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Role of prescribed medication in the development of iron deficiency anaemia in adults—a case–control study

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ABSTRACT

Objective To estimate the strength of association between exposure to selected classes of prescribed medications and the risk of developing iron deficiency anaemia (IDA), specifically considering oral anticoagulants (OACs), antidepressants, antiplatelet agents, proton pump inhibitors (PPIs) and non-steroidal anti-inflammatories.

Design A case–control study involving the analysis of community repeat prescriptions among subjects referred with IDA, and unmatched controls referred as gastroenterology fast-tracks for other indications. Multivariable logistic regression modelling was used to calculate ORs for the association between IDA presentation and each medication class, adjusted for age, sex and coprescribing. For those classes showing significance, it was also used to calculate risk differences between those in the IDA group with or without haemorrhagic lesions on investigation.

Results A total of 1210 cases were analysed—409 in the IDA group, and 801 in the control group. Significant associations were identified between presentation with IDA and long-term exposure to PPIs (OR 3.29, 95% CI: 2.47 to 4.41, p<0.001) and to OACs (OR 2.04, 95% CI: 1.29 to 3.24, p=0.002). IDA was not associated with long-term exposure to any of the other three drug classes. In contrast to the relationship with PPIs, the association with OACs was primarily in the IDA sub-group with haemorrhagic lesions.

Conclusion Long-term exposure to PPIs and OACs are independently associated with the risk of developing IDA. There are grounds for considering that these associations may be causal, though the underlying mechanisms probably differ.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Iron deficiency anaemia (IDA) is common, particularly in the elderly.
⇒ Although major gastrointestinal (GI) pathology may underly IDA, no convincing cause is found on investigation in the majority of cases.
⇒ While various medications have plausible mechanisms, the evidence that prescription medication predisposes to IDA is limited.

WHAT THIS STUDY ADDS

⇒ Long-term (but not short-term) exposure to proton pump inhibitors (PPIs) and oral anticoagulants (OACs) are associated with an increased risk of presenting with IDA.
⇒ Long-term exposure to antiplatelet therapy does not predispose to IDA.
⇒ The association with OACs is predominantly limited to those with underlying haemorrhagic lesions in the GI tract, while the association with PPIs is independent of this—implying different mechanisms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While association does not prove causation, the findings could potentially influence prescribing practice, particularly of PPIs in those with unexplained recurrent IDA.
⇒ The findings strengthen the case for continuing antiplatelet therapy in the face of IDA.
⇒ Finally, they may influence the decision regarding the need for invasive investigation of IDA—weakening the case for those on a PPI who are at low risk of major underlying pathology, while strengthening it for those taking OACs.

INTRODUCTION

Iron deficiency anaemia (IDA) is the consequence of impaired bone marrow production of erythrocytes due to depletion of body iron stores. It is a major global healthcare issue, with multiple causes primarily relating to reduced assimilation and/or enhanced loss of iron.[1 2]

In the UK, about 30% of cases of IDA in adult males and non-menstruating females prove on investigation to have an underlying cause in the upper or lower gastrointestinal (GI) tract. A variety of pathologies may contribute, with malabsorption (most commonly due to coeliac disease) in around 4% of cases.[1–3] However, the majority are accounted for by mucosal lesions due to inflammatory, vascular or neoplastic pathology, with the common final pathway of enhanced chronic GI blood loss.[1–4] Because of the cancer link,

unexplained IDA in these groups is a recognised indication in the UK for fast-track investigation.[5 6]

Further investigation may reveal pathology in the small bowel or renal tract in a small percentage of additional cases. However, the majority of episodes of IDA in the adult UK population remain unexplained.[3 4] The IDA cohort referred for further investigation is relatively elderly,[3] a group who frequently take prescribed medications. The question frequently arises as to whether such medication may be contributing to the development of IDA, and therefore whether it should be discontinued. In the individual case, this can be difficult to answer, particularly if the indication for continuing therapy is strong.

Many drugs have a plausible mechanism for influencing iron balance in the GI tract, and therefore potentially the risk of development of IDA. Examples would include enhanced chronic blood loss through impairment of haemostasis (anticoagulants, antiplatelet agents and selective serotonin reuptake inhibitors), mucosal damage (non-steroidal anti-inflammatories) or both (aspirin), and impairment of iron absorption (proton pump inhibitors, PPIs).

