Intravenous iron and safety: is the end of the debate on the horizon?

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Iron is essential for the production of red blood cells and is the most common nutritional deficiency worldwide, both in developed and developing countries[1,2]. In medical, surgical and critically ill patients iron deficiency and iron-deficiency anaemia are frequent. The latter is associated with reduced quality of life, decreased physical and cognitive performance and adverse clinical outcomes, also because it increases the likelihood of allogeneic blood transfusion[3,4]. Nevertheless, the detection, evaluation, and management of iron-deficiency anaemia and iron-restricted erythropoiesis (formerly known as functional iron deficiency) still seem to be unmet medical needs[5]. In addition, although there is consensus that the objective of successful treatment of iron-deficiency anaemia is the adequate and quick supply of iron to increase haemoglobin levels to normal values within 4-6 weeks and to replenish iron stores, the route of iron administration is still a matter of debate[6].

As correctly pointed out by Auerbach and Macdougall in the review article published in this issue of Blood Transfusion[7], the argument is fostered by persistent safety concerns entrenched in "the misinterpretation and misinformation of the clinical nature of minor infusion reactions", exacerbated by the inappropriate or unnecessary use of premedication and by "inferences made about the relative safety of the available formulations" extrapolated from spontaneous adverse event reporting systems and not taking into account data from the most reliable method for a comparative safety analysis, namely a well-conducted prospective trial[8].

The limitations of spontaneous adverse event reporting systems have been identified by the U.S. Food and Drug Administration (FDA), which states that resulting data "cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population"[9]. In fact, "there is no certainty that the reported event (adverse event or medication error) was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event".

Frequently, intravenous iron remains an underutilised therapeutic tool even though oral iron may not always be able to restore iron levels quickly enough to avoid blood transfusion, or it may not be tolerated or may not be absorbed appropriately from the gastrointestinal tract, including in cases of hepcidin-mediated inhibition of oral iron absorption[10].

Recently, the European Medicines Agency (EMA) issued the "New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines"[11]. According to the EMA's Committee for Medicinal Products for Human Use (CHMP): (i) intravenous iron medicines are used when oral iron cannot be used or do not work, especially in dialysis patients, in the peri-operative period, or in the presence of gastrointestinal absorption disorders; (ii) the benefits of intravenous iron exceed its risks, provided that adequate measures are taken to minimise the risk of allergic reactions; (iii) data on the risk of hypersensitivity come mainly from spontaneous, post-marketing reports and the total number of life-threatening and fatal events reported is low; (iv) these data cannot be used to detect any differences in the safety profile of the different iron medicines.

As far as concerns the safety of intravenous iron preparations, Auerbach and Macdougall conclude that "based on all prospective and intra-institutional retrospective studies, when high molecular weight iron dextran is avoided the remaining formulations are safe, and probably much safer than most physicians realise"[7].

In this regard, we consider that the risk profile of pharmacological alternatives to allogeneic blood transfusion, such as intravenous iron therapy, should also be compared to the risk of death and major morbidity resulting from transfusion therapy. In fact, although haemovigilance and progress are improving transfusion safety, these events occur in association with, respectively, 1 in 322,580 and 1 in 21,413 components issued, as estimated from Serious Hazards Of Transfusion (SHOT) data in 2012[12].

The CHMP, being aware that "all intravenous iron preparations can cause serious hypersensitivity reactions which can be fatal", has stated that "all prescribers should inform patients of the risk and seriousness of a hypersensitivity reaction and the importance of seeking medical attention if a reaction occurs". The

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Committee has also produced the following information and recommendations for healthcare professionals with the aim of improving patients' safety: (i) intravenous iron should only be administered when both "staff trained to evaluate and manage anaphylactic and anaphylactoid reactions" and "resuscitation facilities" are immediately available; (ii) a test dose is no longer recommended; (iii) if a hypersensitivity reaction occurs, "healthcare professionals should immediately stop the iron administration and consider appropriate treatment"; (iv) "patients should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following each injection of an intravenous iron medicine"; (v) Intravenous iron-containing products are contraindicated in patients with hypersensitivity to a specific active substance, excipients, or other parenteral iron products; (vi) the risk of hypersensitivity is higher "in patients with known allergies or immune or inflammatory conditions and in patients with a history of severe asthma, eczema or other atopic allergies"; and (vii) "intravenous iron products should not be used during pregnancy unless clearly necessary" and they "should be confined to the second or third trimester, provided the benefits of treatment clearly outweigh the potential serious risks to the foetus such as anoxia and foetal distress".

Interestingly, iron deficiency is a common nutritional deficiency among women of childbearing age and, in this regard, a recent prospective study on intravenous ferric carboxymaltose for anaemia in pregnancy did not indicate a drug-related negative impact on the foetus, and, consistently with existing observational reports, showed that ferric carboxymaltose is safe and effective in this setting. The safety profile of intravenous iron was assessed and confirmed through the monitoring of foetal heart rate[13].

Although misinterpretation of adverse events caused underuse of this important treatment modality, intravenous iron has earned an undeniable, relevant role in blood saving protocols due to the large amount of available clinical and experimental data[14].

For this reason the value of intravenous iron in blood management is continuously and progressively increasing and its use is being recommended in several clinical settings by recently published evidence-based guidance documents such as the Spanish Consensus Statement on alternatives to allogeneic blood transfusion, namely the 2013 update of the "Seville Document"[15]. According to this multidisciplinary guideline the administration of *intravenous iron* is *recommended* for: (i) cancer patients, as an adjuvant to erythropoiesis-stimulating agents, for correcting chemotherapy-induced anaemia (grade 1A); and (ii) patients with post-partum anaemia or inflammatory bowel disease-associated anaemia (grade 1B). The use of intravenous iron is *suggested*: (i) in the perioperative period, for anaemic patients scheduled for orthopaedic, gynaecological or gastrointestinal surgery (grade 2B); (ii) without erythropoiesis-stimulating agents, for treating radiotherapy- or chemotherapy-induced anaemia in cancer patients (grade 2B); and (iii) for treating postoperative anaemia after cardiac, obstetrics and gynaecological or orthopaedic surgical procedures (grade 2C).

On the other hand, the administration of *oral iron* in the postoperative period is *not recommended* (grade 1B), and no recommendation could be made for iron therapy in critically ill patients.

In addition, it should be stressed that, unlike erythropoiesis-stimulating agents, intravenous iron has no major influence on the regulation of erythropoiesis (it will not increase haemoglobin levels beyond recommended ranges), but it does inhibit iron deficiency-induced thrombocytosis (it reduces platelet counts) and, therefore, does not increase thrombotic risk[16,17].

In conclusion, we believe that the article by Auerbach and Macdougall certainly makes useful reading for those clinicians who have been "taught that intravenous iron is dangerous"[7]. Moreover, as "for nearly half a century, parenteral iron has been considered dangerous and for use only in extreme situations and when oral iron was not tolerated"[18], we sincerely hope that it will not take as long to abandon these recommendations "supported by little more than folklore"[19] in favour of more robust and evidence-based guidelines such as those included in the aforementioned "Seville Document".

Conflict of interest disclosure

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