Variation in intravenous iron use internationally and over time: the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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ABSTRACT

Background. To examine patterns of intravenous (IV) iron use across 12 countries from 1999 to 2011.

Methods. Trends in iron use are described among 32 192 hemodialysis (HD) patients in the Dialysis Outcomes and Practice Patterns Study. Adjusted associations of IV iron dose with serum ferritin and transferrin saturation (TSAT) values were also studied.

Results. IV iron was administered to 50% of patients over 4 months in 1999, increasing to 71% during 2009–11, with increasing use in most countries. Among patients receiving IV iron, the mean monthly dose increased from 232 ± 167 to 281 ± 211 mg. Most countries used 3 to 4 doses/month, but Canada used about 2 doses/month, Italy increased from 3 to almost 6 doses/month and Germany used 5 to 6 doses/month. The USA and most European countries predominantly used iron sucrose and sodium ferric gluconate. A significant use of iron dextran was limited to Canada and France; iron polymaltose was used in Australia and New Zealand; and Japan used ferric oxide saccharate, chondroitin polysulfate iron complex and cideferron. Ferritin values rose in most countries: 22% of patients had ≥800 ng/mL in the recent years of study. TSAT levels increased to a lesser degree over time. Japan had much lower IV iron dosing and ferritin levels, but similar TSAT levels. In adjusted analyses, serum ferritin and TSAT levels increased significantly by 14 ng/mL and 0.16%, respectively, for every 100 mg/month higher mean monthly iron dose.

Conclusions. IV iron prescription patterns varied between countries and changed over time from 1999 to 2011. IV iron use and dose increased in most countries, with notable increases in ferritin but not TSAT levels. With rising cumulative IV iron doses, studies of the effects of changing IV iron dosing and other anemia management practices on clinical outcomes should be a high priority.

INTRODUCTION

Appropriate anemia management remains a challenge for clinicians caring for patients with advanced chronic kidney disease (CKD), requiring balance in the use of erythropoiesis-
stimulating agents (ESAs) and intravenous (IV) iron. There are large international variations in ESA prescription patterns in hemodialysis (HD) patients [1–3]. Several factors have influenced ESA dosing patterns recently, including publication of the Normal Hematocrit trial, CREATE, CHOIR and TREAT [4–7], which advocate caution about prescribing ESAs to target near-normal hemoglobin concentrations and label changes, such as the US Food and Drug Administration’s recent labeling requirements regarding limiting ESA exposure [8]. The introduction of a new payment structure for HD in Japan resulted in lower ESA doses and an increase in IV iron use and a similar trend has been seen to date in the USA [9, 10].

It is well accepted by clinicians that an adequate supply of iron to HD patients is important. Judicious use of IV iron improves maintenance of hemoglobin and permits the use of lower doses of ESAs [11–14], although the resultant effect on patient outcomes has not yet been established. IV iron has also been recently studied for the treatment of iron deficiency and anemia associated with conditions such as inflammatory bowel disease, pregnancy and the post-partum period, heavy uterine bleeding, congestive heart failure, cancer- and chemotherapy-induced anemia, blood donation and bariatric and elective surgery [15–25].

Worldwide, clinicians have a choice of many IV iron products. Numerous factors may affect that choice, including national clinical practice guidelines [26–34], regulatory and marketing influences and different risks of adverse events (hypersensitivity, infection, mortality, oxidative stress) between products [35–45]. The optimal approach to IV iron therapy in dialysis patients is unknown. For example, the most effective and safe maintenance doses and dosing intervals and the correct ratio of ESA-to-iron dose are incompletely known, as are the risks of chronic, repeated exposure to IV iron. The most accurate blood markers of iron stores have not been established. There are inadequate studies to evaluate possible differences in efficacy and safety between various IV iron products. Thus, despite widespread use, IV iron prescription practices are likely to exhibit considerable international variation and little is known about these patterns.

As a precursor to an analysis of IV iron dosing patterns and clinical outcomes, this study analyzes data collected during sequential phases of the Dialysis Outcomes and Practice Patterns Study (DOPPS) to examine patterns and trends in IV iron use and markers of iron stores across 12 nations between 1999 and 2011.

