Safety of intravenous injection of iron saccharate in haemodialysis patients

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Abstract
Background. The most frequent i.v. iron preparations used for haemodialysis patients are iron dextran, iron gluconate and iron saccharate. Possible side effects include anaphylactic reactions due to preformed antibodies to dextran or vascular reactions due to unbound iron during treatment with iron gluconate or iron saccharate.

Methods. Four dosage regimens of i.v. iron saccharate therapy were studied: 10, 20, 40 and 100 mg, which were given over a time period of 1 min after the end of the dialysis session. Iron metabolism parameters (serum iron concentration, transferrin saturation and serum ferritin levels) were measured at 0, 1, 5, 15 and 30 min after application and immediately prior to the next dialysis session. All 18 regular haemodialysis patients studied received recombinant human erythropoietin (rHuEpo).

Results. Serum iron levels and transferrin saturation increased significantly following i.v. injection of all doses of iron saccharate. Iron 'oversaturation' of transferrin iron binding did not occur in patients with transferrin levels >180 mg/dl. However, in patients with transferrin levels <180 mg/dl the injection of 100 mg iron saccharate resulted in a transferrin saturation of 102.6±39.5% (two patients with transferrin levels of 87 and 92 mg/dl had transferrin saturations of 119.8 and 149.7%, two patients with transferrin levels of 148 and 171 mg/dl had transferrin saturations of 77.9 and 63.1%, respectively). Serum ferritin levels remained unchanged during the post-injection period and increased by the next dialysis session following injection of 100 mg iron saccharate by 165%.

Conclusion. It is concluded that intravenous iron saccharate injection (10–100 mg even within 1 min) does not result in 'oversaturation' of transferrin iron binding if serum transferrin levels are >180 mg/dl (high-risk patients: transferrin <100 mg/dl). This may explain, at least in part, the minimal side effects observed during the i.v. application of iron saccharate.

Key words: erythropoietin; iron saccharate; transferrin saturation; ferritin; haemodialysis

Introduction

The routine administration of i.v. iron in renal failure patients was advocated early in the pre-rHuEpo era, based on the fact that dialysis patients lose large amounts of blood [1,2]. Eschbach et al. [3] pointed out that i.v. iron therapy may result in iron overload and/or anaphylactoid reactions. Therefore, oral iron therapy was recommended for all renal failure patients and i.v. iron was reserved for patients who did not tolerate oral iron preparations, who were unreliable, and whose serum ferritin levels fell despite oral iron ingestion. The first clinical studies using rHuEpo to correct renal anaemia of haemodialysis patients indicated that large amounts of iron are required for efficient haemopoiesis [4,5]. It is now well established that depletion of iron stores and development of absolute and/or functional iron deficiency represent the most important reasons for hyporesponsiveness to rHuEpo therapy in haemodialysis patients.

Absolute and functional iron deficiency might be overcome by oral iron substitution. Most of the clinical studies using oral iron formulas failed to replenish or maintain iron stores in haemodialysis patients. Several recent clinical studies have clearly demonstrated that i.v. iron therapy in haemodialysis not only maintains iron stores, but also results in a decrease of required rHuEpo dosage [6,7]. A recent consensus report recommended i.v. iron therapy for haemodialysis patients with absolute or functional iron deficiency [8].

The most frequently used i.v. iron preparations are iron dextran, iron gluconate and iron saccharate. However, many physicians are reluctant to use i.v.
iron preparations due to possible life-threatening side effects. In some countries i.v. iron preparations have been withdrawn from the market. The side effects of i.v. iron preparations can be caused by anaphylactic reactions due to preformed antibodies to dextran, which is mainly used in the UK and North America. Another possibility is the toxic effect of excess iron which might be released by less stable iron complexes such as iron gluconate. Recently, Zanen et al. [9] demonstrated the possibility of ‘oversaturation’ of transferrin during i.v. iron gluconate therapy in haemodialysis patients.

The aim of the present study was to evaluate the safety of i.v. injection of iron saccharate at a dosage of 10, 20, 40 or 100 mg, and the resulting serum iron concentration, transferrin saturation and serum ferritin levels in haemodialysis patients.

