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COMMENTARY

Evaluating Plasma Pharmacokinetics of Intravenous Iron Formulations: Judging Books by Their Covers?

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Intravenous (IV) iron formulations provide a clinical treatment option for patients when iron supplementation is required but oral administration is unsuitable because of intolerance or lack of efficacy. IV iron use is increasing worldwide, especially in the chronic kidney disease (CKD) population [1]. Pharmacokinetic (PK) analysis of IV iron formulations is challenging unless the compound can be directly measured or it is manufactured with a radiolabelled form of iron (e.g. ^{59}Fe) to distinguish the IV iron formulation from endogenous serum iron [2]. It is also not well appreciated by clinicians that IV iron formulations exhibit zero-order or capacity-limited metabolism by the reticuloendothelial system [3]. This results in longer residence time in plasma with higher administered doses, especially with larger molecular weight formulations [3]. Commercially available IV iron formulations consist of an iron oxyhydroxide core surrounded by carbohydrate shells of various sizes and polysaccharide branch characteristics in colloidal suspensions [4]. The size of commercially available IV iron–carbohydrate complexes range from 5 to 100 nm and thus meet the definition for nanoparticles, enhancing the complexity of PK studies of these agents [4].

In this issue of *Clinical Pharmacokinetics*, Mueller-Plock et al. [5] evaluate plasma ferumoxytol data from healthy subjects and CKD patients, using a population PK approach seeking to bridge the PK profiles between populations with iron deficiency anaemia. This is arguably one of the larger PK analyses of IV iron plasma data to date, and ferumoxytol offers the distinct advantage of being able to be directly measured by nuclear magnetic resonance. The authors show that, as previously published, ferumoxytol plasma concentration–time profiles were best fitted with a two-compartment model with nonlinear elimination, consistent with the known capacity-limited metabolism by the reticuloendothelial system [3].

A limitation of Mueller-Plock et al.'s analysis, as well as the collective published data on IV iron plasma PK, is that these data likely represent an oversimplification of the PK profile of IV iron–carbohydrate complexes. Ferumoxytol is a superparamagnetic iron oxide nanoparticle (SPION), which was originally developed for use in magnetic resonance imaging (MRI). Biodistribution data for SPIONs demonstrate that different carbohydrate shell structures determine the relative uptake by endothelial and lymphatic cells, as well as by the reticuloendothelial system [6]. Thus, analysis of only short-term plasma PK provides limited information on the ultimate disposition and fate of these agents. Ultimately, the complexity of IV iron–carbohydrate nanoparticle formulations has important implications with regard to both efficacy and safety in treatment of iron deficiency anaemia. These agents have not been well studied with regard to comparative biodistribution, metabolic fate, and potential extracellular and intracellular deposition profiles, and further evaluation of these agents is urgently needed. Analysing short-term plasma data to infer IV iron–carbohydrate PK profiles has been typically acceptable for IV iron registry trials; however, on the basis of the SPION data in the MRI literature, these agents exhibit complicated PK and pharmacodynamic (PD) profiles, which can differ vastly between agents because of carbohydrate shell heterogeneity [6]. Thus, although short-term plasma PK profiles among groups of healthy and

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diseased subjects appear to exhibit little variability, there is a paucity of data studying repeated-dose administration and compartmental PK of IV iron formulations.

To evaluate factors that may affect ferumoxytol PK among healthy subjects and CKD patients, the authors incorporated several covariates into the proposed model [5]. Covariates included in the model were demographic data (age, body weight, body mass index, sex and ethnicity), healthy subjects versus CKD patients, clinical iron indices (serum iron, transferrin saturation, total iron binding capacity, unsaturated iron binding capacity and haemoglobin), receiving haemodialysis or not, and body weight loss during haemodialysis (pre–post body weight). While none of the baseline iron parameters exhibited a significant relationship to any of the model parameters, it must be recognized that iron indices used clinically to assess iron availability (i.e. transferrin saturation) and storage (i.e. ferritin) are actually of little value in assessing overall iron status [7]. Ferritin is an acute phase reactant and thus can be spuriously elevated in states of chronic inflammation, such as CKD [7]. This is especially relevant in haemodialysis patients, who have high inflammatory burdens. Serum concentrations of pro-inflammatory cytokines are highly elevated in haemodialysis patients, and this is associated with upregulation of hepcidin, a 25-amino-acid protein, which inhibits transport of iron from ferritin to transferrin, resulting in a syndrome known as reticuloendothelial blockade [7]. In the current ferumoxytol PK analysis, plasma concentrations of ferumoxytol increased slightly in haemodialysis patients post-administration [5]. The authors cite receiving haemodialysis treatment as the "plausible sole cause of the difference between populations" in their population PK model [5]. They suggest that a reduction in the volume of the central compartment by ultrafiltration during haemodialysis treatment is the probable reason for this observation. This could in fact be true; however, differences in the capacity-limited metabolism threshold induced by the dialysis process, background inflammation or the pro-inflammatory stimulus of the IV iron compound itself cannot be definitively excluded as playing a role in the unexpected short-term profile observed in haemodialysis patients [8]. Additionally, as noted by the authors, the observed dose-normalized concentrations up to only 20 h after the first dose post-administration are presented. Previously published PK data for ferumoxytol administered as two consecutive 510 mg doses administered 24 h apart have suggested that in healthy volunteers, linear elimination of this agent does not occur until approximately 5 days post-dose. This could be even more protracted in haemodialysis patients; however, the haemodialysis study data included in this analysis did not include time points after 96 h.

In summary, Mueller-Plock et al. [5] present a well-executed population PK meta-analysis approach to extrapolate findings in healthy volunteers and CKD patients to other populations with iron deficiency anaemia, given the comparable short-term PK between the two populations. As the authors themselves acknowledge, "more physiological approaches may be warranted to better describe the fate of the iron once it has been released from the ferumoxytol complex, including potential differences between healthy volunteer and CKD populations" [5]. As clinical use of these complex agents continues to increase, a judicious alignment of industry, regulatory bodies and clinicians is necessary to ensure that the PK and ultimate fate of IV iron formulations are adequately assessed to optimize safety and efficacy in patients receiving treatment for iron deficiency anaemia.

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