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# Low Plasma Iron Levels Associated to Drug Treatment in Polymedicated Patients: A Case-Control Study

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***Authors' contributions***

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## ABSTRACT

**Aim:** To identify the drug class and/or duration of treatments causing hyposideremia.
**Study Design:** Retrospective case-control study.
**Place and Duration of Study:** Departments of Internal Medicine and Pharmacy, Aragón Health Services Services Hospital Real de Nuestra Señora de Gracia, between January 2019 and December 2019.
**Methodology:** The records of prescripted medicines of all patients admitted to Internal Medicine service, for various indications, along a 1-year period (2019), which were ultimately analized according to association with hyposideremia.
**Results:** It was identified several drugs associated with low plasma iron levels: acetylcysteine and apixaban, which would increase the risk of hyposideremia. On the contrary, we found that allopurinol, duloxetine and simvastatin would protect against the appearance of hyposideremia.

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**Conclusion:** Acetylcysteine and apixaban, alone or in combination with different pathologies, would be capable of inducing, and on dependence of the duration of treatment and/or of the concomitant pathology, hyposideremia, iron deficiency and, in certain cases, anemia constituting a major health problem.

*Keywords: Anemia; elderly; iron; polypharmacy; side effects; sideremia.*

## 1. INTRODUCTION

According to bibliographic data obtained from a literature review, anemia prevalence is 17% in older people (>65 years) [1]. It appears because of three general causes: (i) blood loss/nutritional deficiencies (34%) [2], 20% of which is caused by iron deficiency linked to folic acid and/or Vit B12 [2], (ii) chronic illness/inflammation or chronic renal failure (32%) and (iii) unexplained anemias (34%) [1]. The mechanisms of anemia include the dysregulation of the inflammatory response (e.g. dysregulation of hepcidin expression), co-morbid medical conditions (e.g. infectious diseases) and polypharmacy [3]. Indeed, the fact that approximately 20% of anemias in the elderly are caused by iron deficiency emphasizes the importance of the recognition of the diagnosis of iron deficiency, especially for those older than 65 years who show a propensity for polypharmaceutical usage [4].

Regarding polypharmacy and the related low iron plasma levels, few pharmaco-epidemiological studies have been carried out and many of those that have include patients with multiple comorbidities that affected iron loss [5]. The low frequency of hematological side effects of drugs, along with the fact that pharmaco-epidemiology studies have historically relied on the information provided by the patient or searches of paper medical records, complicate such research [5].

However, owing to increasing access to electronic medical records and the large administrative databases that contain them, the way that exposures and therapeutic outcomes are defined, measured and validated (including for drugs) has now changed. Indeed, advances in computer technology and the exponential growth in data from medical and prescription records (i.e. secondary databases) and its rising availability have created new opportunities for pharmaco-epidemiology research in recent decades. Thus, the interest in their use in pharmaco-epidemiological studies to evaluate drug therapies in real-world practice has increased [6]. Because of this, we aimed to identify the drug class and/or duration of treatment associated with hyposideremia through a pharmaco-epidemiological study based on electronic medical and prescription records.

## 2. MATERIALS AND METHODS

For this, a case-control study was carried out. The sample comprised all the polymedicated patients (number of drugs per patient greater than or equal to five) admitted to the internal medicine service of the Hospital Real de Nuestra Señora de Gracia (Zaragoza, Spain) in 2019. The main variables were patient-day exposure to a drug (T-day) and iron plasma levels (Fe; half-life serum Fe 90 min);transferrin levels were not considered because the value of its half-life (8-10 days), in many cases, exceeded the average stay in Internal Medicine Service (7.5 days); and plasma ferritin values (half-life 24 h), they will not be considered, because as it is an indirect marker of the total amount of iron stored in the body and is used as a diagnostic test for iron deficiency anemia, which is established after a period of variable time but, in most of the cases, higher than the average stay (7.5 days). Data on these variables were obtained from the assisted electronic prescription system (Dominion) and laboratory records, respectively. Those patients without data on Fe and/or those with a previous diagnosis of anemia, heart failure and inflammatory processes, mainly, were excluded.

