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Editorial Open Access

Iron Chelation Therapy for Treatment of Cardiac Hemochromatosis

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Editorial

Hemochromatosis is a clinical syndrome caused by abnormal accumulation of iron in parenchymal organs leading to organ toxicity and dysfunction. Cardiac hemochromatosis is a cardiomyopathy due to primary iron-overload cardiomyopathy which causes congestive heart failure. Patients with cardiac hemochromatosis may be asymptomatic early in the disease. Once heart failure develops, there is rapid deterioration. Cardiac hemochromatosis is characterized by a dilated cardiomyopathy with dilated ventricles, reduced ejection fraction, and reduced fractional shortening. Deposition of iron may occur in the entire cardiac conduction system, especially the atrioventricular node [1]. Cardiac hemochromatosis should be ruled out in patients with unexplained congestive heart failure.

Myocardial iron load can be quantitatively assessed by cardiac magnetic resonance imaging. Myocardial iron content is accurately predicted by the T2* relaxation time [2]. Aa T2* relaxation time greater than 20 milliseconds predicts a low risk for development of congestive heart failure. Aa T2* relaxation time between 10 and 20 milliseconds predicts a intermediate risk for development of congestive heart failure. These patients probably have myocardial iron deposition. A T2* relaxation time below 10 milliseconds predicts a high risk for development of congestive heart failure, and these patients need iron chelation therapy [3]. In a 662 patients with thalassemia major, congestive heart failure developed within 1 year in 47% of patients with a T2* relaxation time below 6 milliseconds, in 21% of patients with a T2* relaxation time of 6 to 10 milliseconds, and in 0.2% of patients with a T2* relaxation time more than 10 milliseconds [4]. Cardiac arrhythmias occurred within 1 year in 19% of patients with a T2* relaxation time below 6 milliseconds, in 18% of patients with a T2* relaxation time of 6 to 10 milliseconds, and in 4% of patients with a T2* relaxation time more than 10 milliseconds [4]. When the T2* relaxation time is below 20 milliseconds, left ventricular systolic function progressively worsens accompanied by increased left ventricular end-systolic volume and left ventricular mass [5].

Phlebotomy is not an option for treatment of patients with cardiac hemochromatosis who have anemia (secondary iron-overload disorders) or severe congestive heart failure [6]. The therapy of choice for these patients is iron chelation therapy [7]. The iron excretion rate is increased by iron chelating agents through their binding to the iron in plasma and tissues, thereby depleting the body of excess iron [8]. Serum ferritin levels must be monitored periodically. When the serum ferritin level reaches less than 1000 ng/mL, iron chelation therapy should be avoided because the adverse effects of nephrotoxicity, neurotoxicity, and hepatic toxicity from iron chelation therapy outweigh the beneficial effects of further lowering serum ferritin levels [9]. The 3 iron-chelating drugs approved by the United States Food and Drug administration for treatment of chronic secondary iron overload are deferoxamine, deferiprone, and deferasirox.

Deferoxamine is a hexadentate molecule which can bind directly to labile iron in plasma and in tissues including the heart [10]. Deferoxamine has a poor oral bioavailability and a short half-life. This drug is used as a subcutaneous or intravenous infusion. The recommended dose in adults is 40 to 50 mg/kg/day infused over 8 to 12 hours for 5 to 7 days per week. Therapy with use of deferoxamine therapy lowers myocardial iron content approximately 24%, delays onset of cardiac hemochromatosis, reverses early cardiac hemochromatosis, improves left ventricular function, and increases survival in transfusion-dependent patients who have thalassemia [11-14]. However, long-term compliance with use of deferoxamine is poor [15].

Deferiprone is an orally active bidentate iron chelator approved for treating iron overload in transfusion-dependent patients with thalassemia when current chelation therapy is inadequate. The initial dose of deferiprone is 75 mg/kg/day administered in 3 divided doses. The maximum dose of deferiprone is 99 mg/kg/day. Some studies have found that deferiprone is better than deferoxamine in lowering myocardial iron content [16,17]. Combination therapy with deferiprone plus deferoxamine has been found to rapidly lower iron overload and improve cardiac function in iron overload patients with congestive heart failure and unstable hemodynamics [18-20]. Compared to deferoxamine plus placebo, deferoxamine plus deferiprone reduced serum ferritin more (976 ng/mL from deferoxamine plus deferiprone to 233 ng/mL from deferoxamine plus placebo, $p < 0.001$) [20]. The combination of deferoxamine plus deferiprone also improved left ventricular ejection fraction and endothelial function more than deferoxamine plus placebo ($p < 0.001$) [20].

Deferasirox is a tridentate iron chelating drug with good oral bioavailability approved for treatment of iron overload resulting from recurrent blood transfusions. The initial oral dose of deferasirox given once daily is 20 mg/kg/day which can be increased to a maximum dose of 40 mg/kg/day [21]. Deferasirox lowers the serum ferritin level and lowers iron overload of the heart and liver [22-26]. Data from the thalassemia participants' enrolled in the Myocardial Iron Overload in Thalassemia network showed that the cohort of patients treated with oral deferiprone developed less myocardial iron burden and better global systolic ventricular function than the patients treated with oral desferasirox or subcutaneous desferrioxamine [17]. Treatment of cardiac hemochromatosis with phlebotomy plus desferasirox reversed congestive heart failure with severe left ventricular and right ventricular systolic dysfunction [27].

Newer iron-chelating agents that are being investigated for treatment of chronic iron overload disorders include silybin [28], DE ferritin [29], and starch conjugated deferoxamine [30]. The goal is to design an iron chelating agent that is 1) orally active, 2) can cross cell membranes, and 3) can remove iron from specific areas of the body

such as the heart, liver, endocrine organs, and brain, sparing the bulk of physiologically essential iron [31].