The literature in this area is however limited, with a Medline search yielding rather conflicting evidence regarding the relevance of therapy with anticoagulants,[4 7] antiplatelet agents[4 8] and PPIs[9 10] to the pathogenesis of IDA. There is little published evidence either way for non-steroidal anti-inflammatories and antidepressants. As a result, there is no clear guidance—and further research evidence is required to allow a comprehensive systematic review of this important topic.

The primary aim of the current study was to assess for an association between long-term exposure to specific prescribed medications and presentation with IDA in a large study of unmatched case–control design, looking specifically at the five drug groups discussed above. While demonstration of an association does not of course prove causation, the absence of one makes causation much less likely. The secondary aim of the study was to determine whether any associations identified were mediated by subgroups with or without an underlying haemorrhagic lesion (HL) of the GI tract.

METHOD

The IDA group comprised consecutive referrals to the IDA service at Poole Hospital between November 2022 and June 2023 with documentary evidence of underlying iron deficiency, defined as a serum ferritin below the lower limit of normal (30 ug/L for males, 13 ug/L for females) and/or a transferrin saturation of <15%. The control group comprised consecutive fast-track referrals to the gastroenterology department at Poole Hospital between November 2022 and February 2023 for all indications other than IDA. All subjects were aged 18 years or older.

Each subject's electronic patient record was evaluated at the time of referral to define demographic data, referral indication and blood test results including haemoglobin levels and iron indices—although the majority of the control group did not have results for iron studies, as there was no clinical indication for testing. The control group were offered investigation as clinically indicated, resulting in a wide range of functional and organic diagnoses.

The electronic record for those in the IDA group was reviewed at a later date, to establish whether full GI investigation had taken place, and if so, to determine whether an HL had been revealed. An HL was defined as any inflammatory, vascular or neoplastic abnormality felt by the responsible clinician to have contributed to the development of IDA—broadly, all major GI pathology identified apart from coeliac disease, where the mechanism of iron deficiency is malabsorption rather than chronic blood loss.[11]

The Dorset Care Record (DCR), a personal electronic healthcare database generated in primary care and containing individual repeat prescription lists, was used to determine exposure to each class of medication. In a few instances, it was not possible to access subject blood test results and/or their DCR, and these cases were excluded.

The five classes of medication assessed were (1) oral anticoagulants (OACs—vitamin K antagonists and DOACs), (2) antidepressants (all subclasses), (3) oral antiplatelet agents (aspirin and P2Y12 inhibitors), (4) PPIs and (5) non-steroidal antiinflammatories (all subclasses). For each censored drug, the duration of prescribed exposure was estimated. For the purposes of the analysis, cumulative repeat prescription duration was defined as short-term if less than 12 months, or long-term if 12 months or more. The data for each subject were anonymised prior to analysis by the clinical team overseeing their management such that no identifiable personal data (including name, hospital number, postcode, date of birth or age to anything closer than year) was in the data set at the point of analysis.

Power calculations were based on an arbitrary expected drug exposure rate of 20% in the control group and a 1:2 case to control ratio. For an OR of 1.5 at the 5% significance level (two-sided test) and a power of 80%, the total sample size requirement for the study was estimated to be 1200 participants—400 cases and 800 controls.

Multivariable logistic regression modelling was used to calculate ORs and 95% CIs for the association between the IDA presentation and each drug class, adjusted for age, sex and concurrent drug exposure. The model was constructed according to the formula: Logit (probability of IDA) = β0 + β1age + β2sex + β3OAC + β4AD + β5AP + β6NS + β7PPI (where OAC, anticoagulant; AP, antiplatelet therapy; NS, non-steroidal anti-inflammatory; PPI, proton pump inhibitor and AD, antidepressant). Linearity, independence, multicollinearity, influential values, pseudo R^2 and the Hosmer-Lemeshow test were examined to check the validity of the fitted logistic regression model and the goodness of fit.

Table 1 Descriptive statistics of the study groups

	IDA group	Control group
Number of cases	409	801
Female—number (%)	245 (59.9)	427 (53.3)
Age (years)—median (IQR)	71 (61–80)	68 (56–78)
Haemoglobin (g/L)—median (IQR)	111 (97–118)	135 (126–144)

IDA, iron deficiency anaemia.