We considered as cases all T-days on which Fe levels were equal to or less than 50 mcg/dL and as controls all T-day exposure drug data when Fe levels were greater than 50 mcg/dL, according to normal range from our hospital biochemical laboratory. Thus, Group I (cases) composed patients' T-days with Fe ≤ 50 mcg/dL and Group II (controls) composed of patients' T-days with Fe>50 mcg/dL. These groups were compared with respect to the different drugs under study (as potential risk factors).

Finally, to measure the likelihood of the association between hyposideremia and drug exposure, odds ratios (ORs) were calculated for each of the drugs studied and interpreted using the Bonferroni correction and ORs equivalent to Cohen's "d" criteria to include effect size

measures:Cohen's d = 0.2 (small), 0.5 (medium), and 0.8 (large) association corresponding to ORs of weak (1.5-1.68), moderate (2.4-3.5) and strong(4.1-6.7) significance, respectively.

Data on the concomitant infection processes could differ markedly between the groups. Hence, to avoid influencing factors that may bias the results, concomitant infection processes, constituting the most important confounding variables for hyposideremia, were controlled for. To do this, we summarized them into a single multivariable confounder score, composed of the diagnoses of infection processes (including gastrointestinal, genitourinary, pneumonia and fever) and, to check the effect measure modifier of this single multivariable confounder, we performed a formal statistical test to assess the statistically significant differences in the effect and, finally, was measured using an additive scale based on risk differences(OR or 1/OR corresponding to the risk of certain drug-(1-OR) corresponding to the risk of infectious diseases) and presented in an easy-to-interpret way (ORs with confidence intervals).

To calculate the sample size, the exposure value in the control group corresponding to the drug with the lowest proportion (0.0016), an α of 0.001 and a desired power of 0.8 was used, resulting in a sample size (for cases and controls, separately) of 23789.

## 3. RESULTS AND DISCUSSION

Data on main variables (T-days and Fe), anthropometric characteristics and infectious comorbidities of patients belonging to groups I and II are shown in Table 1.

Regarding the anthropometric characteristics shown in Table 1, either there is no difference or it is very small, such as age and weight; In the case of the Barthel index score, measured prior to admission, it indicates “severe” dependency in group I and moderate dependence in group II. Finally, plasma iron levels and percentage of infectious diseases are part of the variables under study.

The total number of drugs analyzed was 51% and 47% of patients presented with hyposideremia during admission. The data on patient´s T-day for different drugs in the two groups under study are shown in Table 2.

In Table 2, its showed crude T-day data on drugs with OR>1 and p<.001 (("p" level of statistical significance according to the Bonferroni correction for the 51 drugs tested is equal to P<0.05/51=0.0009~0.001)), acetyl-cysteine, apixaban, mirtazapine, risperidone and sertraline, which had OR values of 2.2, 2.4, 2.0, 1.9 and 1.9, respectively, present a small to moderate risk of displaying hyposideremia, according to the criteria of Cohen's "d" (OR=1.68–3.47 for weak-moderate association). However, adjusting by the diagnosis of infectious diseases (see Table 1: 35% in Group II vs. 27% in Group I; OR=1.5, p<.001), as the most important confounding variable, the risk of hyposideremia is only associated to those drugs whose OR>1.68 (calculated as, OR

