RETROSPECTIVE STUDY ON THE FREQUENCY AND CAUSATIVE MECHANISMS OF CHRONIC GASTRITIS IN AN INTEGRATIVE MEDICINE CENTER IN TÎRGU-MUREŞ

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Abstract: *The aim of this study was to establish the main classes of drugs incriminated in the occurrence of chronic gastritis as well as the evaluation of the main therapeutic protocols. 315 medical letters of patients diagnosed with chronic gastritis registered in the database of an Integrative Medicine centre in Tîrgu-Mureş between 2012-2017 were analised. The frequency of gastritis was comparative, as prevalence, among the studied age groups, the causative factors varying among them. The incriminated medication in the occurrence of gastritis was represented by substances such as non-steroidal anti-inflammatory drugs, levothyroxine, coumarin anticoagulants, modern anticoagulants or platelet antiaggregant drugs. Proton pump inhibitors are most commonly used for the treatment of chronic gastritis, but also prokinetic, antispasmodic or probiotic are frequently used. Because several pathologies, including environmental and dietary factors are incriminated, the correct treatment implies not only prescription appropriate medication but also lifestyle changes.*

INTRODUCTION

Nowadays, the frequency of chronic gastritis is increasing, explained by the daily stress of the population, by a irregular lifestyle (the consumption of processed foods containing irritating compounds for the gastric mucosa, disrespect of a correct meal timetable, excessive consumption of coffee, carbonated drinks and alcoholic beverages and smoking), but also through the consumption of drugs with ulcerogenic potential.

PURPOSE

The aim of this study was to identify the main risk factors for the occurrence of chronic gastritis and the main therapeutic approaches of this pathology.

MATERIALS AND METHODS

315 medical letters belonging to patients diagnosed with chronic gastritis registered in an integrated medical centre in Tîrgu-Mureş were evaluated to identify the main causative factors of this disease. From the medical letters, the following data were obtained: the origin of the patients (urban or rural area), the age of the patients, the everyday lifestyle (consumption of coffee, alcohol, tobacco), exposure to stress factors by self-estimation (on a scale from 1 to 10), *Helicobacter pylori* infection, endoscopic confirmation of gastritis.

Therapeutic approaches in patients who underwent chronic treatment for other comorbidities were evaluated to identify the causative agents of gastritis and possibly drug interactions.

The study was a retrospective review of the medical letters from 2012-2017 and was approved by the Ethics Commission for Scientific Research of the University of Medicine and Pharmacy Tîrgu-Mureş (No. 70/14.04.2017).

RESULTS

Of the total patients (n = 315), 136 (43%) were males and 179 (57%) were females.

Because it is known that drinking alcohol, caffeine or smoking increases the risk of gastritis, patients have been asked to confirm a possible consumption of these substances. In the selected group, most of the patients were aged 40-49 who also consumed higher quantities of alcohol and coffee, followed by those aged 60-69, 50-59, 30-39, respectively 20-29. The number of patients aged up to 20 years and over 70 was lower. Although patients have confirmed that they consume coffee, most have denied any alcohol consumption.

Patients were also asked to assess the degree of stress they are subjected to daily on a scale from 1 to 10, 1 being the lowest level of stress and 10 increased stress levels. Stated stress levels (SSL) of at least 7 by self-evaluation were considered significant. The distribution of patients by age category and lifestyle are shown in table no. 1.

Table no. 1. Patients' distribution by age and life style (SSL>7)

Age	No.	Smoking	Alcohol	Coffee	SSL>7
20-29	42	10	7	18	20
30-39	58	20	23	40	33
40-49	70	10	22	49	30
50-59	59	8	21	43	28
60-69	60	4	15	42	21
70-79	19	0	4	11	6
80-89	7	0	0	6	2

Identified drug and infectious factors

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs), levothyroxine or oral anti-platelet/anticoagulants, respectively *Helicobacter pylori* infection, were the main factors causing chronic gastritis.

Among the NSAIDs included in the treatment protocols that could be incriminated in the pathology of gastritis were ketoprofen (n = 4), ibuprofen (n = 11), nimesulide (n = 2), diclofenac (n = 5) or others not mentioned in medical letters (n =

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11). They were removed from the treatment protocol when this was possible.

