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Continued Caution Recommended in Use of Intravenous Iron Preparations

To the Editor: We read with interest the report of the well-performed study of Avni et al[1] on the safety of intravenous (IV) iron administration published in the January 2015 issue of *Mayo Clinic Proceedings*. After carefully analyzing more than 100 published randomized, controlled trials (RCTs) that included more than 10,000 patients, the authors concluded that there is no increased risk of serious adverse effects (SAEs) with IV iron preparations compared with other oral iron preparations or placebo and that IV iron formulations are safe and may be given to iron-deficient individuals without fear of infection or cardiovascular events. Although the authors rightfully acknowledged in their discussion the substantial limitations of RCTs to detect rare SAEs, we think that several aspects of the studies included in the meta-analysis and postmarketing signals represent serious limitations to such a strong recommendation.

First, as rightfully mentioned by the authors, risk of bias analysis found that allocation concealment was unclear in almost half of the trials and that only 18% of the assessed studies were double-blind trials. Also, most included trials (80%) did not specify how severity was defined. Although beyond the control of the authors, the fairly low quality of included studies could decrease the validity of their findings. Finally, for many relative risks for SAEs, confidence intervals were borderline, which could also be regarded as an additional limitation for their recommendation.

Second, the authors did not take into account postmarketing signals coming from spontaneous reporting to pharmacoepidemiology surveillance programs. This factor was not the purpose of their research and thus is fully understandable. However, many cases of SAEs including anaphylaxis and death were reported to several national pharmacoepidemiology surveillance programs. After a careful reevaluation of the risks and benefits of IV iron, the European Medicine Agency and the Agence Nationale du Médicament et des Produits de Santé in France drastically tightened the procedures for IV iron administration.[2] This change had immediate practical consequences for the prescribers and their patients.[3] Swissmedic (the official body responsible for collecting all postmarketing adverse effects reports in Switzerland) announced 239 severe reactions following carboxymaltose administration only between 2010 and 2013. There were 3 deaths, including 1 secondary to an anaphylactic reaction. Causality between IV iron administration and death was less evident for the other cases (one cerebral haemorrhage 3 weeks after iron administration and one fetal death). Furthermore, 185 anaphylactic reactions, including 21 cases of shock were reported.[4] For ferumoxytol, 3 SAEs and 1 death were reported.[4] Following several reports of SAEs including deaths following ferumoxytol administration, Health Canada endorsed important new safety information on ferumoxytol in November 2014.[5]

One of the goals of postmarketing reporting is to capture SAEs that are too rare to be observed in RCTs or are only apparent when the drug in question is administered to other populations with different characteristics, such as children, pregnant women, or elderly people. The same applies for severe drug interactions (and potential SAEs), which are rarely captured in RCTs in which coadministration of other drugs is much rarer than in real life. Between 2002 and 2011, 19 such drugs were withdrawn from the market after pharmacoepidemiological studies signaled SAEs.[6]

In summary, the analysis of Avni et al[1] is correct. All IV iron formulations remain effective drugs. However, in view of their findings and of the current postmarketing signals, their conclusions should be somewhat more nuanced. Serious infusion reactions are reported more often with IV iron preparations, either in RCTs or in postmarketing surveillance programs, and this issue should not be forgotten. Prescribers should continue to use intravenous iron cautiously, as has already been recommended.[2,3,5]

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In reply—Continued Caution Recommended in Use of Intravenous Iron Preparations

We thank Dr Cachat and colleagues for their interest in our article and for the valuable information they are reporting. We tried to conduct an unbiased systematic review, but we are aware of the shortcomings of using published results of randomized, controlled trials (RCTs) to report severe adverse events: severe events are too rare to be captured by RCTs (this is why we included all trials on intravenous iron), recording of adverse events might be less rigorous and more biased than that of the primary outcome in such studies, the patients included in RCTs might not be representative of the patients given the drug in clinical practice, and for some medications, the time frame for identifying the adverse events might be the wrong one.

Postmarketing surveillance adds valuable information, but we should remember that it lacks comparison, and some of the patients given iron have severe underlying disorders. Further, the quality of the reported data might be problematic.

As clinicians, we need to weigh all available data when offering intravenous iron to our patients, and the postmarketing surveillance should be part of these data.

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Familial Transient Global Amnesia

To the Editor: We acclaim the excellent, comprehensive review of transient global amnesia (TGA) by Arena and Rabinstein[1] in the February 2015 issue of *Mayo Clinic Proceedings*. Considering the unknown pathophysiology of TGA, we note the authors make minimal mention of the possible contribution of genetics (on page 267). We request that the authors comment further on this possibility.

We report herein our experience with 2 sisters who presented with classic episodes of TGA. The first sister was a 57-year-old woman who suddenly became amnesic after having intercourse with her husband. Her husband noticed that she could not remember their sexual act right after they finished, and she kept repeating the same questions several times over. Approximately 1 year later, her 71-year-old sister presented. That morning, she said she had a mild headache and was "not feeling well." On the drive home from church, she kept asking the same questions repeatedly and could not recall having been at church just a few minutes before.

Neither sister had other neurologic or systemic symptoms. Their presentation examination results were normal except for poor short-term memory. Other than having impaired memory for the events associated with their presentations, they were back to normal the following day. The first sister had experienced a transient ischemic attack 7 years before. Neither had a history of stroke, head trauma, seizures, migraines, or episodes of memory loss.

The second sister's work-up included brain magnetic resonance imaging, which revealed an isolated punctate region of hyperintense signal on diffusion-weighted imaging in the left hippocampus but no signal changes on the T2-weighted or fluid-attenuated inversion recovery sequences. The magnetic resonance imaging study was not repeated.

We are not the only clinicians who have encountered familial cases of TGA. Among the most prominent published series is that of Corston and Godwin-Austen,[2] who described 4 brothers who each had had multiple attacks. Segers-van Rijn and de Bruijn[3] described a family in which 4 of 8 siblings had TGA experiences, one of whom had 2 episodes. Dupuis et al[4] described twin sisters who experienced multiple episodes of TGA associated