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Original Article

The contribution of clinical and pathological predisposing factors to severe gastro-duodenal lesions in patients with long-term low-dose aspirin and proton pump inhibitor therapy

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ABSTRACT

Background: Preventive strategies developed to avoid the complications of antiplatelet therapies recommend the evaluation of risk factors for gastrointestinal events and indicated gastroprotective strategies.
Aim: We aimed to assess the impact of predisposing factors - histological findings, concomitant drug consumption, comorbidities, symptoms, social habits, *Helicobacter pylori* infection - on severe gastro-duodenal lesions in patients with low-dose aspirin and concomitant protective therapy with proton pump inhibitors (PPI).
Method: We enrolled 237 patients with LDA and PPI therapy, referred for upper digestive endoscopy, divided into two groups according to the severity of their endoscopic lesions (172 patients with no or mild endoscopic lesions and 65 patients with severe endoscopic lesions).
Results: In the univariate logistic regression model, the factors associated with severe gastro-duodenal lesions were gender (OR = 1.87, 95% CI: 1.04–3.41), anticoagulants (OR = 2.40, 95% CI: 1.26–4.53), gastric atrophy and/or intestinal metaplasia (OR = 1.85, 95% CI: 1.04–3.32), congestive heart failure (OR = 2.59, 95% CI: 1.16–6.62), anaemia (OR = 3.01, 95% CI: 1.67–5.47) and smoking (OR = 4.29, 95% CI: 1.57–12.32). In the final model, anticoagulants ($p = 0.041 < 0.05$) and anaemia ($p = 0.019 < 0.05$) were risk factors for severe lesions via multivariate regression analysis, while for active/inactive chronic gastritis and smoking a positive dependency with a tendency towards statistical significance ($p < 0.10$) was noticed for severe gastric lesions.
Conclusions: In patients treated with low-dose aspirin and gastroprotective therapy with proton pump inhibitors we have enough evidence to consider co-treatment with anticoagulants and anaemia important predictors for severe endoscopic lesions, while other factors such as inflammation in gastric biopsies, congestive heart failure, co-treatment with clopidogrel and smoking tended to have a positive influence on risk for severe gastro-duodenal lesions.

1. Introduction

Antithrombotic therapy is widely used for the treatment and prevention of cardiovascular and cerebrovascular diseases. Worldwide, one of the most frequently used medication in this respect is low-dose aspirin (LDA, 75–325 mg/day). Its extensive usage in daily practice is limited due to the gastrointestinal (GI) side effects [1,2]. The risk of serious bleeding episodes (especial GI), as well as dyspeptic symptoms reduce the adherence to LDA therapy [3]. Nowadays, it is accepted that LDA treatments may generate mucosal damage even at very low doses, being responsible for the increasing prevalence of drug related bleeding episodes [3]. The aging population and the increasing number of LDA prescriptions frequently associated with other antithrombotic drugs further increase the drug related GI complications [4].

Preventive strategies developed to avoid the complications of antiplatelet therapies recommend the evaluation of risk factors for GI events (*Helicobacter pylori-H. pylori* infection, age > 70 years, concomitant use gastrotoxic drugs, previous ulcers) [5–8] and indicated gastroprotective strategies. Use of proton pump inhibitors (PPI) and eradication of *H. pylori* infection are the most important recommended strategies. Previous studies have shown conflicting data regarding the role of *H. pylori* infection and GI side effects of non-steroidal anti-inflammatory drugs, including LDA. Many factors seem to influence this complex interplay:

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germ virulence, genetic host background, gastritis phenotype, age of infection and maybe other individual factors. Hence, preventive strategies should not be the same for the worldwide population [3].

1.1. Scope

We aimed to assess the impact of pathological and clinical predisposing factors (histological findings, concomitant drug consumption, comorbidities, symptoms, social habits, *H. pylori* infection) on severe gastro-duodenal lesions in patients with long-term LDA and PPI therapy.

2. Methods

2.1. Data collection

We enrolled patients with chronic LDA and PPI therapy referred for an upper digestive endoscopy between September 2012 and December 2015. Patients attended UDE for the following reasons: digestive symptoms, anaemia or screening for GI bleeding risk (before the initiation of combined antithrombotic therapy, before major surgery). A written consent was obtained from every patient. Medical records and patients' interview had to confirm the daily administration of aspirin 75–125 mg/day (accessible doses in Romania) and PPI (pantoprazole 20–40 mg/day, esomeprazole 20–40 mg/day, omeprazole 20–40 mg/day) for at least three months prior to the investigation.

General data were collected using a structured interview and medical records. We registered the medical history, current symptoms, concomitant use of other drugs (NSAID, acenocumarol, low-weight molecular heparin-LWMH) as daily administration of a regular dose for at least two weeks before endoscopy. We considered a positive history of peptic ulcer disease the presence of suggestive findings on previous endoscopy or radiology examinations, as well as the presence of diagnosis and specific treatments in the medical records of these patients. We used a direct interview and medical records to check for comorbidities.