Subjects and methods

Patients

Eighteen patients (mean age 55±15 years, 8 females, 10 males) undergoing regular haemodialysis treatment were studied. Primary kidney disease was unknown in five patients, five patients suffered from chronic glomerulonephritis and two patients from diabetic nephropathy. Haemolytic uraemic syndrome, Orelaransus intoxication, Goodpasture syndrome, analgesic nephropathy, vascular nephropathy and pyelonephritis were the causes of end-stage renal disease in the other six patients. None of the patients had evidence of iron overload, infection, inflammation or malignancy. Erythropoietin (Erypo, Cilag, Austria) dosage in all 18 haemodialysis patients was adjusted to achieve a target haemoglobin level of 11 g/dl. The patients included in this study had been on thrice weekly low-dose i.v. iron therapy prior to the begin of this study. All patients had stable haemoglobin values and showed no adverse reaction to previous iron saccharate injection. Informed consent was obtained from all patients.

Iron administration

Four regimens of i.v. iron therapy were used: 0.5 ml (10 mg iron), 1 ml (20 mg iron), 2 ml (40 mg iron) and 5 ml (100 mg iron) of iron saccharate (Ferrivenin, 100 mg/5 ml amoule, Laevosan, Austria). Iron saccharate was injected into the venous lumen of a permanent dialysis catheter or into the venous dialysis needle after the end of the dialysis session. A 10 ml syringe was filled with the appropriate amount of iron saccharate, the syringe was connected to the catheter or to the dialysis needle, the patient’s blood was aspirated to yield a volume of 9 ml, followed by injection (approximately 1.5 ml/10 s) in a continuous infusion for 1 min.

Iron metabolism parameters were measured at 0, 1, 5, 15 and 30 min and immediately prior to the next dialysis session. Blood samples were drawn either from the arterial lumen of a central venous catheter or from the arterial dialysis needle avoiding tourniquet contraction. Blood pressure and heart rate were monitored in order to document potential adverse events during the 30 min after start of each iron injection.

Patients were randomized as follows: patient 1 received 10 mg iron saccharate, patient 2 100 mg, patient 3 20 mg, patient 4 40 mg, patient 5 received again 10 mg iron saccharate and so on. After the first investigations four patients refused to participate further in the following studies due to the time-consuming blood sampling procedure (these patients had not experienced any side effects of i.v. iron therapy). One patient was transferred to another haemodialysis unit. In summary, five of the 18 patients received all four doses, one patient three doses, eight patients two doses and four patients one dose of i.v. iron saccharate.

All four groups were comparable with respect to serum iron levels and transferrin saturation. The mean ferritin level in the 10 mg group was 228±137 μg/l, in the 20 mg group 320±136 μg/l, in the 40 mg group 274±155 μg/l, and in the 100 mg group 171±82 μg/l.

Laboratory parameters

Serum iron levels (normal range for females 40–150 μg/dl, for males 60–150 μg/dl) were measured on a BM Hitachi 747 analyser (Boehringer Mannheim, Mannheim, Germany). Serum ferritin (normal range for premenopausal females 8–120 μg/l, for postmenopausal females, 30–300 μg/l, and for males 18–440 μg/l) was determined turbidimetrically on a BM Hitachi 911 analyser (Boehringer Mannheim). Transferrin (normal range for females 180–405 mg/dl, for males 200–380 mg/dl) was measured on a nephelometric analyser (Behring AG, Marburg, Germany). Transferrin saturation was calculated as follows: serum iron (μg/dl) × 70.9/transferrin (mg/dl).

Statistical methods

Data were calculated as mean values ±SD. Differences of paired and unpaired data were calculated using Student’s t-test. P<0.05 was considered to be significant.

