Intravenous Iron Alone for the Treatment of Anemia in Patients With Chronic Heart Failure

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South East Thames Regional Ethics Committee and the United Kingdom National Research Ethics Service approved the study. Informed consent was obtained from all participants.

RESULTS

Sixteen anemic patients (Hb <12 g/dl) with stable CHF (age 68.3 ± 11.5 years, 12 men, 9 from the United Kingdom; and 7 from the United States) participated New York Heart Association (NYHA) functional class II and the remainder class III, left ventricular ejection fraction 26 ± 13% (mean ± SD) received a maximum of 1 g of iron sucrose by bolus intravenous injections over a 12-day treatment phase in an outpatient setting. Mean follow-up was 92 ± 6 days.

Hemoglobin rose from 11.2 ± 0.7 to 12.6 ± 1.2 g/dl (p = 0.0007), Minnesota Living with Heart Failure (MLHF) score fell (denoting improvement) from 33 ± 19 to 19 ± 14 (p = 0.02), 6-min walk distance increased from 242 ± 78 m to 286 ± 72 m (p = 0.01), and all patients recorded NYHA class II at study end (p < 0.02). Changes in MLHF score and 6-min walk distance related closely to changes in Hb (r = 0.76, p = 0.002; r = 0.56, p = 0.03, respectively). Of all baseline measurements, only iron and transferrin saturation correlated with increases in Hb (r = 0.60, p = 0.02; r = 0.60, p = 0.01, respectively). There were no adverse events relating to drug administration or during follow-up.

CONCLUSIONS

Intravenous iron sucrose, when used without concomitant EPO, is a simple and safe therapy that increases Hb, reduces symptoms, and improves exercise capacity in anemic patients with CHF. Further assessment of its efficacy should be made in a multicenter, randomized, placebo-controlled trial.

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Anemia co-exists in up to 55% of patients with chronic heart failure (CHF) (1), and retrospective analyses of therapeutic trials in CHF patients have found anemia at trial entry to be an independent risk factor for hospitalization and death (2). The combination of erythropoietin (EPO) and intravenous or oral iron has been shown to improve cardiac function, symptoms, and peak oxygen consumption in patients with CHF and anemia (3,4). Although intravenous iron alone increases and maintains hemoglobin (Hb) in patients with renal disease (5), there are no reported studies into the effects of intravenous iron alone in patients with CHF and anemia.

METHODS

Patient population. We conducted a prospective, uncontrolled, open-label study of the intravenous administration of iron sucrose (Venofer; Vifor, Switzerland) in patients with systolic heart failure and Hb ≤12 g/dl who had been stable on standard heart failure medication for ≥6 weeks.
RESULTS

Seventeen patients were enrolled, and 16 completed the study. The mean age was 68.3 ± 11.5 years, and 12 participants were men. Heart failure was due to coronary artery disease in 13, dilated cardiomyopathy in 2, and valve disease in a single patient. At study entry, 9 participants had NYHA class II symptoms, the remainder class III. Mean left ventricular ejection fraction was 26 ± 13%. All patients were taking loop diuretics, 15 were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 5 were taking beta-blockers, and 8 were taking aldactone. Mean follow-up was 92 ± 6 days. Fourteen patients received 5 doses (1,000 mg) of iron sucrose, and 2 patients received 3 doses (mean dose 950 ± 137 mg).

**Effect of iron sucrose on hematologic parameters.** Hemoglobin rose from 11.2 ± 0.7 to 12.6 ± 1.2 g/dl (p = 0.0007) (Fig. 1), serum iron from 9.2 ± 4.4 to 13.7 ± 4.8 μmol/l (p = 0.009), ferritin from 87 ± 113 ng/ml to 217 ± 185 (p = 0.004), and transferrin saturation from 16.0 ± 9.5 to 24.6 ± 8.4% (p = 0.009). Of all baseline measurements, only iron and transferrin saturation correlated with increases in Hb (r = 0.60, p = 0.02; r = 0.60, p = 0.01, respectively). Furthermore, when divided into tertiles according to change in Hb, patients demonstrating the greatest response were those with the lowest baseline iron levels (p = 0.006 vs. the tertile with the lowest response). Although there was no change in serum creatinine or calculated creatinine clearance (Cockcroft-Gault formula), there was a trend toward a fall in cystatin C concentration (1.71 ± 0.52 to 1.50 ± 0.53 mg/l, p = 0.08), suggesting improved glomerular filtration rate.

