High dose intravenous iron: a note of caution

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Keywords: chronic kidney disease; high dose intravenous iron; toxicity

Introduction

The majority of patients with chronic kidney disease are anaemic. Iron deficiency should be corrected before treatment with recombinant human erythropoietin (rhuEpo) or novel erythropoiesis stimulating protein (NESP) is initiated. During maintenance rhuEpo or NESP therapy, iron supplementation is needed to prevent hyporesponsiveness to these drugs. On the other hand, iron supplementation is not without side-effects, particularly if high dose intravenous (i.v.) iron is administered.

Effects of iron overload on the cardiovascular system

Animal studies

In vivo studies showed that iron overload may result in cardiomyopathy, manifested by ventricular arrhythmias and heart failure [1]. Alterations of glutathione peroxidase activity and increases in cytotoxic aldehyde concentrations in the heart may contribute to iron-induced heart failure [1]. Extracellular hydroxyl radical formation is not responsible for iron-mediated cardiotoxicity [2]. This does not, however, exclude that myocardial iron toxicity is the result of free radical damage generated intracellularly. Experimental data demonstrate that vitamin E (\( \alpha \)-tocopherol) completely inhibits mitochondrial iron toxicity without affecting iron uptake or release. In contrast, the mild cardioprotective effect of ascorbate occurs in association with decreased cellular iron uptake [3].

Iron is an essential catalyst in the oxidation process. Macrophages require iron to oxidize low-density lipoprotein (LDL) cholesterol [4]. Rats fed a high-cholesterol, iron-deficient diet have lower levels of antibodies to oxidized LDL cholesterol, and less aortic atherosclerosis than rats fed a high-iron diet [5].

Iron overload augments the development of atherosclerotic lesions in rabbits on high-cholesterolaemic or normocholesterolaemic diet [6].

In contrast, a recent study by Kirk et al. [7] suggests that elevated serum and tissue levels of iron induced by a 2% carbonyl iron diet are not atherogenic in apoE-deficient mice. Dietary iron overload caused a 30% rise in plasma triglycerides and cholesterol, but reduced the severity of atherosclerosis by 50%. Failure to elevate hepatic levels of heme oxygenase mRNA (induced by oxidative insults) and of protein-bound dityrosine and ortho-tyrosine (markers of metal-catalyzed oxidative damage) also does not support the hypothesis that elevated levels of tissue iron promote LDL oxidation and oxidative stress in vivo [7]. However, iron overload in apoE-deficient mice was induced by the oral route, whereas it is probably the intravenous route of iron administration that is particularly dangerous in dialysis patients.

Iron status and cardiovascular disease in man

The amount of aortic iron deposition is directly associated with the severity of atherosclerosis [8], and cellular iron overload causes ventricular arrhythmia and heart failure [9]. Kiechl et al. [10] found a strong correlation between serum ferritin concentration and the likelihood of new carotid lesion formation along with the progression of atherosclerotic lesions present at baseline. Participants in the study, whose iron stores declined, showed less carotid atherosclerosis. The ratio of the serum concentration of transferrin receptor to that of ferritin (TfR/ferritin) correlates with the risk of acute myocardial infarction (AMI). Patients with TfR/ferritin ratios in the lowest tertile had almost three times the risk of AMI compared with patients in the top tertile [11]. A serum ferritin concentration of \( \geq 200 \mu g/l \) may double the risk of AMI in elderly patients, particularly in the presence of other risk factors such as hypercholesterolemia, diabetes and/or smoking [12]. However, the majority of human observational studies do not support the hypothesis that high levels of body iron stores increase the risk of coronary heart disease [13,14]. One possible explanation could be that serum ferritin in end-stage renal disease is not only elevated due to iron overload, but also due to infection or inflammation, which are additional risk factors for cardiovascular disease [15].

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Effect of iron depletion on cardiovascular disease

Experimental and human data suggest that iron depletion protects against ischaemic heart disease [16]. Even small elevations of serum ferritin are associated with an increase in carotid atherosclerosis in men and in women with intact kidney function [10]. Volunteer blood donation is associated with significant decrease in atherosclerosis and vascular events [17,18].

Iron may cause cardiovascular disease by oxidation of LDL cholesterol and/or endothelial dysfunction. Lowering of body iron stores by blood letting results in a 44% decline in serum ferritin concentration, a 20% decrease in maximal oxidation velocity, and a 33% increase in oxidation resistance [19]. Moreover, iron chelation by deferoxamine improves endothelial function in patients with coronary artery disease [20]. Iron depletion protects against ischaemic heart disease, explaining the low risk observed in menstruating women [21].

Genetic disease association studies

Homozygosity for the Cys282Tyr or the His63Asp mutation in the haemochromatosis gene (gene locus: HFE) confers a substantial risk for iron overload, whereas heterozygous individuals may present with slightly elevated iron stores [22]. Increased cardiovascular event rates were reported in individuals with an iron loading genotype [23–25]. The HFE Cys282Tyr mutation was associated with a relative risk factor for AMI of 2.3 in men [24] and with an increased risk for cardiovascular death in women [23]. However, several small studies did not find a relationship between HFE variants and cardiovascular disease [26,28], although Hetet et al. reported some effect of HFE His63Asp mutation on carotid atherosclerosis of smokers [27]. Furthermore, Rossi et al. [26] could not find an association of HFE Cys282Tyr with carotid artery plaque formation, but subgroup analysis showed some effect of ferritin levels on atherosclerosis in women [26]. A small study also failed to show an association of both HFE mutations on premature atherosclerosis [28]. Thus, controversy still exists regarding the association of iron loading genotypes with cardiovascular disease outcomes.

