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Intravenous delivery of iron dextran: 23 years-experience in a single institution

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ABSTRACT

Objective: To analyze the clinicopathologic characteristics of patients with iron deficiency anemia treated with intravenous iron in a Specialty Hospital.

Material and method: A retrospective study was performed including patients older than 15 years with iron deficiency anemia who were treated with intravenous iron dextran from 1987 to 2010. Clinical/electronic records of patients registered in the hematology service of the 20 de Noviembre Hospital, Mexico City, between July and August 2010 were included, obtaining the data requested in the data collection sheet to evaluate the following variables: sex, age, date of infusion, lab results with a period of no longer than 1 month ago iron administration, involving serum levels of hemoglobin (<12 g/dL in women and <14 g/dL in men to define the presence of anemia), hematocrit, mean corpuscular volume and hemoglobin percentage of corrected reticulocytes red cell distribution width (RDW), iron profile (serum iron, transferrrin, transferrin saturation index, total capacity and latent iron binding), ferritin and Perls staining.

Results: 761 infusions were done, 110 men and 651 women, average age 52 years, mean Hb and iron deficiency 8.7g/dL of 1,285mg/dL were performed. The main causes were diseases associated with lower gastrointestinal bleeding (48%), including those secondary to treatment (not chronic peptic rheumatological disease, rheumatologic disorders, arthropathy and hepatic cirrhosis) and abnormal uterine bleeding (27%). In 49% of cases there were at least 2 cases and 79% were administered multiple drugs, of these, 45% were potentially harmful to the gastrointestinal mucosa (NSAIDs, antiplatelet agents, oral anticoagulants and steroids) and 27% had polypharmacy (> 5 drugs). There were 111 patients in recurrent anemia, with an average of 3 infusions per patient in this group and an interval of 55 weeks. The number of reported serious adverse events was 0.26% and no cases of anaphylaxis or treatment-related death were found.

Conclusions: The main causes of iron deficiency anemia are associated with upper gastrointestinal bleeding diseases, although half of the cases have more than one cause, including administration of harmful drugs to the gastrointestinal mucosa and polypharmacy. There is a low incidence of severe anaphylactic effects with a high level of security.

Key words: iron deficiency anemia, iron dextran.

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Administración de hierro dextrán endovenoso: 23 años de experiencia en una sola institución

RESUMEN

Objetivo: conocer las características clínico-patológicas de los pacientes con anemia ferropénica tratados con hierro endovenoso en un Hospital de Alta Especialidad.

Material y método: estudio retrospectivo en el que se incluyeron pacientes mayores de 15 años de edad con anemia ferropénica tratados con hierro dextrán endovenoso atendidos entre 1987 y 2010. Se revisaron los expedientes clínicos electrónicos de los pacientes registrados en el Servicio de Hematología del Centro Médico Nacional 20 de Noviembre de la Ciudad de México de julio de 1987 a agosto de 2010 que cumplieran con los criterios de inclusión. Se obtuvieron los datos necesarios solicitados en la hoja de recolección de datos para evaluar las siguientes variables: sexo, edad, fecha de infusión, resultados de laboratorio con un lapso no mayor a un mes antes de la administración del hierro, que incluyeron concentraciones séricas de hemoglobina (cifra <12 g/dL en mujeres y <14 g/dL en hombres para definir la existencia de anemia), hematócrito, hemoglobina y volumen corpuscular medio, porcentaje de reticulocitos corregidos, ancho de distribución eritrocitaria, perfil de hierro (hierro sérico, transferrrina, índice de saturación de transferrina, capacidad total y latente de fijación de hierro), ferritina y tinción de Perls.

Resultados: se realizaron 761 infusiones, 110 hombres y 651 mujeres, con edad promedio de 52 años. La hemoglobina media fue de 8.7 g/dL y el déficit de hierro de 1,285 mg/dL. Las principales causas fueron enfermedades asociadas con sangrado del tubo digestivo bajo (48%), que incluyeron las secundarias a tratamiento (enfermedad ácido péptica, trastornos reumatológicos, artropatías crónicas no reumatológicas y cirrosis hepática) y el sangrado uterino anormal (27%). En 49% de los casos había al menos dos causas y 79% recibía múltiples fármacos; de éstos, en 45% eran potencialmente nocivos para la mucosa gastrointestinal (antiinflamatorios no estereoides, antiagregantes, anticoagulantes orales y esteroides) y 27% tenía polifarmacia (recibían más de cinco fármacos). En 111 pacientes hubo recurrencia de la anemia, con promedio de tres infusiones por paciente en este grupo e intervalo de 55 semanas. El porcentaje de efectos adversos graves reportados fue de 0.26% y no se encontró ningún caso de anafilaxia o muerte asociada con el tratamiento.