The χ^2 test of independence was used to examine the association between drug class and IDA status, and standardised Pearson residuals were used to assess the nature of the dependence between the variables. For each drug class, a logistic regression model adjusted for age and sex was used to investigate the excess risk conferred by HL status in the IDA group—the results were expressed as risk differences (RDs) with 95% CIs. For all analyses, the R programming language was used, and the significance level was set to 0.05.

As an observational study involving the analysis of fully anonymised data with no direct patient interaction or intervention, ethics approval was not required. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in the reporting of this study.[12]

RESULTS

Following exclusions for incomplete data sets or duplication, there were 409 subjects in the IDA group and 801 in the control group available for analysis. The descriptive statistics for the two groups are shown in table 1, revealing as anticipated that the IDA group were marginally older, with a greater proportion of females and a lower haemoglobin. Across the study groups (n=1210), drug exposure of any duration was identified in 157 (13.0%) for OACs, 202 (16.7%) for antidepressants, 205 (16.9%) for antiplatelet agents, 574 (47.4%) for PPIs and 52 (4.3%) for non-steroidal anti-inflammatories.

Analysis confirmed the presence of multiple relationships between the study variables. The association was particularly strong between the prescription of PPIs and that of OACs, antiplatelet therapy and non-steroidal anti-inflammatories (p<0.001 for each)—as anticipated, given the widespread use of PPI therapy to minimise the risk of GI side-effects of other drug classes. There were also statistically significant associations between the prescription of (a) PPI and antidepressants, and (b) non-steroidal anti-inflammatories and antidepressants. Finally, the prescription prevalence of all drug groups was associated with both sex (commoner in females) and increasing age.

Statistical assessment of validity and goodness of fit of the logistic regression model based on the criteria outlined in the Method section was satisfactory. As shown in table 2, the model revealed a strong association between long-term PPI exposure and IDA (OR 3.29, p<0.001). A statistically significant association was also demonstrated between long-term OAC exposure and IDA (OR 2.04, p=0.002). Figure 1 shows the relationship between exposure to long-term prescription of these two drug classes within the two study groups according to age, showing a consistent relationship across all age-groups.

The interaction between long term PPI and OAC exposure was not statistically significant, indicating that the prolonged coprescription of PPIs and OACs was additive in terms of the risk of presenting with IDA. IDA was negatively associated with short-term antidepressant exposure (OR 0.25, p=0.001), but not with long-term therapy. IDA was not associated with antiplatelet or non-steroidal anti-inflammatory exposure of any duration.

Analysis of the IDA cohort revealed that 98 (24.0%) did not undergo full investigation of the upper and lower GI tract—this was for a variety of reasons, but in most cases was due to major comorbidity and/or patient preference. Of those that completed full investigation, 84 (27%) proved to have pathology felt to be relevant to the development of IDA, while 227 did not. Of those with pathology, the breakdown was coeliac disease (10), neoplastic disease—carcinoma or advanced adenoma (26), inflammatory lesions with mucosal breaching (35) and vascular malformations (15)—two cases had dual pathology. Thus, 74 cases met the criteria for an HL outlined above (HL+), while 237 did not (HL–).

While long-term PPI and OAC exposure were both associated with presentation with IDA, there were major differences in their respective associations with HL status within the IDA cohort. Analysis of the crude data (figure 2) showed that 18/74 (24.3%) of the HL+ IDA subgroup were on long-term OAC therapy, compared with 22/237 (9.3%) of the HL– subgroup and 50/801 (6.2%) of the control group. The respective figures for long-term PPI therapy were 47/74 (63.5%), 144/237 (60.8%) and 220/801 (27.5%).

Considered from the perspective of RD, subjects in the IDA group with long-term OAC exposure had a 24% (95% CI: 8% to 40%) higher crude probability of HL+ than those with no OAC exposure. Following adjustment for sex and age a significant RD persisted, with an excess of 21 HL+ per 100 (RD 21%, 95% CI: 4% to 37%). In contrast, the adjusted risk of presenting with IDA was unrelated to HL status for long-term PPI exposure (RD –2%, 95% CI –13% to +9%). In brief, OAC exposure was predominantly associated with the HL+ subgroup, while the risk associated with PPI exposure was independent of HL status.

DISCUSSION

The findings of this case–control study demonstrate that among adults in the UK, presentation with IDA has a strong association with long-term PPI therapy, a moderate link with long-term anticoagulation, but no association

Table 2 Multivariable logistic regression analysis of drug class exposure in the IDA versus control group, subdivided by duration of exposure.

