A Multinational European Study of Anaphylaxis Among Recipients of Intravenous Iron

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BACKGROUND

- Anaphylaxis (ANA) related to intravenous (IV) iron treatment is a poorly characterized safety concern in Europe.
- A postauthorization safety study requested by the European Medicines Agency assessed the risk of ANA in IV iron users in Europe. A multidatabase study approach was required to evaluate this rare safety outcome.

OBJECTIVE

- To assess the risk of ANA in users of IV iron overall, by IV iron groups (iron non-dextrans and iron dextran), and by individual types.

DISCLOSURES

- This study was funded by a consortium of IV iron manufacturing companies through a contract with RTI Health Solutions (RTI-HS) that funds all other participating research centres. The contract provides the research team independent publication rights.
- L Gutierrez, C Franzoni, S Perez-Gutthann, L Rasouliyan, KJ Rothman, N Saigi-Morgui, J Fortuny, JA Overbeek, E Smits, P Blin, R Lassalle, C Droz-Perroteau, N Moore, M Linder, I Odsbu, V Ehrenstein, A Timmer, G Toft, T Schink, J Reinold, and B Kollhorst work for entities that perform independent research work for government agencies, private entities, and pharmaceutical companies.
- G von Gersdorff, M Schaller, and K Rascher did not have disclosures to share.
- J Dress was the Head of the Unit M4 "Information System for Health Care Data (Data Transparency)" of the German Institute for Medical Documentation and Information (DIMDI), Cologne, Germany, which processed applications from RTI-HS and charged user fees. Since May 26, 2020, DIMDI was integrated into the BfArM.
- The Intravenous Iron Consortium is a consortium of 17 IV iron manufacturing companies that participated in this Joint postauthorization safety study.

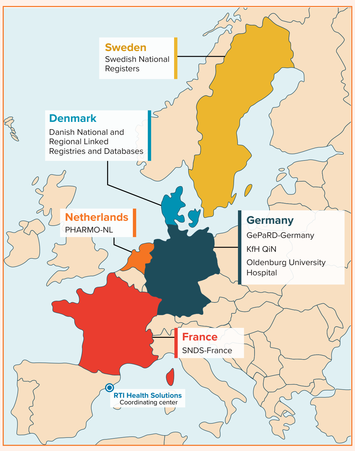
METHODS

- EUPAS register number: EUPAS20720/ENCePP Seal obtained

Data Sources and Study Period

- National- or regional-level data from five countries: Denmark, the Netherlands, France, Germany, and Sweden (Figure 1)
- Data: 1999-2017, varying by data source

Figure 1. Study Data Sources



GePaRD = German Pharmacoepidemiological Research Database; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO = PHARMO Database Network; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

Study Design

- Cohort study of users of IV iron in the study populations; eligibility criteria in Figure 2.
- Cohort of IV penicillin users, where feasible, to assess the performance of the ANA identification algorithm.
- Main analysis: time at risk was Day 0 (same day of administration of a study drug) for data sources capturing drug administration data. For data sources capturing drug dispensing or lacking an exact date of ANA diagnosis, the time at risk was Day 0 and Day 1 after dispensing/administration of IV iron (Figure 3).

Figure 2. Study Design

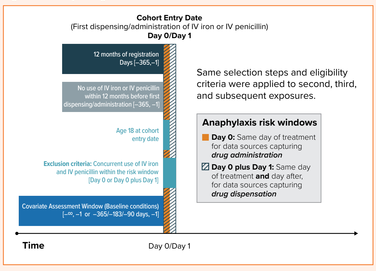
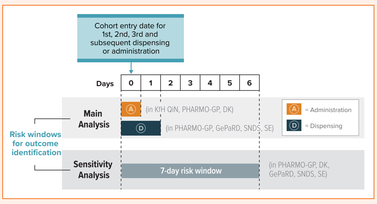


Figure 3. Time at Risk



DK = Denmark; GePaRD = German Pharmacoepidemiological Research Database; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO = PHARMO Database Network; SE = Sweden; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