Conclusiones: las principales causas de anemia ferropénica son las enfermedades asociadas con sangrado del tubo digestivo alto, aunque la mitad de los casos tiene más de una causa, como la administración de fármacos nocivos para la mucosa gastrointestinal y la polifarmacia. Existe baja incidencia de efectos anafilácticos graves.

Palabras clave: anemia por deficiencia de hierro, hierro dextrán.

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BACKGROUND

Fifteen years ago, the National Public Health Institute of Mexico reported a 50.7% prevalence of iron deficiency anemia in a sample of 152 children between 6 and 36 months of age. On the other hand, Casanueva et al. conducted a review of 46 epidemiological, observational, clinical studies and government programs made between 1939 and 2005 to determine the prevalence of iron deficiency anemia in women of reproductive age in the last 6 decades, and they found that there is a decline from 39.6 to 15.5% for non-pregnant women, i.e. a decrease of >20% and a decrease of 10% in pregnant women, 35-25%, still a high prevalence.[1-8]

The latest information in our country about prevalence of anemia was obtained through the National Health and Nutrition Examination Survey conducted in 2006 (ENSANUT 2006) conducted by the National Public Health Institute. This information was obtained from a sample of 48,600 households, with a homogeneous distribution of gender, 52.1% of women and 47.9% men; the prevalence by socioeconomic status (SES) was also analyzed and an inverse relationship was found, i.e., the higher the socioeconomic level, the lower the prevalence of anemia, and it was reported 20% in the lower SES, and 14% in the higher SES.[7,9-11]

In our country and in the rest of the world there still exists an unjustified but generalized fear in relation with the use of iron dextran, this fear comes mostly from the anaphylactic effects described in the first forms of high molecular weight endovenous iron, a condition that had an impact on the safety profile.[12-14]

Until recently, iron dextran was the only parenteral iron presentation in the USA and Mexico.[15-17] Its main advantage is the ability to receive the total dose of iron deficiency in a single infusion and the possibility to perform intramuscular administration;[15] however, a disadvantage is a higher incidence of adverse effects as compared with other presentations.[16-19] (Table 1).

Various studies conducted to date have shown that, with the exception of high molecular weight iron dextran (HMWID), serious adverse effects that endanger life are rare.[18-20] Chertow et al., on a review of 14.9 million iron infusions of low molecular weight iron dextran (LMWID) administered over a period of two years (1998-2000), by far the study with the largest number of patients, found great variability in the frequency of reported adverse effects between 0.004-91%, which was attributed to the great clinical heterogeneity (different patient groups), sample size of the studies and different definitions of adverse effects; however, the number of serious adverse effects such as respiratory depression, anaphylactic reaction and death was low (9 deaths, 7 respiratory depressions and 28 anaphylactic reactions among the 14.9 million infusions studied).[19]

MATERIAL AND METHOD

A retrospective study was performed with patients >15 years of age diagnosed with iron deficiency anemia referred to the Department of Hematology of the 20 de Noviembre National Medical Center (CMN20N), Mexico City, who had been treated with intravenous iron dextran. Patients treated with oral iron or who had not accepted the intravenous treatment were excluded and patients with incomplete records were removed.

Clinical histories of patients registered in the Department of Hematology of the CMN20N from July 1987 to August 2010 and that met the inclusion criteria and the necessary data requested in the collection data sheet were reviewed.

Table 1. Adverse reactions and hypersensitivity of the several parenteral iron presentations

	Iron Dextran	Ferric saccharate	Ferric gluconate
Severe anaphylactic reaction	0.6-0.7%	0.002%	0.04%
Hypersensitivity index	0.2-3%	0.005%	0.4%
Hypersensitivity (per one million doses)	8.7	2.6	3.3
Adverse effects	Up to 50	Up to 36	Up to 35

The causes of iron deficiency anemia, primary indications for initiating an intravenous iron therapy, number of infusions performed in each patient and interval thereof were identified; this record was made individually to gain knowledge of the general data mentioned in the previous paragraph, as well as for knowing the number of drugs taken at diagnosis, each of which were recorded, those considered potential producers of gastrointestinal mucosal damage (NSAIDs, antiplatelet agents, anticoagulants, steroids and possible combinations) were classified and finally, the adverse effects record attributed to iron dextran infusion and number of cases that developed anaphylaxis and death was intentionally sought.