**Table 1. Data on patient´s anthropometrics and infectious comorbidities of patients belonging to groups I and II. Mean value (standard deviation, SD), otherwise will be indicated.**

| Variable, units | Group I (cases) | Group II (controls) | P(t, $\chi^2$or Z test) |
|---|---|---|---|
| **Number of patients in the group, n** | **484** | **537** | |
| Number of patient-day exposure, n | 26704 | 24302 | |
| Iron plasma levels, mcg/dL | 31.9 (±10.6) | 88.1 (±31.5) | <.001 |
| Gender (female), n | 252 (52%) | 274 (51%) | .102 |
| Age, years | 78.9 (±12.2) | 75.3 (±15.6) | <.001 |
| Height, cm | 158.9 (±8.1) | 158.2 (±20.9) | .4894 |
| Weight, kg | 69.1 (±13.4) | 72.1 (±14.3) | <.001 |
| Body mass index, kg/m$^2$ | 27.4 (±5.2) | 28 (±5.6) | .0773 |
| Barthel index score, points | 48.9 (±36.1) | 76.5 (±25.2) | <.001 |
| Infectious processes, n | 131 (27) | 189 (35) | <.001 |
| **Number of excluded patients in the group, n** | **343** | **71** | |
| Anemia, n | 0 | 19 (5.5%) | |
| Heart failure, n | 23 (6.7%) | 26 (7.4%) | |
| Others causes, n | 320 (93.3%) | 303 (87.1%) | |

**Table 2. Data on patient´s T-day for different drugs in the two groups under study: group 1 (cases=patient´s T-day with 50<Fe) and group 2 (controls=patient´s T-day with 50>Fe) and their attributed risk (odds ratio, OR)**

| Drug (T-day) | Group I (cases) | Group II (controls) | OR>1 | P (Z test) |
|---|---|---|---|---|
| Acetylcysteine | 204 | 84 | 2.2 | <.0001* |
| Amlodipine | 197 | 133 | 1.4 | .0076 |
| Apixaban | 98 | 38 | 2.4 | <.0001* |
| Ceftriaxone | 408 | 245 | 1.5 | <.0001* |
| S-citalopram | 146 | 96 | 1.4 | .0132 |
| Metamizol | 688 | 469 | 1.3 | <.0001* |
| Mirtazapine | 169 | 76 | 2.0 | <.0001* |
| Pantoprazole | 218 | 142 | 1.4 | .0019 |
| Risperidone | 150 | 71 | 1.9 | .0001* |
| Sertraline | 99 | 46 | 1.9 | .0002* |
| **Drug (T-day)** | **Group I** | **Group II** | **OR<1** | |
| Alopurinol | 25 | 60 | 0.4 | <.0001* |
| Carvedilol | 59 | 89 | 0.6 | .0026 |
| Duloxetine | 16 | 50 | 0.3 | <.0001* |
| Lansoprazole | 150 | 162 | 0.8 | 0.1296 |
| Levofloxacin | 215 | 219 | 0.9 | 0.2385 |
| Levothyroxine | 180 | 257 | 0.6 | <.0001* |
| Methylprednisolone | 395 | 491 | 0.7 | <.0001* |
| Quetiapine | 199 | 224 | 0.8 | .0284 |
| Ramiprile | 84 | 142 | 0.5 | .0001* |
| Simvastatin | 37 | 117 | 0.3 | .0001* |

*Fe = plasma iron levels, mcg/dL; group I = patient´s T-day with Fe <50 mcg/dL; group II = patient´s T-day with Fe <50 mcg/dL; OR = odds ratio; T-day = nº patient-day exposure to a drug; *p <.001("p" level of statistical significance according to the Bonferroni correction for the 51 drugs tested is equal to P<0.05/51=0.0009~0.001)*

corresponding to the risk of the drug - (1-OR = 0.5) corresponding to the risk of infectious disease): acetyl-cysteine and apixaban.

On the contrary, from the analysis of the crude T-day data on drugs with OR<1 and p<.001, allopurinol, duloxetine, ramipril and simvastatin, which had OR values of 0.4, 0.3, 0.5 and 0.3, respectively, behave as protectors of small or moderate intensity, according to the criteria of Cohen's "d"(OR=1.68–3.47 for weak-moderate significance), with respect to the appearance of hyposideremia. However, again adjusting by the diagnosis of infectious diseases (see Table 1: 35% in Group II vs. 27% in Group I; OR=1.5, p<0.001), protection from hyposideremia is only present for those drugs whose 1/OR>1.68 (calculated as, 1 / OR corresponding to the risk of the drug - (1-OR = 0.5) corresponding to the risk of infectious disease): allopurinol, duloxetine and simvastatin.