References

1. Aronow WS, Meister L, Kent JR (1969) Atrioventricular block in familial hemochromatosis treated by permanent synchronous pacemaker. Arch Intern Med 123: 433-435.
2. Wood JC (2009) History and current impact of cardiac magnetic resonance imaging on the management of iron overload. Circulation 120: 1937-1939.
3. Pepe A, Positano V, Santarelli MF, Sorrentino F, Cracolici E, et al. (2006) Multislice multiecho T2* cardiovascular magnetic resonance for detection of the heterogeneous distribution of myocardial iron overload. J Magn Reson Imaging 23: 662-668.
4. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, et al. (2009) Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 120: 1961-1968.
5. Cheong B, Huber S, Muthupillai R, Flamm SD (2005) Evaluation of myocardial iron overload by T2* cardiovascular magnetic resonance imaging. Tex Heart Inst J 32: 448-449.
6. Fabio G, Minonzio F, Delbini P, Bianchi A, Cappellini MD (2007) Reversal of cardiac complications by deferiprone and deferoxamine combination therapy in a patient affected by a severe type of juvenile hemochromatosis (JH). Blood 109: 362-364.
7. Kontoghiorghes GL, Eracleous E, Economides C, Koinagou A (2005) Advances in iron overload therapies: prospects for effective use of deferiprone (L1), deferoxamine, the new experimental chelators ICL670, GT56-25, LINA11 and their combinations. Curr Med Chem 12: 2663-2681.
8. Glickstein H, El RB, Link G, Breuer W, Konijn AM, et al. (2006) Action of chelators in iron-loaded cardiac cells: Accessibility to intracellular labile iron and functional consequences. Blood 108: 3195-3203.
9. Kontoghiorghes GL, Kolnagou A, Peng CT, Shah SV, Aessopos A (2010) Safety issues of iron chelation therapy in patients with normal range iron stores including thalassemia, neurodegenerative, renal and infectious diseases. Expert Opin Drug Saf 9: 201-206.
10. Olivieri NF, Brittenham GM (1997) Iron-chelating therapy and the treatment of thalassemia. Blood 89: 739-761.
11. Mamtani M, Kulkarni H (2008) Influence of iron chelators on myocardial iron and cardiac function in transfusion-dependent thalassaemia: a systematic review and meta-analysis. Br J Haematol 141: 882-890.
12. Davis BA, O'Sullivan C, Jarritt PH, Porter JB (2004) Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. Blood 104: 263-269.
13. Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, et al. (2004) Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. Br J Haematol 127: 348-355.
14. Pennell DJ, Carpenter JP, Roughton M, Cabantchik Z (2011) On improvement in ejection fraction with iron chelation in thalassemia major and the risk of future heart failure. J Cardiovasc Magn Reson 13: 45.
15. Modell B, Khan M, Darlison M (2000) Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. Lancet 355: 2051-2052.
16. Pepe A, Rossi G, Capra M (2010) A T2* MRI prospective survey on heart and liver iron in thalassemia major patients treated with deferasirox versus deferiprone and desferrioxamine in monotherapy (abstract 4267). Blood 116: 1731.
17. Pepe A, Meloni A, Capra M, Cianciulli P, Prossomariti L, et al. (2011) Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison determined by quantitative magnetic resonance imaging. Haematologica 96: 41-47.
18. Beris P1 (1995) Introduction: management of thalassemia. Semin Hematol 32: 243.
19. Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V (2010) Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol 148: 466-475.
20. Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, et al. (2008) Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. J Cardiovasc Magn Reson 10: 12.
21. Chirnomas D, Smith AL, Braunstein J, Finkelstein Y, Pereira L, et al. (2009) Deferasirox pharmacokinetics in patients with adequate versus inadequate response. Blood 114: 4009-4013.
22. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, et al. (2006) A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood 107: 3455-3462.
23. Pennell DJ, Porter JB, Cappellini MD, El-Beshlawy A, Chan LL, et al. (2010) Efficacy of deferasirox in reducing and preventing cardiac iron overload in beta-thalassemia. Blood 115: 2364-2371.
24. Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, et al. (2011) Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood 118: 884-893.
25. Pennell DJ, Porter JB, Cappellini MD, Chan LL, El-Beshlawy A, et al. (2012) Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with Î²-thalassemia major. Haematologica 97: 842-848.
26. Wood JC, Kang BP, Thompson A, Giardina P, Harmatz P, et al. (2010) The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores. Blood 116: 537-543.
27. Chow CH, El-Amm C, Liu W, Pastva S, Sipahi I, et al. (2013) Reversal of severe biventricular dysfunction from cardiac hemochromatosis with iron removal. Circ Heart Fail 6: e14-15.
28. Borsari M, Gabbi C, Ghelfi F, Grandi R, Saladini M, et al. (2001) Silybin, a new iron-chelating agent. J Inorg Biochem 85: 123-129.
29. Barton JC1 (2007) Drug evaluation: deferitrin (GT-56-252; NaHBED) for iron overload disorders. IDrugs 10: 270-281.
30. Harmatz P, Grady RW, Dragsten P, Vichinsky E, Giardina P, et al. (2007) Phase Ib clinical trial of starch-conjugated deferoxamine (40SD02): a novel long-acting iron chelator. Br J Haematol 138: 374-381.
31. Poggiali E, Cassinerio E, Zanaboni L, Cappellini MD (2012) An update on iron chelation therapy. Blood Transfus 10: 411-422.