Iron deficiency was calculated based on the hemoglobin level that was documented with the following iron deficiency formula = (kgx75) x (0.45-[Ht/100]) +500 as well as the number of applications necessary to correct the same.

Statistical analysis

Statistical analysis was performed with SPSS v16 system. Nominal variables were expressed as percentages and numerical variables with central trend measures (mean ± SD and/or ranges). Demographic data and laboratory tests were expressed with mean, standard deviation, frequency and ranges, as appropriate.

In order to understand the relationship between nominal and numerical variables, Student T and Chi square tests were performed, and the statistical significance values that obtained a value of $p < 0.05$ were established.

RESULTS

From July 1987 to August 2010, 761 iron dextran infusions were documented: 110 in men and 651 in women, a total of 531 patients, of whom 420 required a single infusion and 111 received more than one, with an average of patient infusions of 3 (2-18) and an interval of 55 weeks (8-294) between them. The average age of the population was 52 years old (15-84) with a male:female ratio of 1:6, mean hemoglobin was 8.7 g/dL, iron deficiency average was 1,285 mg (700-2,380) and for diagnostic confirmation Perls staining in bone marrow was required only in 13% of cases. The baseline characteristics of the patients are shown on Table 2.

The main pathological entities that caused iron deficiency anemia were diseases that generate blood loss because due to upper gastrointestinal (GI) tract damage, or secondary to treatment (acid peptic disease, rheumatologic disorders, non-rheumatologic chronic arthropathy and liver cirrhosis) covering 48% of the cases. The second cause was gynecological diseases that generated abnormal uterine bleeding (AUB) with 27% of cases; in third place, were diseases that affected the lower GI tract (angiodysplasia, diverticular disease, hemorrhoids and other causes such as post-radiation proctitis) with 13% of cases and in the last place was for malabsorption disorders (including chronic non-specific ulcerative colitis and Crohn's disease) with 4% of cases and others,

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Table 2. Baseline characteristics of patients (n = 531)

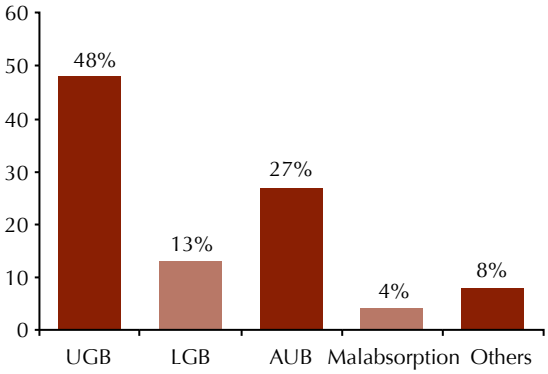
Variable	Result
Age (years)	52 (15-84)
Sex, no. (%)	
Men	110 (14.5)
Women	651 (85.5)
Hemoglobin (g/dL)	8.7 (4.1-12.5)
Hematocrit (%)	28.8 (15.7-40)
MCV (fL)	71.2 (51-98)
MCH (pg)	21.6 (13.2-32.9)
RCDW (%)	19.3 (13.5-33.1)
Transferrin (mg/dL)	336 (140-584)
TSI (%)	5.1(0.7-30)
Fe^{++} (µg/dL)	19.8 (4-80)
TBC (µg/dL)	427(211-781)
LBC (µg/dL)	407 (136-766)
Ferritin (ng/mL) *	7.8 (2-29)
Iron deficit	1285 (700-2,380)
Perls staining, no. (%)€	69 (13)

MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; RCDW: red cell distribution width; TSI: transferrin saturation index; Fe^{++}: serum iron; TBC: total binding capacity; CLF: latent binding capacity.
* Performed in 64 patients only.
€ Performed at diagnosis only.

among which the low iron intake, solid tumor malignancies, post-surgical subjects, hypothyroidism, etc., which represented 8% of cases. Iron deficiency associated with low iron intake alone was found only in 2 cases. (Figure 1 and Table 3).