Results

Effect of i.v. iron saccharate on serum iron levels

Serum iron levels increased significantly in all four patient groups (Fig. 1). The mean serum iron level of the 10 mg group rose from 38.1±22.9 to 48.7±20.3 μg/l 1 min after injection (P<0.0005), to 43.3±21.9 μg/l 5 min after injection (P<0.0005) and to 40.0±22.7 μg/l 15 min following injection (P<0.05). At 30 min (39.6±21.1 μg/l) and prior to the next haemodialysis session (38.5±18.4 μg/l) serum iron levels did not differ from the serum iron concentration before iron saccharate injection. The mean serum iron levels of the 20 mg group rose from 56.0±34.5 to 74.6±36.1 μg/l (P<0.005) 1 min following iron saccharate injection and to 64.6±33.9 μg/l (P<0.05) after 5 min. At 15 (60.5±33.5 μg/l) and 30 (58.5±31.8 μg/l) min as well as prior to the next dialysis session (45.5±20.8 μg/l) serum iron levels did not vary from the serum concentration before iron saccharate injection. The mean serum iron levels of the 40 mg group rose from 45.3±18.4 to 87.2±26.4 μg/l after 1 min (P<0.0005), to 67.6±19.1 μg/l after 5 min (P<0.0005), to 56.5±18.5 μg/l after 15 min (P<0.005) and to 54.8±19.3 μg/l after 30 min (P<0.0005). Directly prior to the next dialysis session serum iron level did not differ from the serum concentration before iron saccharate injection (47.8±
30.0 μg/l). The mean serum iron levels of the 100 mg group rose from 44.9 ± 21.4 to 144.2 ± 28.7 μg/l after 1 min (P < 0.0005), to 120.4 ± 30.9 μg/l after 5 min (P < 0.0005), to 92.3 ± 25.4 μg/l after 15 min (P < 0.0005), to 80.4 ± 24.3 μg/l after 30 min (P < 0.0005) and to 55.7 ± 20.9 μg/l directly prior to the next dialysis session (P < 0.005).

**Effect of i.v. iron saccharate on transferrin saturation**

Transferrin saturation increased significantly 1 min (from 12.8 ± 8.6 to 16.4 ± 8.1%; P < 0.0005), 5 min (to 14.8 ± 8.7%; P < 0.0005), 15 min (to 13.5 ± 8.7%; P < 0.05) and 30 min (to 13.5 ± 8.5%; P < 0.05) after i.v. injection of 10 mg iron saccharate, but transferrin saturation values prior to the next dialysis session remained unchanged (13.0 ± 5.2%). Transferrin saturation increased significantly 1 min (from 20.0 ± 10.8 to 27.2 ± 12.3%; P < 0.0005), 5 min (to 23.6 ± 11.7%; P < 0.005), 15 min (to 21.7 ± 10.8%; P < 0.05) and 30 min (21.5 ± 11.2%; P < 0.05) following 20 mg of iron saccharate injection. Immediately before the next dialysis session transferrin saturation decreased to 18.8 ± 11.8%. Transferrin saturation of the 40 mg group increased significantly 1 min (from 18.8 ± 15.7 to 36.5 ± 22.9%; P < 0.0005), 5 min (to 28.3 ± 19.3%; P < 0.0005), 15 min (to 23.6 ± 17.4%; P < 0.005) and 30 min (to 23.0 ± 17.1%; P < 0.005) following injection of iron saccharate. Prior to the next dialysis session transferrin saturation was not different from the values before iron saccharate injection (22.2 ± 23.7%). Transferrin saturation of the 100 mg group increased significantly 1 min (from 20.4 ± 20.9 to 62.1 ± 39.4%; P < 0.005), 5 min (to 53.3 ± 35.8%; P < 0.005), 15 min (to 39.4 ± 26.8%; P < 0.005) and 30 min (to 35.2 ± 25.4%; P < 0.05) following iron saccharate injection as well as directly prior to the next dialysis session (to 24.6 ± 21.3%; P < 0.05) (Fig. 2).

The results for the 100 mg group could be subdivided as follows. Transferrin saturation was 38.9 ± 9.4% in seven haemodialysis patients with serum transferrin levels >180 mg/dl. In contrast, four patients with serum transferrin levels <180 mg/dl displayed a mean transferrin saturation of 102.6 ± 39.5% (Fig. 3). Two of these patients with very low transferrin levels (87 and 92 mg/dl) had very high transferrin saturation (‘oversaturation’) with values of 119.8% and 149.7%.

**Effect of i.v. iron saccharate on serum ferritin levels**

Serum ferritin levels remained unchanged during and immediately following i.v. injection of 10, 20, 40 and 100 mg iron saccharate (Fig. 4). A significant increase of ferritin levels up to 165% (171 ± 82 to 273 ± 124 μg/l;
Fig. 2. Time course of transferrin saturation following i.v. administration of 10, 20, 40 or 100 mg iron saccharate after haemodialysis (HD) treatment. *P<0.05 compared with 'minute 0'.