**Effect of iron sucrose on symptoms and exercise capacity.** At follow-up, all patients were in NYHA functional class II (p < 0.02 vs. baseline), and MLHF score also fell (denoting improvement) from 33 ± 19 to 19 ± 14 (p = 0.02). Mean 6MW distance increased from 242 ± 78 m to 286 ± 72 m (p = 0.01). Changes in MLHF score and in 6MW distance correlated strongly with increases in Hb (r = 0.76, p = 0.002 and r = 0.56, p = 0.03, respectively) (Fig. 2). Left ventricular ejection fraction did not significantly change (27 ± 12% at study end).

**GI pathology and response to iron sucrose.** Of the 14 patients that underwent GI endoscopy, 6 had gastroesophageal reflux disease, 1 peptic ulcer disease, and 1 a benign colonic polyp. The remainder had no identifiable disease. Those with GI pathology did not have lower serum iron, ferritin, or transferrin saturation at baseline nor did they demonstrate a greater increase in Hb compared with those without GI pathology (p = NS for all comparisons).

**Safety and tolerability.** Iron sucrose was well tolerated with no instance of local or systemic adverse reactions. During follow-up, no patients were hospitalized, and none died. There were no changes to loop diuretic dose, and there was no statistical difference between baseline and completion body weights.

**DISCUSSION**

This study demonstrates that intravenous administration of iron sucrose to patients with CHF and anemia results in a significant increase in Hb, a reduction in symptoms, and an improvement in exercise capacity. These effects were achieved without simultaneous EPO therapy.

Iron deficiency is present when transferrin saturation is <16% and ferritin <30 ng/ml (6). Seven patients (44%) in this study were iron deficient by these criteria, and they had the greatest response to iron sucrose (increase in Hb 2.1 ± 1.3 g/dl vs. 0.9 ± 1.0 g/dl in the iron replete group, p = 0.06). Iron status is also the leading determinant of EPO responsiveness in patients with chronic renal failure, and concomitant intravenous iron is an essential adjunct in this context. We found no association between GI pathology and iron deficiency or response to iron, suggesting dietary factors or malabsorption may also influence iron status in patients with CHF.
Given that the risk of death in CHF increases with small reductions in Hb (2), modest increases in Hb should confer significant clinical benefits. This is supported by the observations that peak oxygen consumption in CHF correlates with Hb levels (7), and the correction of anemia improves this measure of exercise capacity (4). The mean increase in Hb in this study was 1.4 ± 1.3 g/dl (range: −0.7 to +3.1 g/dl) for a treatment phase of just 5 to 17 days encompassing only 4 or 6 hospital visits. Others have recorded mean increases of 2.6 g/dl (3) and 3.3 g/dl (4) using a combination of EPO and iron in similar CHF groups. Although the EPO/iron combination may result in a greater response than iron alone, there are clearly individuals who have a dramatic hematologic and clinical response to the latter.

The fact that we recorded no adverse events relating to the administration of iron sucrose or during follow-up is consistent with other safety data concerning the use of this drug. After a total of 2,297 injections of iron sucrose in 657 patients with renal failure, Macdougall and Roche (8) reported adverse events in only 2.5%. All were short-lived, and no patient required hospitalization. Furthermore, iron sucrose appears safe in patients with known intolerance of other parenteral iron preparations (9).

Intravenous iron sucrose, without concomitant EPO, is a simple and safe therapy that increases Hb, reduces symptoms, and improves exercise capacity in anemic patients with CHF. Further assessment of its efficacy should be made in multicenter, randomized, placebo-controlled trials.

**Figure 2.** Relationships between change in hemoglobin and changes in Minnesota Living with Heart Failure (MLHF) score and 6-min walk (6MW) distance.

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**REFERENCES**