Exposure

- Any IV iron
  - Iron dextran
  - Iron non-dextrans
    - Iron carboxymaltose
    - Iron isomaltoside
    - Iron sucrose
    - Iron gluconate
- Any IV penicillin

Outcome

- Anaphylactic reaction or severe immediate hypersensitivity reaction following exposure to a study drug.
- Algorithms used to identify ANA events rely on both specific diagnostic codes for ANA and ANA symptoms, signs, and treatments.
- A main case-finding algorithm was used for the main analysis (Figure 4). An expanded more sensitive algorithm that relied on evidence of adrenalin use as a proxy for ANA and classified death within the risk window as an ANA event, was used for a sensitivity analysis (Figure 4).

Analysis

- Data source analyses were conducted using a common protocol and analysis plan, with local adaptations.
- A combined analysis of aggregated data from each data source was conducted by the coordinating center.
- Crude incidence proportions (IPs) of ANA for each IV iron exposure group and IV penicillin cohort per 10,000 person-years with 95% confidence intervals (CIs) were estimated.
- Crude risk ratios (RRs) and risk differences (RDs) of ANA for IV iron dextran versus IV iron non-dextrans with 95% CIs were estimated.
- Beta-binomial–derived combined IPs, RRs, and RDs with 95% CIs were estimated, as few events were expected.

Figure 4. Main and Expanded Anaphylaxis Algorithm

A — Criterion A

INPATIENT SETTING

Specific anaphylaxis codes

T88.6 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered)

OR

T80.5 (anaphylactic shock due to serum)

OR

T78.2 (anaphylactic shock, unspecified) (i.e., the reason for admission, if this information is available)

OR

Epinephrine/adrenaline administration (Y51.4, predominantly alpha adrenoreceptor agonists; Y51.5, predominantly beta-adrenoreceptor agonists, not elsewhere classified; or Y51.9, other and unspecified drugs primarily affecting the autonomic nervous system)

B — Criterion B

OUTPATIENT SETTING

Specific anaphylaxis codes

T88.6 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered)

OR

T80.5 (anaphylactic shock due to serum)

OR

T78.2 (anaphylactic shock, unspecified)

OR

Epinephrine/adrenaline administration (Y51.4, predominantly alpha adrenoreceptor agonists; Y51.5, predominantly beta-adrenoreceptor agonists, not elsewhere classified; or Y51.9, other and unspecified drugs primarily affecting the autonomic nervous system)

AND

A code for one or more of the following symptoms, procedures, or treatments:

- Bronchospasm (J98.01, acute bronchospasm)
- Stridor (R06.1)
- Hypotension (I95.0, idiopathic hypotension; I95.2, hypotension due to drugs; I95.81, other hypotension, postprocedural; I95.89, other hypotension; I95.9, hypotension unspecified)
- Angioedema (T78.3 angioneurotic edema)
- Admission/transfer to intensive care unit (health encounter codes as available in each data source)
- Injection of diphenhydramine (Y43.0, antiallergic and antiemetic drugs); injection of corticosteroids (Y42.0, glucocorticoids and synthetic analogues)
- Oxygen (T41.5 therapeutic gases or other data source–specific procedural codes for oxygen administration, as appropriate)
- Cardiac arrest with successful resuscitation (I46.0); cardiac arrest, unspecified (I46.9)
- Death

C — Criterion C

INPATIENT SETTING

Unspecific hypersensitivity codes

T88.7 (unspecified adverse effect of drug or medicament)

OR

T78.4 (allergy unspecified)

OR

Y44.0 (adverse effects in therapeutic use: iron preparations and other antihypochromic-anaemia preparations) (i.e., the reason for admission, if this information is available)

AND

A code for one or more of the following symptoms, procedures, or treatments:

- Bronchospasm (J98.01, acute bronchospasm)
- Stridor (R06.1)
- Angioedema (T78.3 angioneurotic edema)
- Injection of diphenhydramine (Y43.0, antiallergic and antiemetic drugs); injection of corticosteroids (Y42.0, glucocorticoids and synthetic analogues)
- Oxygen (T41.5 therapeutic gases or appropriate procedural codes for oxygen administration)

AND

A code for one of the following symptoms, procedures, or treatments:

- Hypotension (I95.0, idiopathic hypotension; I95.2, hypotension due to drugs; I95.81, other hypotension, postprocedural; I95.89, other hypotension; I95.9, hypotension unspecified)
- Admission/transfer to intensive care unit (health encounter codes as available in each data source)
- Cardiac arrest with successful resuscitation (I46.0); cardiac arrest, unspecified (I46.9)

A code of death by itself may substitute any of the 8 codes listed above.

