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Letter to the Editor

Cardiovascular outcomes of intravenous iron in perspective of clinical trials and the use of different iron preparations

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To the Editor:

In November 2014, an article by Kuo et al. [1] suggested a role of an intravenous (i.v.) iron sucrose preparation in leukocyte–endothelium interactions and atherogenesis based on results in cell culture assays, a mouse model and patients with chronic kidney disease (CKD). The authors reported that circulating mononuclear cells (MNCs) isolated from CKD patients who have received the iron sucrose preparation produced higher levels of intracellular superoxide than those from untreated CKD patients or healthy subjects. Also serum levels of soluble cell adhesion molecules were higher than in the control subjects. These results were corroborated by results in mice with uninephrectomy and by in vitro assays using cultured human aortic endothelial cells. Overall, the authors concluded that therapeutic iron may have a causative role in cardiovascular complications in patients with CKD.

This conclusion should be considered only with caution and in the context of the used iron preparation. Actually, a double-blind, placebo-controlled clinical study that investigated i.v. iron sucrose in anemic patients with CKD and chronic heart failure (CHF) did not report cardiovascular complications after 6 months follow-up but showed improvements in myocardial functional parameters (New York Heart Association [NYHA] score, 6-minute walk test) and cardiac dimensions in the i.v. iron group [2,3]. Recently presented 5-year follow-up data showed significantly lower hospitalization and mortality rates in the i.v. iron group [4]. In two other double-blind, placebo-controlled studies in patients with CHF and iron deficiency (FAIR-HF, CONFIRM-HF), i.v. iron (ferric carboxymaltose)-treated patients showed fewer hospitalizations for cardiovascular reasons in addition to significant functional improvements [5,6]. Based on the FAIR-HF results, the European Society for Cardiology considered i.v. iron for the treatment of iron deficiency in heart failure patients in its 2012 guideline and recommended an iron deficiency screening in all patients suspected of having heart failure [7].

Effects of different i.v. iron complexes (iron sucrose, ferric gluconate, iron dextran and ferric carboxymaltose) on oxidative stress and inflammation (i.e. established risk factors of cardiovascular outcomes in CKD patients) have been investigated in a head-to-head comparison in a non-anemic rat model [8]. Analysis of cardiac, renal and hepatic tissue samples in this study showed significant signs of oxidative stress and inflammation in response to ferric gluconate, a compound known to release high amounts of labile iron [9], whereas iron sucrose and ferric carboxymaltose showed no significant changes compared with saline control. Similarly, a study in CHF patients randomized to 16 weeks of iron sucrose or no treatment showed no difference in malondialdehyde levels (a marker of lipid peroxidation) between the two groups [10]. Notably, also a comparison of the iron sucrose originator product (Venofer®, Vifor Pharma, Switzerland) and six different follow-on preparations (better called iron sucrose similars) showed significant differences in oxidative stress and inflammatory response markers [11].

Based on information that is only available from the supplementary material of the Kuo article (Nang-Kuang Pharmaceutical mentioned as manufacturer of the used iron sucrose), we assume that an iron sucrose similar, namely Fe-Back, has been used in their studies [1]. In the head-to-head comparison of iron sucrose originator and iron sucrose similars [11], Fe-Back was associated with significantly greater increases in oxidative stress, markers of inflammation (tumor necrosis factor-α, interleukin-6), off-target iron deposition, elevation of liver enzymes and proteinuria than the iron sucrose originator. Physico-chemical analyses further revealed a three-fold higher molecular weight of Fe-Back compared with the iron sucrose originator (162 kDa vs. 45.7 kDa; requirement according to US Pharmacopeia is 34–60 kDa). This suggests that Fe-Back is either a very different molecule or forms substantial aggregates. Moreover, Fe-Back had a completely differently shaped polarogram compared with the originator product, indicating a very different redox behavior of the similar product, and also exhibited high lot-to-lot variability in physico-chemical parameters, which may result from variations in the manufacturing processes. Overall, Fe-back can hardly be considered pharmaceutically equivalent to the iron sucrose originator.

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Table 1
Markers of oxidative stress, nitrosative stress and inflammatory response in the aorta (Ao) and mesenteric arteries (MA) of non-anemic rats treated with iron sucrose originator, the iron sucrose similar Fe-Back or saline control (Day 28).