Ferritin levels and cardiovascular disease in end-stage renal disease

Iron potentially contributes to cardiovascular complications in end-stage renal disease patients. Serum ferritin is a marker for morbidity and mortality in haemodialysis patients. An elevated serum ferritin concentration is a strong predictor of hospitalization, and an increase of 500 μg/l in serum ferritin is associated with a 2.7-fold relative risk of death [29]. In our experience, haemodialysis patients with serum ferritin >600 μg/l do show an increased overall 4-year mortality, even in the absence of elevated C-reactive protein [30]. Another study involving 5833 haemodialysis patients showed that patients who received more than ten 100 mg doses of i.v. iron over 6 months had a higher relative risk of hospitalization (1.12 vs 0.92) and death (1.11 vs 0.93) than haemodialysis patients receiving 10 or less doses of i.v. iron [31].

Effect of vitamin E on iron-induced changes

A single oral dose of vitamin E attenuates lipid peroxidation in patients on haemodialysis receiving i.v. iron [32]. Vitamin E therapy reduces composite cardiovascular disease end-points and myocardial infarction in maintenance haemodialysis patients [33].

Acute adverse events of high-dose intravenous iron

The use of parenteral iron dextran may result in anaphylactoid reactions occurring even at test doses. On the other hand, a negative dextran allergy test does not mean the patient will not have a reaction in the future [34]. A recent study [35] demonstrates the safety and efficacy of iron sucrose in 23 haemodialysis patients with hypersensitivity reactions to iron dextran. A total of 16 patients experienced mild reactions to iron dextran and seven patients developed severe complications such as hypotension with dyspnoea, or heart arrest (n=5) and bronchospasm, cough or dyspnoea (n=2). The authors prospectively examined adverse events and vital signs after administering 100 mg of i.v. iron sucrose in each of 10 consecutive dialysis treatment sessions. No serious adverse drug reactions after a total of 223 doses of iron sucrose were observed in these dialysis patients with hypersensitivity to iron dextran. Self-limited episodes of metallic taste occurred in one patient and apparent infusion rate-related pruritus occurred in another patient. It was concluded that iron sucrose at a dose of 100 mg can be administered safely and effectively by i.v. push (5 min) or infusion (15–30 min) without a test dose [35]. Hoigne et al. [36] analysed 160 000 doses of 100 mg iron sucrose administered to patients undergoing regular haemodialysis, calculated as 8100 patient-years. No cases of life-threatening adverse reactions occurred. There were five to seven instances of rapidly reversible hypotension, 10 cases of flushing, one case of urticaria and one case of vomiting with diarrhoea [36].

An allergy event reporting rate of 3.3 cases per million doses per year has been published for iron gluconate, compared with a rate of 8.7 reported allergy events per million doses per year for iron dextran. There were no reported fatalities with iron gluconate among the reports of allergic events, in contrast to 31 fatalities among the 196 allergy/anaphylaxis cases reported with iron dextran [37]. In a prospective, cross-over, blinded, placebo- and historically controlled study, 1117 maintenance haemodialysis patients were treated with both placebo and a single bolus of 125 mg iron gluconate. Of these patients, 73 (6.5%) had a history of hypersensitivity to iron dextran. The rate of
blinded ‘life-threatening’ reactions was 0.09% (1/1117), indicating an important advance using iron gluconate as compared with iron dextran [38].

In the study by Prakash et al. [39], peritoneal dialysis patients received either iron dextran or iron sucrose infusions of 500 mg each, twice, 1 week apart. Both iron preparations were infused over 4–5 h if the patient remained asymptomatic after a test dose. One anaphylactic reaction was observed in each group. It is, however, unclear whether the severe adverse event occurring in one of the iron sucrose-treated patients was related to this iron preparation per se or to the large dose of iron sucrose administered. There was a trend toward increased peritonitis rates after high-dose iron infusions during the 6-month study period. According to Chandler et al. [40], iron sucrose doses up to 300 mg may be given safely over 2 h, but doses of 500 mg should be administered as an infusion over ≥3.5 h. Side effects (vertigo, hypotension, lumbago, vomiting) occurred in 0.9% of the patients receiving 100 mg iron sucrose over a period of 10 min, but in 5.9% of the patients receiving 200 mg iron sucrose. Slower administration of this iron sucrose dose did not lead to any side effect [41].

Iron overload and disturbed host defence

Finally, iron affects both bacterial virulence and host defence mechanisms, since iron is an important growth factor for bacteria and a prerequisite for clinically important infections. We found a significant inhibition of intracellular killing of bacteria by polymorphonuclear leukocytes in haemodialysis patients with serum ferritin levels > 650 μg/l (mean value 912 μg/l) [42].

Conclusion

Epidemiological data suggest that iron is an important factor in the process of atherosclerosis, but the exact mechanism and the sites of the interaction between macrophages, endothelial cells, iron and low-density lipoprotein are still unknown [43]. The ‘iron hypothesis’, suggesting that iron depletion protects against ischaemic heart disease, is biologically plausible [44]. On the other hand, end-stage renal disease patients require adequate iron therapy to benefit from treatment with rhuEpo or NESP. Optimizing the monitoring of iron parameters includes the determination of the percentage of hypochromic red blood cells [45] and/or the reticulocyte haemoglobin content [46], in addition to ferritin and transferrin saturation. This may allow correction of renal anaemia on an individual basis, thereby lowering the iron need per patient and hopefully reducing acute adverse events and long-term complications of iron therapy.

References

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