RESULTS

- Owing to the characteristics of the data sources used in the study, drug exposure captured mostly reflected ambulatory drug dispensing.
- When the number of events was between 1 and 4 in Denmark, the corresponding estimates are reported as ranges to comply with data protection regulations.
- Table 1 shows the main study results.
  - Overall, 304,210 first-time IV iron treatments were identified.
  - Up to 16 cases of ANA were identified; IP: up to 0.51 per 10,000 first IV iron treatments.
  - The IPs for IV iron groups were based on a small number of events among IV iron dextran users.
  - Results on specific IV iron types are not shown due to the low numbers.
  - Among 231,294 first penicillin treatments, 30 cases of ANA occurred; IP: 1.16 per 10,000 first treatments.

Table 1. Risk of Anaphylaxis After Treatment With IV Iron and IV Penicillin

	First Treatments	Second Treatments	Third and Subsequent Treatments
Overall IV iron			
Treatments (patients), n	304,210	148,099	3,103,486 (105,634)
ANA events, n	Min, 13; max, 16[a]	3	10
IP (95% CI)	Min, 0.38 (0.17-0.88); max, 0.51 (0.28-0.97)[a]	0.25 (0.07-0.94)	0.02 (0.00-0.13)
Iron dextran			
Treatments, n	6,387	3,084	9,508
ANA events, n	0	1	0
IP (95% CI)	0 (0 to > 9,995)	3.33 (0.48-23.3)	0 (0 to > 9,995)
Iron non-dextran			
Treatments, n	297,813	145,015	3,093,988
ANA events, n	Min, 13; max, 16[a]	2	10
IP (95% CI)	Min, 0.44 (0.16-1.24); max, 0.55 (0.23-1.34)[a]	0.25 (0.06-1.06)	0.03 (0.00-0.19)
RR (95% CI)[b]	Min, 0 (0.00 to > 9,995); max, 0 (0.00 to > 9,995)	13.1 (1.26-146)	0 (0 to > 9,995)
RD (95% CI)[b]	Min, −0.44 (−1.02 to > 9,995); max, −0.55, (−1.14 to > 9,995)	3.08 (0.12-23.1)	−0.03 (−0.13 to > 9,995)
IV penicillin			
Treatments, n	231,294		
ANA events, n	30	NA	NA
IP (95% CI)	1.16 (0.78-1.73)		

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; NA = not applicable; RR = risk ratio; RD = risk difference.

[a] The number of events identified in Denmark was between 1 and 4. The exact number cannot be disclosed because of data-protection rules aimed at preventing the identification of individuals. Therefore, IPs per 10,000 first treatments are reported as a minimum and maximum range.

[b] RRs were calculated for iron dextran vs. non-dextrans; RDs were calculated for iron dextran minus iron non-dextrans.

CONCLUSIONS

- Sizeable numbers of IV iron and IV penicillin users were identified.
- The IP of ANA among IV iron users was lower than expected based on estimates from recent United States studies (i.e., 0.51 per 10,000 in our study vs. 2 to 4.8 per 10,000 first uses of IV iron in the United States).[1,2]
  - Our study captured only a small fraction of in-hospital and specialty clinic use of IV iron and IV penicillin, the settings where most use of these drugs is likely to happen.
  - IV iron captured through pharmacy ambulatory dispensing as first use may reflect repeated use, resulting in an underestimation of the IPs of ANA.
- The IP of ANA in users of penicillins was consistent with the risks reported in the literature, supporting the adequacy of the ANA identification algorithm.
- The results of the study do not suggest a high risk of ANA among users of IV iron in the studied patient populations.

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