In 49% of cases at least 2 causes of iron deficiency anemia were documented simultaneously in the same patient, and the diseases associated with upper GI tract bleeding plus gynecological diseases characterized by abnormal uterine bleeding by 33% of cases were the most common associations.

When dividing patients into groups according to the number of drugs taken at diagnosis of anemia, it was observed that 53% used <5 drugs, 26% >5 drugs and 21% used no drugs, i.e. almost 80% of cases routinely ingested drugs. Of these, in 45% of cases the drug used was a potential



UGB: upper gastrointestinal bleeding; LGB: lower gastrointestinal bleeding; AUB: abnormal uterine bleeding.

Figure 1. Main causes of iron deficiency anemia (n=531 patients).

Table 3. Main causes of iron deficiency anemia (n=531 patients)

Cause of anemia	No. (%)
Associated to upper gastrointestinal bleeding	**256 (48)**
Gastritis, hiatus hernia, gastric and duodenal ulcer	112 (21)
Rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis and others)	64 (12)
Non-rheumatic joint disease	27 (5)
Cirrhosis of the liver (portal hypertension/ esophageal varices)	53 (10)
Associated with lower gastrointestinal bleeding	**69 (13)**
Angiodysplasia	21 (4)
Hemorrhoids	12 (2.3)
Diverticular disease	18 (3.3)
Other causes of lower gastrointestinal bleeding	18 (3.3)
Gynecological diseases	**143 (27)**
Malabsorption (nonspecific chronic ulcerative colitis, Crohn's disease)	**21 (4)**
Other causes	**42 (8)**

cause of bleeding of the gastrointestinal mucosa, including 9% of cases that took a combination of them and the remaining 55% took other drugs. The average number of drugs taken was 3 per patient. Note that in neither case a GI mucosal protective drug was included.

The number of adverse events reported were only 2 (0.26%): one case of chest pain and another of dyspnea; it is worth noticing that the first event occurred in a patient with a history of ischemic heart disease and trivascular disease; however, in both cases symptoms disappeared when the infusion was stopped and finally, there were no reports of anaphylaxis or death associated with the infusions.

The correlation between the number of ingested drugs and the severity of the anemia had a p value of 0.07, and the correlation between the severity of the anemia and various etiologies had a p value of 0.9.

DISCUSSION

In our study we found that those pathologies that affect the upper GI tract were the main cause of iron deficiency anemia and they generated acute and chronic blood loss through various mechanisms which, in some instances, can be attributed to the disease and in others it may result from the treatment(s) employed, and in some other cases they were secondary complications associated with certain diseases (i.e. liver cirrhosis); these diseases affected almost half of our population (48%).

The second cause were gynecological disorders evidenced by abnormal uterine bleeding, mostly attributed to uterine adenomyosis or myomatosis, which represent just over a quarter of our population (26%). Therefore, in our experience the main cause of anemia in our patients were the losses higher than the daily iron intake and not the low iron intake as is the case in the general population; perhaps this is related in part to the socioeconomic status of our population corresponding to medium low/high as opposed to the low socioeconomic level of most of the subjects in the general population who develop this problem, based on the different literature reviewed.

On the other hand, since our patients were 15 years of age or older and presented rare diseases or sometimes multiple diseases simultaneously and require specialized attention it is far from being considered as a representative sample of the general population. Therefore, we do not seek to establish the main causes of iron deficiency anemia in our country, but we do venture that these may be the causes of iron deficiency anemia in patients requiring parenteral iron therapy to correct said deficiency in a third level Hospital, of which there are no comparable studies, at least in our country. Maslovsky et al. reported a series of cases in patients treated at a Primary Care Hospital and found that the main causes of iron deficiency anemia treated with parenteral iron were metrorrhagia and kidney failure with 36% and 24% respectively, and only 10% of cases were attributed to upper GI disease.[21] In Mexico, the main data are those published in the ENSANUT 2006,[9] which included subjects of all ages of various socioeconomic and levels in the general population, which found, as mentioned previously, a higher prevalence of anemia in children, a higher degree in early age and in women of reproductive age, with the highest incidence in pregnant women, in addition to the observation that there is a larger increase associated with age and low socioeconomic status. It should be noted that in this registry no pathological causes or etiology of anemia were reported.