Out of 12 patients included in the study who were treated with levothyroxine to correct hypothyroidism one patient presented *Helicobacter pylori* infection.

Platelet antiaggregant drugs used in treatment protocols included acetylsalicylic acid (75-150 mg) and clopidogrel. All patients with clopidogrel treatment (n = 5) have been prescribed pantoprazole. The choice is justified considering the possible interactions between clopidogrel and other proton pump inhibitors (PPI) such as omeprazole, esomeprazole and to a lesser extent lansoprazole. Regarding oral anticoagulants, 5 patients were treated with acenocoumarol and 3 with dabigatran, drugs incriminated in gastric haemorrhage.

Of the 315 patients, the presence of *Helicobacter pylori* infection was determined in 301, of which 39 were positive. In order to eradicate the infection, a triple combination was used: two antibiotics and a PPI. Among patients who have been confirmed for *Helicobacter pylori* infection, there were also people who had previously received antibiotic treatment (tetracycline - Tetr., Amoxicillin - Amoxi., Clarithromycin - Clarithro., Levofloxacin - Levo.) without obtaining *Helicobacter* eradication, in these cases a change of medication was applied, as shown in table no. 2

Table no. 2. Antibiotics prescribed for eradicating *Helicobacter pylori* infection

Antibiotic	Tetr.*	Amoxi.*	Claritro.*	Levo.*
Before	2	8	5	1
After	0	9	6	3

From the medical letters, it was found that most of them were smokers and cigarette smoke may decrease the effectiveness of antibiotic treatment, especially with the combination of amoxicillin + clarithromycin.

Therapeutical options

For the treatment of chronic gastritis, PPIs, especially esomeprazole and pantoprazole, were preferred, the latter being particularly prescribed to patients with other pathologies to avoid drug interactions that could result from the enzyme inhibition of CYP2C9, CYP2C19 and CYP3A4 isoforms of cytochrome P450 by omeprazole and its active metabolite, esomeprazole.

In patients already receiving omeprazole /esomeprazole treatment, the interactions with chronic medication (presented in table no. 3) were assessed before re-evaluating anti-secretory treatment. It is expected that concomitant administration with enzyme inhibitors would produce increased plasma concentrations.

Table no. 3. Interactions between omeprazole /esomeprazole and chronic medication prescribed to the patient

Omeprazole +	Interaction	Consequences	Clinical relevance
Verapamil	CYP3A4	↑verapamil plasm. conc.	excessive bradicardia
Indapamide	CYP3A4	↓ Mg plasm. conc.	muscle spasms, tremor or seizures /arrhythmias
Atorvastatin	CYP3A4	↑ atorvastatin plasm. conc.	myopathy and/or rhabdomyolysis
Etoricoxib	CYP3A4	?	?
Alprazolam	CYP3A4, CYP2C9	↑ alprazolam plasm. conc.	drowsiness and respiratory depression
Donepezil	CYP3A4	↑ donepezil plasm. conc.	?

DISCUSSIONS

The reduced number of patients under the age of 30 is explained by the fact that the risk of gastritis increases with aging and the increase in coffee, alcohol or tobacco consumption, correlated with a stressful lifestyle in the active adult population. Also over 40 years, patients are diagnosed with various chronic conditions requiring drug therapy that may present gastric side effects.

Chronic gastritis can be caused by many endogenous and / or exogenous factors (drugs, alcohol, smoking, irritating spices, *Helicobacter pylori* and *Gastrospirillum homini* infections, hygiene-food deficiencies, excessive stress and effort).

Lifestyle is an important factor for the occurrence of chronic gastritis. Caffeine stimulates acid secretion due not only to caffeine's mechanism of action but also to other organic substances in the coffee composition. It activates pepsinogen and stimulates the release of gastrin. Coffee consumption leads to relaxation of the inner esophageal sphincter as a result of inhibition of phosphodiesterase and increased concentration of cyclic adenosine monophosphate (AMPc) in tissues, which promotes gastroesophageal reflux. Eaten foods do not necessarily produce chronic gastritis directly, but they can favour *Helicobacter pylori* infection.