	Short-term exposure (<1 year)			Long-term exposure (≥1 year)		
Drug class	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Oral anticoagulants	1.68	0.92 to 3.06	0.090	**2.04**	1.29 to 3.24	**0.002**
Antidepressants	**0.25**	0.10 to 0.54	**0.001**	1.19	0.81 to 1.74	0.400
Antiplatelet agents	1.33	0.54 to 3.08	0.500	1.36	0.94 to 1.98	0.100
Proton pump inhibitors	1.38	0.84 to 2.21	0.200	**3.29**	2.47 to 4.41	**<0.001**
Non-steroidal anti-inflammatories	1.16	0.33 to 3.74	0.800	1.93	0.97 to 3.95	0.060

Statistically significant results are in bold.
IDA, iron deficiency anaemia.

with treatment with antiplatelet agents, non-steroidal anti-inflammatories or long-term antidepressants.

The apparent negative association between short-term antidepressant therapy and IDA was not anticipated. Our speculation is that this finding might reflect confounding due to an excess of antidepressant prescribing in the control group in the months leading up to presentation, given that a proportion of subjects in this group had functional symptoms such as dyspepsia or bowel disturbance driven by psychosocial factors and/or psychological stress.

Various forms of bias need to be addressed in a study of this type, and for this reason potential confounders such as age, sex and coprescribed medications were incorporated into the analysis. In addition, the primary analysis focused on long-term medication exposure, since this is not only more likely to be relevant to the pathogenesis of IDA (a chronic process) but also minimises the risk of protopathic bias[13]—a situation where medication (such as a PPI) is falsely incriminated because it is prescribed for an indication (such as a peptic ulcer) which is the actual cause of the outcome in question (in this case, IDA).

More difficult to control for is the potential bias introduced by 'medicalised' subjects, who are arguably more likely to have been prescribed medications, and also more likely to have had a blood count checked—and so found to have IDA. It is therefore reassuring that long-term exposure to three of the drug classes assessed showed no difference between the two groups.

The study has several other potential weaknesses. First, iron studies were not routinely undertaken in the control group, so some cases may have had latent IDA—however, this might be expected to lessen any observed prescribing differences between the groups. Second, compliance with medication is rarely 100%, so prescription does not equate to ingestion—but this is likely to apply to both study groups. Finally, the findings for non-steroidal anti-inflammatories carry the major caveat that over-the-counter usage will not register in this study.

As always with case–control studies, a key question is whether exposure in the control group accurately reflects exposure in the population as a whole. The evidence for PPI therapy is that it does—a recent UK population study revealed a similar age-related prevalence to the findings in this study, peaking at around 30% in those aged over 60.[14] Published national prescribing data show that although there is considerable variation in PPI prescription rates across the country, the per capita figures for our local integrated care system (NHS Dorset) are close to the national average.[15]

It is important to stress the point that the demonstration of an association does not prove causation. The Bradford

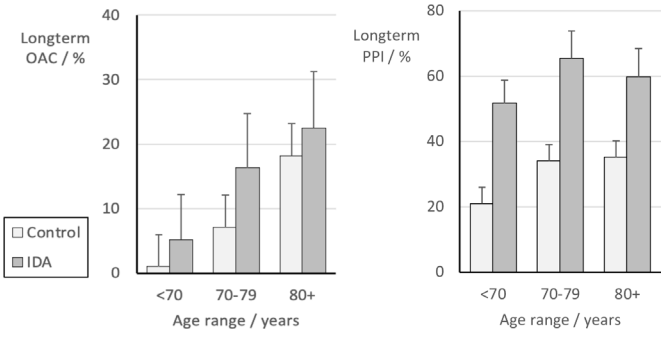

Figure 1 The crude prevalence of long-term prescription of (A) oral anticoagulants, and (B) proton pump inhibitors for the two study cohorts, broken down by age-group (bars indicate SE). IDA, iron deficiency anaemia; OAC, oral anticoagulants; PPI, proton pump inhibitors.