A large proportion of our patients received initial treatment with oral iron without success, either because of adverse effects or lack of correction of anemia, which was the reason for iron dextran administration. Having said this, it is very interesting to note that almost half of our patients had more than one cause for the development of iron deficiency anemia and a little less than 10% had more than two causes simultaneously, it is also interesting that the main associated symptom was the presence of abnormal uterine bleeding and diseases related to upper gastroin-

testinal bleeding in one third of the cases and exclusively affecting females, i.e., one in three women. These findings support the complexity of the reasons that lead to the development of iron deficiency anemia in patients treated at high specialty hospitals, as well as the difficulty that exists in obtaining appropriate responses to "conventional" therapies based on oral iron, and the need for multiple iron infusions in some cases.

The average age in our population was over 50 years old, probably because they were subjects with chronic diseases that required long-term treatments. On the other hand, there was a clear predominance of females, which may be related largely to the leading causes of anemia found: gynecological disorders, rheumatic diseases, as well as certain lower gastrointestinal pathology as hemorrhoids, colitis, among others; but it is also worth noticing that despite this difference in gender, abnormal uterine bleeding was not the main cause of iron deficiency anemia as is common in the general population.

Drug intake seems to have an important role in the development of iron deficiency anemia, largely due to its relation to gastrointestinal bleeding which is the main cause of anemia found in our study, where we observed that over 75% the cases took at least one drug and in almost half of the cases it turned out to be a drug with potential harmful effects on the gastrointestinal mucosa (NSAIDs, antiplatelet, oral anticoagulant, steroids, etc.); even in a few cases (9%) there was a combination of these drugs, which undoubtedly further increased the risk of mucosal damage and bleeding, producing chronic losses through the upper gastrointestinal tract, which are known to be up to 3-4 mL/day which is equivalent to 1.5-2 mg iron/day, which in turn will finally cause anemia. In fact, by dividing patients according to the number of drugs taken at diagnosis it is observed that more than a quarter had polypharmacy, i.e. took >5 drugs, which may be related in the same way to the development of damage to the gastrointestinal mucosa and to the development of iron deficiency anemia, even though they are not identified as potentially damaging to the gastrointestinal mucosa. It should be mentioned that the use of protectors of the GI mucosa was not included in the analysis of the number of drugs used, but it should be noted that said group of drugs lowers gastric pH which certainly reduces iron absorption in the duodenum effectively, adding yet another mechanism to the development of iron deficiency anemia or lack of response to conventional treatment with oral iron.

The number of iron dextran infusions in most patients (420/531) was performed during a single hospitalization, but it is noted that when there was a deficit greater than 1,000 mg, which occurred in most cases because the average iron deficiency reported was 1,285 mg, the dose of iron dextran was split into two infusions given on consecutive days during the same hospitalization. However, in 20% of patients (111/531) it was necessary to perform multiple infusions with an average of 3 infusions per patient. Although in the majority of cases 2 infusions were performed, there were cases in which more than 10 infusions were administered required, mostly in patients with non-curable diseases and/or that required long-term treatment, thus creating a vicious cycle that did not eliminate the mechanism which caused anemia. Moreover, the interval between infusions in this latter group of patients was 55 months on average, i.e. >1 year, which supports the efficacy of iron dextran in the treatment of iron deficiency anemia, although it should be mentioned that there were isolated cases with intervals as short as 8 weeks and others over 5 years; in the first group, subjects with great losses were found who suffered from angiodysplasia of the gastrointestinal tract and those who presented multiple risk factors for developing concurrent anemia (multiple pathologies and treatments with drugs that damage the gastrointestinal

mucosa or increase the risk of bleeding). Thus, compared to other presentations of intravenous iron as ferric gluconate and ferric saccharate, iron dextran has a greater advantage and usefulness in patients with large iron deficit by shortening treatment and recovery time.

Finally, from the total number of infusions made, there were only 2 documented non-fatal adverse reactions: a case of chest pain in a patient with known ischemic heart disease with trivascular disease and one case of dyspnea in a patient with gonarthrosis; there were no cases either of anaphylaxis or death reported.

We found less than 1% of adverse events (0.26%), which in our opinion ensures iron dextran safety in the treatment of iron deficiency anemia. These findings are similar to those reported by Critchley et al.,[18] who conducted a systematic review of multiple studies where there is a low risk of adverse effects with low molecular weight iron dextran compared with high molecular weight iron dextran and ferric gluconate; likewise, Chertow et al.,[19] in the review of approximately 14.9 million iron infusions of various types, observed a low risk of severe reactions such as respiratory depression, severe anaphylactic reaction or death (<0.01%).

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