Smoking can also stimulate clorhidric acid (HCl) and pepsinogen secretion, reduce pancreatic bicarbonate flow, may reduce pyloric tone, which promotes gastric reflux. Smoking also diminishes the protective mucus layer, decreases the synthesis of prostaglandin E2, by catecholamine influx, disrupts the microcirculation, leads to the increase of the carboxyhaemoglobin in the blood thus decreasing the amount of oxygen, reduces the gastric motility, thus prolonging the gastric evacuation and disturbs the epithelial repair by depressing the synthesis of salivary growth factor.(1)

Of NSAIDs, ibuprofen is the most commonly used. Since ibuprofen is marketed under the OTC (over the counter) regimen, it is very accessible to patients without the need for a prescription. Although it is considered to be better tolerated at the gastric level, it can also have irritant effect on the mucosa, especially in the case of long-term administration due to non-selective inhibition of cyclooxygenases, this mechanism decreasing the synthesis of gastric cytoprotective prostaglandins.(2)

Regarding levothyroxine treatment, it is recommended to be administered in the morning on the empty stomach, as it is better absorbed at acid pH, which may contribute to irritation of the gastric mucosa.(3) In these patients, however, administration of PPIs is not indicated due to increased gastric pH due to anti-secretion medication and decreased levothyroxine uptake, in which case it is necessary to readjust the dose of medication to correct hypothyroidism.(4) The bioavailability of levothyroxine is also affected by *Helicobacter pylori* infection or caffeine. In this case, the patients diagnosed positively with *Helicobacter pylori* were not prescribed PPIs or other gastric antisecretory drugs, but most patients were coffee users (10 patients out of 12).(5,6)

For patients using clopidogrel, pantoprazole was prescribed as PPI for pharmacological reasons. Administration of other PPIs (omeprazole, esomeprazole) would result in therapeutic inefficiency of clopidogrel by preventing its bioactivity in the liver. This bioactivation occurs at the CYP2C19 isoform of the cytochrome P450, PPIs previously mentioned, being enzyme inhibitors of CYP2C19.(7,8,9)

In case of treatment with oral anticoagulants (acenocoumarol, dabigatran), the PPI should be chosen with caution, as the inter-individual and intra-individual variability of

the pharmacological response at a given dose is due to the CYP2C9 polymorphism. Any possible metabolic interaction in this enzyme pathway should be avoided because even a slight increase in plasma concentrations of acenocoumarol may lead to overdosage with the risk of haemorrhage as it has a narrow therapeutic index.(12) The use of omeprazole, esomeprazole and lansoprazole should also be avoided.(13)

For dabigatran, the risk of interaction in the hepatic metabolic process with PPIs is therapeutically negligible, *in-vitro* and *in-vivo* studies demonstrating that concomitant use does not significantly alter the pharmacokinetics of the anticoagulant.(14)

CONCLUSIONS

The frequency of gastritis presents the same prevalence in age groups 30-39, 40-49, 50-59 and 60-69, respectively, for the following reasons: the young active population is subject to increased daily stress, consumes a large amount of caffeine and a large number of people smoke, the latter being risk factors for the occurrence of chronic gastritis.

Older people suffer from various conditions and require chronic treatment, many of which have side effects at the gastric level, either due to the irritant effect, by preventing the formation of protective mucus or by favouring bleeding. For patients included in the study, we identified the presence of NSAIDs, levothyroxine, coumarin and modern anticoagulants and platelet antiaggregant respectively.

PPIs are most commonly used for the treatment of chronic gastritis, although omeprazole and esomeprazole present an increased risk for drug interactions because of their enzyme-inhibiting effect. However, lately there has been a preference for prescribing pantoprazole, a gastric antisecretory that does not alter the pharmacokinetics of concomitant medication. In addition, prokinetic, antispasmodic or probiotic are often prescribed.

Although the presence of *Helicobacter pylori* infection has been confirmed in a small number of patients, eradication of the infection may cause problems, particularly in smokers or overweight people, even if the therapeutic prescription is respected.

In the emergence of this type of pathology several factors are being incriminated, including environmental and dietary factors, therefore, the correct treatment implies not only the prescription of adequate medication but also the change of lifestyle.

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