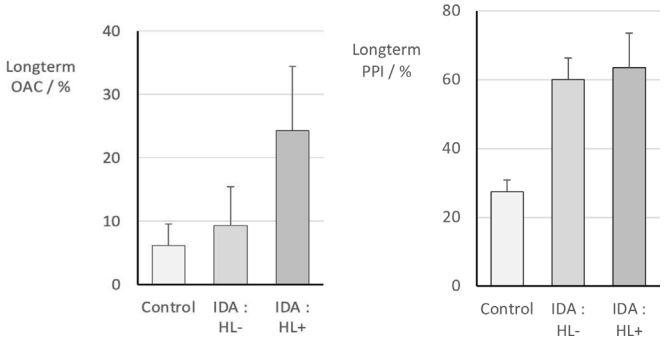

Figure 2 The crude prevalence of long-term prescription of (A) oral anticoagulants, and (B) proton pump inhibitors within the two study cohorts, subdivided according to the absence (HL–) or presence (HL+) of a haemorrhagic lesion in the IDA group (bars indicate SE). IDA, iron deficiency anaemia; PPI, proton pump inhibitors; OAC, oral anticoagulants.

Hill criteria are useful indicators of whether an identified association is likely to be causal.[16] Applying these to the current study the effect size, temporality, specificity and plausibility would all support a causal link between long-term PPI exposure and the development of IDA. There is also a degree of consistency with some though not all of the published literature, as discussed below.

The present study adds to the accumulating evidence from case reports including the effects of drug withdrawal[17 18] and case series[19] that long-term PPI therapy may in some cases predispose to the development of IDA. The literature is contentious however—no effect on the results of iron studies was found on long-term follow-up within two randomised controlled trials[9] or of a large cohort of patients with Zollinger-Ellison syndrome.[20]

Two large community-based case–control studies looking specifically at acid-suppressant therapy have demonstrated an association between PPI therapy and the risk of developing IDA, with ORs of 3.6[10] and 2.5[21]—comparable to the findings in our study. These studies were however of rather different design, being analyses of electronic databases of rather younger populations—the average subject age was under 60 in both. Furthermore, neither study takes into account the potentially important confounding effects of coprescribed drugs such as anticoagulants—by not recording them,[10] or by excluding all subjects taking aspirin, clopidogrel, warfarin or non-steroidal anti-inflammatory drugs.[21] A similar association between PPI therapy and the risk of IDA was reported in a limited meta-analysis based on a small and rather heterogeneous group of original studies.[22]

While the mechanism by which PPIs might predispose to IDA is not fully understood, it is plausible that it reflects impairment of iron absorption in the proximal small bowel[23]—either due to the reduced bioavailability of dietary iron resulting from hypochlorhydria,[24] or perhaps through direct upregulation of hepcidin expression.[25] The results of our study would suggest that either way, the effect is independent of the presence of an HL in the GI tract.

The literature regarding the role of other prescribed medications in the pathogenesis of IDA is extremely limited. Our findings also suggest that long-term anticoagulation may predispose to the development of IDA, though with anticoagulants the effect occurs preferentially in those with confirmed haemorrhagic GI pathology. The implication is that the effect of OACs (unlike that of PPIs) is primarily through accentuating chronic blood loss from mucosal lesions. The case could be made for this being a beneficial effect, potentially allowing pathology (in particular cancer) to be diagnosed at an earlier stage, with a correspondingly better prognosis[7 26] and this possibility warrants further study.

A post-hoc analysis of the ASPREE study suggested that low dose aspirin might increase the risk of developing IDA.[27] However, interpretation is difficult because (1) the difference between the treatment and control groups was marginal (headline HR: 1.2), (2) only a minority had serum ferritin levels monitored to assess for iron deficiency and (3) in contrast to popular practice in the UK, the majority given aspirin did not have concurrent prescription of a PPI—which may well have had a bearing on the findings. A randomised controlled trial of naproxen or ibuprofen versus celocoxib in the treatment of arthritis (PRECISION) suggested an increased risk of IDA with the former,[28] but as there was no placebo limb, it is difficult to be certain whether this difference reflected predisposition in the first group or protection in the second.

The major conclusions of this study are that antiplatelet therapy does not contribute to the development of IDA, long-term anticoagulation has a modest influence and the largest effect appears to be exerted by long-term PPI therapy. This raises the possibility that the surge in IDA referrals seen in secondary care over recent years[3] is being driven at least in part by prescribing practice—and strengthens the case for minimising PPI exposure to the population as a whole,[29] and to those with problematic IDA in particular. Clearly further research is needed to confirm our findings and to strengthen the conclusions of a definitive systematic review with meta-analysis, and should include both case–control and cohort studies from primary and secondary care.

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