**MATERIALS AND METHODS**

**Data source and study patients**

The DOPPS is an international prospective cohort study of HD practice patterns and outcomes, with detailed data collected on adult HD patients from representative national samples of dialysis facilities in 12 countries. Phase 1 of the DOPPS collected data from 1996 to 2001; Phase 2 from 2002 to 2004; Phase 3 from 2005 to 2008; and Phase 4 from 2009 to 2011 [46, 47]. Data collection began in Phase 1 in France, Germany, Italy, Japan, Spain, the United Kingdom (UK) and the USA; Phase 2 and beyond included these seven countries plus Australia, Belgium, Canada, New Zealand and Sweden. Ethics approval and informed patient consent were obtained according to local requirements. Patient-level clinical data were obtained by medical record abstraction. Data regarding demographic factors, comorbid conditions, laboratory values, years since end-stage renal disease (ESRD) onset and medication use and dosing were collected at study entry, with laboratory values and medications subsequently updated every 4 months.

For this analysis, data were from an October 1999 cross-section in Phase 1 and the initial cross-sections of randomly selected patients in Phases 2–4. Exclusion criteria included time on dialysis at study start <90 days and missing baseline IV iron dose, resulting in a study population of 32 192 patients.

The main predictor of interest was average monthly IV iron dose (mg/month), calculated from reported dose over the prior 4 months. For those receiving IV iron, the average monthly IV iron dose amount was restricted to 20 to 1000 mg; doses outside this range were capped at the lower limit (0.64% of sample) or the upper limit (0.54% of sample). The average number of monthly doses was calculated similarly to the average dose amount. Type of IV iron preparation was not reported in Japan or the USA during Phase 1; otherwise, only one preparation type was specified per patient. Transferrin saturation (TSAT) values were not collected in Phase 1.

**Statistical methods**

Standard descriptive statistics were used to display trends in IV iron use and dose. Analyses of the association of IV iron dose with subsequent ferritin and TSAT values used data from Phases 2–4, the average IV iron dose amount during the first 4 study months and ferritin and TSAT values from 4 months later. Generalized Estimating Equations [48] were used to account for facility clustering in multivariate models; adjustment of the models included baseline age, sex, race, body mass index, time on dialysis at study start, catheter use for vascular access, ESA dose, hemoglobin, single pool Kt/V, albumin, creatinine, white blood cell count, and comorbidities (coronary artery disease, cancer, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurologic and psychiatric disorders, peripheral vascular disease and recurrent cellulitis).

Statistical analyses used SAS software, Version 9.2 (SAS Institute; Cary, North Carolina, USA).

**RESULTS**

**Iron use**

IV iron was administered to 50% of patients over a 4 month period in Phase 1, increasing to 71% in Phase 4. The percentage of IV iron use rose from 1999 to 2011 in most countries and varied widely by country; in Phase 4, use in Japan was 36% but, among the other countries, use ranged from 70% in Australia–New Zealand to 90% in Belgium (Figure 1a). Figure 1b shows the distributions of the percentage of patients within facilities that were prescribed IV iron by country in
Phase 4, demonstrating large differences in prescribing patterns between facilities.

**IV iron products**

There was large variation in the IV iron product used between countries and from phase to phase within some countries (Table 1). In the USA and most European countries, the predominant IV iron products used were iron sucrose and sodium ferric gluconate. Use of iron dextran exceeded 10% in Canada (all phases), France (Phase 4) and the USA (Phase 2). In some countries, the IV iron product use was relatively stable over time, e.g. the UK, Sweden and Belgium mostly used iron sucrose while Italy and Germany mostly used sodium ferric gluconate. Australia–New Zealand almost exclusively used iron polymaltose, which has limited availability in many other countries. Three products were favored in Japan: ferric oxide saccharate, chondroitin polysulfate iron complex and cideferron (the latter two were unavailable in the other countries). Other countries exhibited large swings from one product to another.

