1 Abstract

Title: Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions

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Keywords: Intravenous iron, anaphylaxis, severe hypersensitivity reactions, cohort study, multidatabase study

Rationale and background: Severe hypersensitivity reactions/anaphylaxis in intravenous (IV) iron treatment are rare. However, this safety concern is poorly characterised in Europe. A multidatabase study approach was required to evaluate this rare outcome. This PASS was requested by the European Medicines Agency Committee for Medicinal Products for Human Use to assess the risk of anaphylaxis in IV iron users in Europe.

Research question and objectives: The primary objective of the study was to assess the risk of anaphylaxis, overall and by groups (iron non-dextrans and iron dextran) and types of IV iron (using iron sucrose as the common reference).

Study design: Multinational cohort study of patients initiating IV iron treatment, conducted in populations covered by sources of routinely collected health and administrative data in Europe. Given that the risk of anaphylactic reactions rapidly decreases after the first administration of a drug (i.e., due to the depletion of susceptibles), the study used a “new-user” design. Risk was estimated using beta-binomial derived combined incidence proportions (IPs) among patients receiving any IV iron medication overall, by groups and individual types. Risk ratios and 95% confidence intervals (CIs) were calculated to compare the risk of anaphylactic reactions at the first (main analysis), second, and third or subsequent IV iron exposure overall and by IV iron groups and individual types. To put the study findings into context, the risk of anaphylaxis was also assessed among users of IV penicillins.

Setting: The study used data from populations covered in six European databases in five countries. Researchers with access to the study databases in Denmark, France, Germany, the Netherlands, and Sweden collaborated with RTI Health Solutions (Spain) as the coordinating centre. The study period varied across data sources, spanning overall from 1999 to 2017.

Patients and study size, including dropouts: The study identified 304,210 patients with a first-recorded IV iron treatment of whom 6,367 (2.1%) were iron dextran users. For the second IV iron treatments, there were 148,099 patients of whom iron dextran users represented 2.1% and for the third and subsequent treatments 3,103,486 treatments in 105,634 patients were captured with iron dextran accounting for 0.3%. For the IV penicillins cohort, there were 231,294 first treatments and 984,000 total treatments.

Variables and data sources: Data sources were the Danish national and regional linked registers and databases, the Système National des Données de Santé (SNDS, French National Health Care Insurance System Database), the German Pharmacoepidemiological Research Database (GePaRD), the Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN) registry in Germany, the PHARMO Database Network in the Netherlands (PHARMO-NL) and the Swedish national registers. Data from the Oldenburg University Hospital in Germany were used to validate the case-identification algorithm adapted to the GePaRD data. The German Institute of Medical Documentation and Information (DIMDI-DaTraV database) could not contribute to the study because of lack of resources.

The study outcome was anaphylaxis identified through a case-identification algorithm based on a previously validated algorithm.

Exposure to IV iron was captured through drug-dispensing data from outpatient pharmacy settings and, in two data sources, from inpatient drug administration. Analyses were conducted at first, second, and third or subsequent IV iron treatments. Validation of potential anaphylaxis events was conducted in the Central Denmark Region and the PHARMO-NL by review of medical records. Validation of the case-identification algorithm was performed through Oldenburg Hospital data.

Results: IV iron treatment in this study reflects only partial use in each country, mostly from ambulatory drug-dispensing data. A high proportion of all third or subsequent IV iron treatments (84%) occurred in the KfH QiN dialysis registry in Germany.

At first IV iron treatment, between 13 and 16 potential cases of anaphylaxis were identified. The resulting IP ranged from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97)[1] per 10,000 first treatments (the IP is reported as a range owing to data-protection rules for counts between 1 and 4). No events among iron dextran users were identified at first IV iron treatment. Risk estimates by groups and types of IV iron were based on a very small number of events.

At first IV penicillins treatment, 30 potential cases of anaphylaxis were identified. The resulting IP was 1.16 (95% CI, 0.78-1.73)[1] per 10,000 treatments.

Discussion: The study found an IP of anaphylaxis that was lower than the estimates of 2 to 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in the recent United States (US) studies (Walsh et al., 2016; Wang et al., 2015). The IP of anaphylaxis in users of penicillins was consistent with the incidences reported in the literature.

Owing to the small number of events no adjusted analyses could be performed, and results presented are potentially subject to confounding.

[1] IPs and 95% CIs estimates in the abstract have been corrected because they were inadvertently not updated in the previous March 24, 2020 and May 06, 2020 final study reports. Please note that all estimates in the text and tables of the report have been reported correctly in all versions of the report.

A potential for misclassification of repeated users of IV iron as first users, because of the impossibility of capturing in-hospital use in most data sources, may have resulted in lower IPs of anaphylaxis.

In spite of its limitations, the results of the study do not suggest a high risk of anaphylaxis among the users of IV iron captured in the studied populations.

Marketing authorisation holder(s): IV Iron Marketing Authorisation Holders Consortium, comprising the following marketing authorisation holders (MAHs): Accord Healthcare Limited, Acino AG, Arrow Génériques, Baxter, Generis Farmacéutica SA, Altan Pharmaceuticals SAU., Laboratoires Sterop SA, Medice Arzneimittel Puetter GmbH & Co. KG, Mylan SAS, Orifarm Generics A/S, Panmedica (Panpharma SA), Pharmachemie BV (Teva), Pharmacosmos A/S, Rafarm SA, Sandoz SAS, Sanofi Aventis Groupe, and Vifor France.

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