2.2. Endoscopy

The UDE findings were recorded. We described mucosal lesions as erythema, petechiae, erosions, or ulcers. Petechiae were defined as haemorrhagic areas with no mucosal defect and erosions as mucosal defects smaller than 5 mm. Defects larger than 5 mm in diameter, extended into the deeper layers of the gastric or duodenal wall were defined as ulcer. We assessed gastro-duodenal lesions using a modified Lanza score (MLS) [9], one of the most frequently cited in literature. For no mucosal lesions a 0 score was given, while for one erosion (mucosal defect smaller than 5 mm) or petechiae (haemorrhagic area without mucosal defect) a score of 1 was attributed. We considered score 2 when 2–10 erosions or petechiae were counted, score 3 for >10 erosions or petechiae and score 4 when an ulcer was present. Patients with gastro-duodenal surgery, varices, active severe bleeding or patients in whom a gastric cancer was discovered were excluded. We also excluded patients with haematological disorders (leukaemia, lymphoma, aplastic or haemolytic anaemia), as well as patients with severe medical conditions (cancer, cardiac, respiratory, liver or kidney end-stage disease).

2.3. Histology

Two biopsy specimens from the antrum and two from the corpus (lesser and greater curvature) were taken for routine histology and were examined by a single pathologist. Biopsy specimens were fixed in formalin, embedded in paraffin and examined with hematoxylin-eosin, PAS-alcian blue and Giemsa staining. *H. pylori* infection was considered negative if *H. pylori* was absent from all biopsy sites and positive if found in at least one histology test. The degrees of mucosal chronic inflammation, activity, *H. pylori* infection, glandular atrophy and intestinal metaplasia were classified into 4 grades according to the Updated Sydney System. Patients without important inflammation, but with prominent foveolar hyperplasia, fibro-muscular replacement of the lamina propria, and congestion of superficial mucosal capillaries were diagnosed as reactive gastropathy. We excluded patients with autoimmune gastritis, dysplasia, and cancer or with an incomplete set of biopsies.

2.4. Statistical analysis

For statistical analysis and graphics the R software v.3.3.1 was applied (R Foundation for Statistical Computing, Vienna, Austria). Demographic and clinical data were summarized as mean ± standard deviation or absolute (relative) frequencies. In order to identify significant difference in terms of quantitative demographic characteristics the Student-*t*-test was used while the difference in frequencies regarding nominal characteristics was tested via Chi-square or Exact Fisher's test.

The risk of advanced gastric lesions (MLS ≥ 3) was tested using the logistic regression method with adjustments for demographic and clinical covariates. We performed multivariate logistic regression analysis to assess independent prognostic factors for advanced gastric lesions in patients with long-term aspirin use and PPI. The regression model was constructed using a purposeful selection of covariates. The initially tested model contained variables with an estimated significance level $p \leq 0.25$ in bivariate analysis and univariate logistic regression together with variables of known clinical importance or relevance. In order to decide which variables remained in the final model, the partial likelihood ratio test was used to compare multiple nested models to assure that the parsimonious model fits as well as the full model. A change in the estimated regression coefficients ($\Delta\beta'$) of >20% between parsimonious and full model was considered an indicator for recognizing a variable as an important contributor to the model. Adjusted odds ratios and associated 95% confidence intervals were also estimated.

In testing of all null hypotheses a two-sided p-value lower than 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical studied parameters

The observed relative frequency of severe gastro-duodenal lesions was 27.4%. There was no significant difference in terms of age between the studied groups (mean ± standard deviation: 65.98 ± 9.05 for controls vs. 67.92 ± 8.71 for cases, t-statistic = −1.49, $p = 0.138$) but there was a significant difference in terms of gender, namely the severe lesions were more frequent in males than in females (33.1% of males had severe lesions vs. 20.9% females).

The significant differences between frequencies of demographic and clinical characteristics in the studied groups are described in Table 1.

In Table 2 we also described those characteristics that showed a tendency to statistical significance.

Other comorbidities observed in the studied samples were: ischemic heart disease (58/65 cases vs. 152/172 controls, $p = 0.853$), cerebrovascular disease (9/65 cases vs. 16/172 controls, $p = 0.310$), liver disease (38/65 cases vs. 91/172 controls, $p = 0.444$), diabetes (21/65 cases vs. 62/172 controls, $p = 0.590$), kidney disease (25/65 cases vs. 52/172 controls, $p = 0.228$) and osteoarthritis (25/65 cases vs. 64/172 controls, $p = 0.859$).

There were no significant differences between cases and controls regarding clopidogrel (17/65 cases vs. 32/172 controls, $p = 0.212$) and NSAIDs therapy (10/65 cases vs. 33/172 controls, $p = 0.574$).

There were no significant differences between cases and controls regarding *H. pylori* status (21/65 cases vs. 52/172 controls, $p = 0.875$), history of PUD (51/65 cases vs. 125/172 controls, $p = 0.408$), reactive

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