**IV iron dose**

Analysis of iron dose by country also reveals large differences. Figure 2a shows the average monthly IV iron doses (excluding patients receiving no IV iron). Overall, the mean monthly IV iron dose increased 21% from 232 mg in Phase 1 to 281 mg in Phase 4. Japan used the lowest monthly IV iron dose, and the quantity diminished over time from 185 to 123 mg/month from Phases 1 to 4. Dose in the USA stayed relatively stable, from 266 to 289 mg/month from Phases 1 to 4. The greatest increases in dose over time were seen in Italy, Spain and France, by 59, 51 and 49%, respectively, from Phases 1 to 4. In Phase 4, the countries using the largest mean doses of IV iron were Italy (347 mg/month) and Belgium (315 mg/month). Figure 2b shows a large variation in the distributions of average monthly IV iron doses (among non-zero doses) across facilities in each country during DOPPS, Phase 4.

**Number of IV iron doses**

Figure 3a shows the average number of IV iron doses/month in patients receiving IV iron, by country and phase. Overall, the average number of doses increased marginally from 3.3 to 3.5 doses/month from Phases 1 to 4. International practice patterns varied widely. While most countries typically used 3 to 4 doses/month, facilities in Germany consistently used 5 to 6 doses/month; Italy increased from 3.2 to almost 6 doses/month. Canada consistently prescribed an average of ~2 doses/month. The dosing frequency was ~3.5 doses/month for iron sucrose, ~3.1 doses/month for iron dextran and ~5 doses/month for sodium ferric gluconate (most common in Germany and Italy). Figure 3b shows distributions of the facility average monthly number of doses administered to patients on IV iron, by country in Phase 4.

**Ferritin levels**

The mean baseline ferritin values by country and phase are shown in Figure 4a. The proportions of patients within facilities with serum ferritin values ≥800 ng/mL, by country in Phase 4, are shown in Figure 4b. Overall, there has been an increase in serum ferritin over time, but with considerable variation between countries. Some countries (e.g. the USA) had an increase in serum ferritin over time and others (e.g. France) experienced a decline in serum ferritin. The proportion of patients within facilities achieving serum ferritin values ≥800 ng/mL, by country in Phase 4, showed considerable international variation with higher facility median ferritin values observed in Australia and New Zealand, Germany, Sweden and the USA. There was a positive association between iron dose and subsequent serum ferritin values. Among patients receiving IV iron (N = 12 496), the serum ferritin levels were 14 ng/mL (95% CI = 9–20, P < 0.001) higher on average, after adjustment, for every 100 mg/month higher mean monthly iron dose. Exploring facility practices, Figure 4c (unadjusted) shows that patients in facilities with higher baseline facility mean IV iron doses had higher ferritin values. After adjustments, the serum ferritin levels were 49 ng/mL higher (95% CI = 33–65; P < 0.001) on average for every 100 mg/month higher facility mean IV iron dose.

**TSAT levels**

The mean baseline TSAT values by country and phase are shown in Figure 5a. Overall, there was very little difference in mean TSAT values over time, ranging from 27.5% in Phase 2 to 29.3% in Phase 4 and very little difference between
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Figure 2: (a) Mean IV iron dose (4-month dose, expressed as mg/month) among patients receiving IV iron, by country and study phase. (b) Distribution of within-facility mean IV iron dose, by country in Phase 4 (2010).

Figure 3: (a) Mean number of IV iron doses (over 4 months, expressed as number/month) among patients receiving IV iron, by country and study phase. (b) Distribution of within-facility mean number of IV iron doses, by country in Phase 4 (2010).

DISCUSSION

The treatment of anemia in patients with CKD continues to evolve. The use of IV iron is likely affected by a number of factors, including individual prescriber preferences, publication of key studies [4–7], changing or emerging clinical practice guidelines [26–34], changes in reimbursement incentives (such as bundling of dialysis-related injectable medications in Japan and the USA), availability of specific IV iron products and marketing influences. We have shown large variability internationally and over time in all facets of prescription practices: choice of product, choice of dose and frequency of administration.