This type of case control study has a generally descriptive function and, therefore, it is not valid for contrasting etiological hypotheses; however, it can suggest them, and their relative speed and low cost make them useful and effective. By way of a limitation, many researchers recommend caution.

Despite this, it should be noted that homeostasis mechanisms for the alteration of iron plasma levels include, among others, the decreased absorption of non-heme Fe, secondary to changes in the pH of the stomach, gastrointestinal bleeding and bleeding losses and increased hepcidin through its induction by interleukin 6 (IL6) and the signal transducer and activator of transcription 3 (STAT3) in response to inflammatory stimuli [7].

In this sense, agreeing with the literature, apixaban [8] would produce hyposideremia due to iron deficiency through mucosal damage and gastrointestinal bleeding. Acetyl-cysteine, with its pro-oxidant activity during inflammatory conditions [9], would also act on the pro-inflammatory cytokines of the IL6–STAT3–hepcidin pathway. By contrast, allopurinol [10] and simvastatin [11] act in a protective manner against the occurrence of hyposideremia on the pro-inflammatory cytokines of the IL6–STAT3–hepcidin signaling pathway by decreasing hepcidin. Finally, duloxetine would act according to mechanisms not described, although pro-inflammatory cytokines, including IL-6, appear to be involved [12].

Hyposideremia occurs early in the course of treatment and/or disease, frequently within the first 24 hours (half-life serum Fe 90 min), whereas the decrease in transferrin levels occurs more slowly (half-life = 8–10 days). Finally, the development of mild to moderate anemia, which is normochromic and normocytic, seems unlikely in people with normal iron stores if the cause is a short duration; however, iron supplementation may be necessary in people with other contributing factors. In any case, measures of serum ferritin may be influenced by iron loading and inflammation, making it difficult to diagnose true iron deficiency if inflammation is also present. As a rule of thumb, a ferritin concentration greater than 150 ng/mL is rare in anemia of inflammation concomitant with absolute iron deficiency. The best way to treat anemia of inflammation is thus based on the underlying chronic conditions, comorbidities and specific needs of the patient [13].

Despite the effect of infectious inflammatory processes on the concurrence of hyposideremia, we identified several medications associated with alterations in serum iron levels. Depending on the duration of treatment and/or concomitant pathology, these medications, alone or in combination with different pathologies, can induce hyposideremia, iron deficiency and, in certain cases, anemia, thereby constituting a major health problem.

By way of a limitation, many researchers recommend caution when using these types of observational clinical studies and warn against the high risk of introducing biases when using secondary databases such as clinical and therapeutic data extracted from medical records and administrative databases. Biases should thus be adjusted by the corresponding corrective measures [6]. However, as one of the strengths of the studies based on secondary databases, note that they reflect routine clinical practice and that, despite not being used to test hypotheses, they are used to generate them.

## 4. CONCLUSION

Based on electronic medical and prescription records and administrative databases, a pharmaco-epidemiological study, aimed to identify the drug class and/or duration of treatment associated with hyposideremia, was carried out.

As result, It was identified several drugs associated with lowering plasma iron levels: acetylcysteine and apixaban and, by contrast, it was found that allopurinol, duloxetine and simvastatin would protect against the appearance of hyposideremia. Accordingly, acetylcysteine and apixaban, alone or in combination with different infectious processes, and on dependence of the duration of treatment and/or of the concomitant pathology, would be capable of inducing hyposideremia, iron deficiency and, in certain cases, anemia constituting a major health problem.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

As our study took place in a spanish public hospital, and since it is an observational study based on the daily clinical routine (electronic prescription and laboratory records) no ethic committee review was required. however, it did need to meet the ethical standards of the declaration of Helsinki.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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