Mean SD	Iron sucrose(Venofer®) (n = 8)	Iron sucrose(Fe-Back) (n = 8)	Control(Saline) (n = 8)
MDA (μM/mg protein)			
A) Ao	3.3 ± 0.4	13.7 ± 0.9*	2.9 ± 0.5
B) MA	3.4 ± 0.5	14.1 ± 1.1*	3.0 ± 0.3
GSH/GSSG ratio			
A) Ao	6.1. ± 0.6	3.8 ± 0.3*	6.8 ± 0.5
B) MA	5.9 ± 0.5	3.5 ± 0.2*	6.6 ± 0.4
GPx (U/mg protein)			
A) Ao	296.3 ± 25.8	386.4 ± 21.1*	275.8 ± 20.2
B) MA	311.9 ± 17.9	394.0 ± 24.0*	300.6 ± 11.7
NT (% positive staining)			
A) Ao	1.1 ± 0.4	9.0 ± 1.3*	0.9 ± 0.3
B) MA	1.3 ± 0.5	9.3 ± 2.0*	1.1 ± 0.4
eNOS (% positive staining)			
A) Ao	2.3 ± 0.6	0.8 ± 0.4*	2.7 ± 0.7
B) MA	2.9 ± 0.3	0.6 ± 0.2*	3.0 ± 0.4
VCAM-1 (% positive staining)			
A) Ao	1.4 ± 0.5	6.9 ± 1.2*	1.1 ± 0.4
B) MA	1.5 ± 0.6	7.3 ± 1.1*	1.2 ± 0.3
IL-6 (% positive staining)			
A) Ao	1.8 ± 0.4	8.6 ± 2.3*	1.4 ± 0.3
B) MA	2.0 ± 0.3	10.5 ± 2.5*	1.8 ± 0.3

Ao aorta; eNOS endothelial nitric oxide synthase; GPx glutathioneperoxidase; GSSG oxidized glutathione; GSH reduced glutathione; IL interleukine; MA mesenteric arteries; MDA malondialdehyde; NT nitrotyrosine; VCAM vascular cell adhesion molecule.
* $p < 0.01$ versus iron sucrose originator and saline control.

Triggered by the publication of Kuo et al. [1], we compared the effects of Fe-Back and the iron sucrose originator on the aorta and mesenteric arteries in our established non-anemic rat model (i.v. administration of 40 mg iron/kg body weight on Days 0, 7, 14, 21 and 28; control group treated with saline) [11]. All animals used in the study received humane care and the study protocol complied with the guidelines of Hospital Alemán, University of Buenos Aires, Argentina. Analysis of tissue homogenates revealed significant distortion of markers of oxidative stress, nitrosative stress and inflammatory response in the aorta and mesenteric arteries in the Fe-Back group compared with the iron sucrose and the saline control group (Table 1). Conversely, no statistically significant differences were observed between the iron sucrose originator and the control group.

While Kuo et al. correctly imply that excessive i.v. iron administration may be associated with potential adverse cardiovascular outcomes, our results, although obtained in a different model, suggest that vascular wall damage as reported by Kuo et al. could be more likely linked to a particular iron sucrose preparation, in that case Fe-Back, rather than i.v. iron in general.

Notably, the European Medicines Agency (EMA) has published a draft reflection paper highlighting EMA's concerns regarding the current experimental and regulatory assessment of iron-based nanoparticles and suggesting non-clinical and clinical data requirements for evaluation [12]. Similar discussions are also ongoing in the US Food and Drug Administration [13].

In fact, i.v. iron complexes are so-called non-biological complex drugs that are not composed of a single and fully characterizable substance such as common small molecule therapeutic substances. This complexity makes them prone to changes in their structure and biological properties even by minute variations in the manufacturing process [14,15]. Therefore, evaluation of products developed with reference to a complex originator drug should include appropriate comparative clinical and/or nonclinical studies that evaluate pharmacokinetics, pharmacodynamics and safety as well as efficacy in relevant patient populations. Unless therapeutic equivalence and similar safety profiles are shown in comparative studies, experts discourage interchange and automatic substitution between non-biological complex drugs and their follow-on (similar) products [16]. Publications should clarify from the outset whether an originator or a similar product was used, especially if the study results may impact clinical decision making and treatment choice.

Conflict of interest

Gabriel Cao and Margarita Angerosa have no conflicts of interest to declare.

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