In our most recent data from 2010, all countries except Japan administered IV iron to >70% of patients over 4 months. Furthermore, our data indicate greater IV iron use over time in all countries, except Belgium, Australia–New Zealand and Sweden, where the percentage of use remained fairly constant or decreased slightly from Phases 2 to 4. These data confirm and extend earlier DOPPS findings, which described wide international variation in IV iron use in 2002–03 [1]. Further, McFarlane et al. [3] examined international trends in anemia management in 11 countries, and showed that there were significant increases in mean monthly IV iron doses in Canada, France, Italy, Sweden and the UK, in mean weekly ESA doses in 9 countries and in mean hemoglobin from DOPPS 1 to 3. Additionally, the DOPPS examined trends in anemia management in Japan from before to after implementation of the bundling payment policy in April 2006 [9, 49]. Those data showed that the proportion of Japanese patients prescribed IV iron increased from 32 to 41% after the policy change. (A bundled payment system provides incentive for facilities to lessen the use of more costly medications, generally favoring approaches such as IV iron prescription to reduce dosing of more expensive ESAs.) Our current findings confirm that, while over time more Japanese patients were receiving IV iron, in Phase 4 the percentage not receiving any IV
Iron over a 4-month period was still much higher than elsewhere.

The quantity of IV iron given varied considerably from country to country. As well as having fewer patients who were prescribed IV iron, Japanese patients receiving IV iron were prescribed the lowest doses, with a median facility IV iron dose of 127 mg/month. Iron doses in Japan declined from Phase 1 to 3, followed by an increase in Phase 4. Although one plausible hypothesis for the lower iron doses in Japan could be the smaller average size of Japanese HD patients, we found that Japanese patients received the lowest milligram iron per kilogram of body weight dosing as well (data not shown). This confirms previous findings of a less aggressive approach to anemia management in Japan, where lower doses of ESAs are administered with lower achieved Hb values [49].

Countries also adopted different approaches to the frequency of IV iron administration. The average number of doses overall (among patients receiving IV iron) was roughly 3.5 doses/month, approximating once weekly administration. Some countries seem to prefer to administer IV iron using small, more frequent maintenance doses (e.g. ∼5 doses/month in Germany and Italy) and others use an approach based upon larger replacement doses given less frequently (Canada had an average dosing frequency of ∼2 doses per month). These trends may be dictated by differences in brands and prescribing information between countries. For example, both Germany and Italy predominantly used sodium ferric
gluconate, which is approved for use in doses of 62.5 mg in Europe but 125 mg in the USA.

Additionally, differences were noted in international choices of IV iron products, and there are interesting within-country trends over time. North American and European countries predominately used iron sucrose or sodium ferric gluconate. Australia and New Zealand used an iron polymaltose product, whereas only Japan administered a chondroitin polysulfate iron complex, ferric oxide saccharate and cideferron, none of which were available in the other countries. There was little use of iron dextran products, except in Canada, and the use in the USA declined sharply from Phase 2 to 3. The reasons for changes in product use over time between countries are speculative, although increasing appreciation of the hypersensitivity risks associated with the higher-molecular weight iron dextran likely contributed [35–37, 43–45]. Some data suggest that low-molecular weight iron dextran is associated with a lower risk for allergic reactions than high-molecular weight iron dextran [50]. Low-molecular weight iron dextran is approved for administration by so-called total dose infusion (TDI) in Europe, but not in the USA. Nevertheless, a recent review has suggested that TDI using low-molecular weight iron dextran may be advantageous in some circumstances (e.g. in home-based dialysis therapies), but whether this practice might become widespread is unknown [51]. Also, large dialysis chains mandate selection of specific products for huge numbers of HD facilities and patients. Changes in the use of products might continue, as recently available agents (e.g. ferumoxytol in the USA, ferric carboxymaltose in Europe, as well as iron similar products in some markets) may be adopted.

