron Chelators for Clinical Use*, U. S. Department of Health, Education, and Welfare, 1975.

15. Brittenham, Gary M.; Griffith, Patricia M.; Niehuis, Arthur W.; McLaren, Christine E.; Young, Neal S.; Tucker, Eben E.; Allen, Christopher J.; Farrell, David, E.; Harris, John W., "Efficacy of Deferoxamine in Preventing Complicatons of Iron Overload in Patients with Thalassemia Major," *N. Engl. J. Med.*, **1994**, *331*, 567-573.

16. Hallaway, Philip E.; Eaton, John W.; Panter, S. Scott; Hedlund, Bo E., "Modulation of Deferoxamine Toxicity and Clearance by Covalent attachment to biocompatible polymers," *Proc. Natl. Acad. Sci. USA*, **1989**, *86*, 10108-10112.

17. Hou, Zhiguo; Whisenhunt, Donnald W.; Xu, Jide; Raymond, Kenneth N., "Potentiometric, Spectrophotometric, and ^{1}H NMR Study of Four Desferrioxamine B Derivatives and Their Ferric Complexes," *J. Am. Chem. Soc.*, **1994**, *116*, 840-846.

18. Anderegg, G.; Raber, M., "Metal Complex Formation of a New Siderophore Desferrithiocin and of Three Related Ligands," *J. Chem. Soc., Chem. Comm.*, **1990**, 1194-1196.

19. Bergeron, Raymond J.; Wiegand, Jan; Dionis, John B.; Egli-Karmakka, Majia; Frei, Joerg; Huxley-Tencer, Alicia; Peter, Heinrich H., "Evaluation of Desferrithiocin and Its Synthetic Analogues as Orally Effective Iron Chelators,"*J. Med. Chem.*, **1991**, *34*, 2072-2078.

20. Bergeron, Raymond J.; Liu, Charles Z.; McManis James S.; Xia, Michael; Algee, Samuel E.; Wiegand, Jan, "The Desferrithiocin Pharmacophore," *J. Med. Chem.*, **1994**, *37*, 1411-1417.

21. Langemann, Klaus, Heineke, Daniel; Rupprecht, Stefan; Raymond, Kenneth N., "Nordesferrithiocin. Comparative Coordination Chemistry of a Prospective Therapeutic Iron Chelating Agent," *Inorg. Chem.*, **1996**, *35*, 5663-5673.