Fig. 3. Transferrin saturation (%) immediately before and immediately after i.v. injection of 100 mg iron saccharate in four patients with serum transferrin levels <180 mg/dl and in seven patients with serum transferrin levels >180 mg/dl. *P<0.05 pre- vs post-injection. In two out of the four patients with transferrin serum levels <180 mg/dl the individual calculated transferrin saturation exceeded 100% (these two patients were the only ones with serum transferrin level <100 mg/dl).

P<0.005) was observed following administration of 100 mg iron saccharate directly prior to the next dialysis session.

Adverse effects of i.v. iron therapy

We observed neither immediate (during the post-injection observation period of 30 min) nor late (until the next dialysis session) adverse effects following i.v. bolus administration of 10, 20, 40 or 100 mg of iron saccharate in this study. Even in patients in whom calculated saturation of transferrin exceeded the normal range, i.v. therapy was well tolerated which probably might be due to iron binding to other proteins (e.g. albumin).

Discussion

Low-dose i.v. iron therapy (20 or 30 mg iron gluconate per haemodialysis session) in rHuEpo-treated patients was first introduced by Allegra et al. [10]. A frequently used schedule is the administration of 100 mg iron every 2 weeks [5,11]. In one of our studies 10, 20, 40 or 100 mg of iron saccharate was given i.v. at each haemodialysis treatment. Using a weekly dose of 30–120 mg of iron saccharate the rHuEpo dosage
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could be reduced to and maintained at a 40% level compared with the rHuEpo dose before i.v. iron supplementation [6]. However, the frequent observation of side effects of i.v. iron preparations resulted in a restricted application in some dialysis centres. Hamstra et al. [12] observed severe immediate reactions in 0.1% of 2019 i.v. iron dextran administrations in 471 patients. Adverse effects of i.v. iron gluconate in haemodialysis patients prompted Zanen and colleagues [9] to study the immediate effect of i.v. iron gluconate on iron levels and transferrin saturation. They infused 62.5 and 125 mg of iron gluconate during the whole dialysis session and compared the results with a short infusion during the last 30 min of haemodialysis treatment. Iron levels increased during short-term infusion of both dosages and during long-term infusion of 125 mg iron gluconate. Consequently, the calculated transferrin saturation exceeded 100%.

In the present study i.v. injection of 10, 20, 40 and 100 mg iron saccharate, given over a period of 1 min after the end of the dialysis session, was demonstrated to be a safe therapy without risk of 'oversaturation' of transferrin iron binding in patients with serum transferrin levels > 100 mg/dl. 'Oversaturation' of transferrin indicated that calculated transferrin iron binding exceeded 100%. This did not necessarily imply that free iron circulated in the blood. Alternatively, it might be possible that iron was bound to other ligands such as albumin and/or other proteins. In an earlier publication [6] we referred to three out of 64 patients who experienced chest pain, loin pain or bronchospasm following administration of 100 mg iron saccharate. Therefore, it could be hypothesized that transferrin saturation transiently exceeded 100% in these patients.

One explanation for the different behaviour of iron kinetics following i.v. therapy with iron gluconate and iron saccharate might be the different stability of the iron complexes associated with variable binding of iron to other plasma proteins and disparities in iron uptake of the reticulo-endothelial system [13].

Iron can be administered intravenously without loss at any time of dialysis [14]. Additionally, an in vitro study showed that iron dextran clearance did not exceed 25 ml/min using nine different haemodialysers made of six different materials. Thus, a dosage regimen does not need to be altered to account for unanticipated removal by haemodialysis [15]. However, we want to stress that i.v. iron saccharate was given after the haemodialysis therapy in the present study.

In summary, bolus injection of 10, 20 or 40 mg iron saccharate after the end of the dialysis session resulted in a mild but significant increase of transferrin saturation. Even bolus injections of 100 mg iron saccharate did not result in 'oversaturation' of transferrin if serum

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**Fig. 4.** Time course of serum ferritin levels following i.v. administration of 10, 20, 40 or 100 mg iron saccharate after haemodialysis (HD) treatment. *P<0.05 compared with 'minute 0'.
transferrin levels exceeded 180 mg/dl (critical range 100–150 mg/dl, high-risk patients <100 mg/dl). Therefore, in high-risk patients low-dose i.v. iron saccharate therapy is recommended. Serum transferrin levels should be >180 mg/dl if 100 mg iron saccharate is given intravenously.

References


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