There is much published literature regarding the use and effectiveness of iron sucrose, dextran, polymaltose and sodium ferric gluconate. However, there is little English literature regarding the effectiveness of a chondroitin polysulfate iron complex (manufacture of which was discontinued in May 2008) and cideferron [34, 49, 52]. There are differences in the physicochemical properties between these IV iron products. Some (e.g. iron dextran) are ‘robust,’ where the iron is slowly released from the complex, resulting in a lower likelihood of a sudden elevation in non-transferrin bound iron after administration [53, 54]. One might speculate that such behavior may result in a lower risk of the development of oxidative stress than less robust colloids such as iron sucrose and sodium ferric gluconate. This may be offset, however, by an elevated risk of dextran-associated allergic reactions [35, 37, 43, 50].

Consistent with greater IV iron dosing, we observed an increase in ferritin levels over time in most countries. As expected, we also found that patients in facilities with greater IV iron dosing had, on average, higher serum ferritin values. In contrast, changes in TSAT levels over time and the associated increase with IV iron dose were less marked. The reason for the discrepant trends of ferritin and TSAT levels is uncertain. One hypothesis is that inflammatory states, common among HD patients and associated with high hepcidin levels, may divert administered iron into storage sites, further increasing ferritin concentrations, but having lesser effects on TSAT. Prescribers may be dosing iron to reach or maintain relatively high TSAT target ranges, resulting in increasing ferritin concentrations but modest, if any, increases in TSAT levels. Indeed, a recent study showed evidence of hepatic iron overload, using magnetic resonance imaging, among HD patients receiving IV iron, even when serum ferritin concentrations were within the target range [55]. Serum ferritin is significantly influenced by underlying inflammatory status and by liver disease, and a high serum ferritin does not necessarily indicate that stored iron will be readily available for erythropoiesis. It is known that both TSAT and serum ferritin concentrations have poor sensitivity and poor specificity as indicators of iron availability for erythropoiesis [56, 57].

The DOPPS study has many strengths. It incorporates a large sample size of HD patients from representative facilities in North America, Europe, Japan, Australia and New Zealand. With detailed and uniform data collection across participating countries, it is able to show alterations in prescribing practices over time, during which there were many observed changes in IV iron products. There are also several limitations. There were many missing TSAT values. The use of several newer IV iron preparations was not captured in detail; specifically, ferric carboxymaltose became available in some European countries in 2006 and ferumoxytol was approved in the USA in 2009, but their prescriptions may not have been captured in a particular study phase if they came into use after the start of the phase or if market penetration was very low. Also, we were unable to fully capture subtle differences in dosing patterns of individual IV iron products—this may be important given the possibility of differences in their potential for causing oxidative stress.

In conclusion, we report an overall increase in IV iron use and administered doses over time in this large international dialysis study, as well as substantial differences within and between countries in the prescription patterns of IV iron, including the proportion of patients treated, size of dose, dosing frequency, resultant total monthly dose and specific products selected. The safety of different IV iron prescribing practices has not been well studied. In light of ongoing increases in the use of IV iron that appear to be occurring along with changes in ESA prescribing information [58], recent payment pressures in the USA [10] and the nascent Kidney Disease: Improving Global Outcomes clinical practice recommendations [59], studies of the effects of changing IV iron dosing and other anemia management practices on clinical outcomes should be a high priority.

**CONFLICT OF INTEREST STATEMENT**

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advisory board and/or speaker of Abbott, Affymax, Amgen-Dompé, Ashai—Casei, Baxter, Bellco, Braun, Farmacosmos, Fibrogen, Fresenius medical Care, Gambro-Hospall, Genzyme, GSK, Roche, Sandoz, Shire, Takeda and Vifor. D.G. has been a consultant for Affymax, Allocure, Alnylam Pharmaceuticals, AMAG Pharmaceuticals, Amgen, Baxter, FibroGen, Rakth Therapeutics, Spectrum Pharmaceuticals and Xenon Pharmaceuticals. He holds stock options from Xenon Pharmaceuticals. N.M. received an educational grant from American Regent. M. and M.I. have no conflicts of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format. Some of these data were presented at the XLVII ERA/EDTA Congress, Munich, Germany, June 2010, and the American Society of Nephrology annual meeting, Denver, CO, November 2010.

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