Chapter 8

Prescription of Proton Pump Inhibitors in Elderly Subjects in Real Life: A Retrospective Study in a Gastroenterology Department

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Abstract

The proton-pump inhibitor (PPI) is an effective and widely used treatment but may cause side effects, especially for the elderly. Materials and methods: this is a cross-sectional study including 45 patients older than 65 years, followed at our outpatient and treated with PPIs for at least a year. The indication for PPI, the results of any endoscopy, and the quality of the tolerance of these molecules is specified by the data folder. During the consultation, we conducted an interrogation to an update of the history and medications to our patients and a type checking of the molecule, the dose, and the quality of the observance. Results: patients were divided into 32 women and 13 men with a mean age of 75 ± 7 years (65–92). The average length of PPI use was 6 ± 4 years (1–16) with a consumption of a double dose for at least 1 year in 28.8% of cases. The prescribed dose was higher than the recommended dose in at least 15.5% of cases. PPIs were well tolerated. One patient had presented a microscopic colitis, revealed by diarrhea regressed after discontinuation of PPIs. Conclusion: PPIs were prescribed in elderly subjects by gastroenterologists, in a university center, with a high dose and long. In our series, this treatment is well tolerated in the elderly.

Keywords: aged person, drug interactions, drug-related side effects, drug utilization, proton pump inhibitors

1. Introduction

Proton pump inhibitors (PPI) constitute a very effective and used treatment at present [1–3]. Previously, they would seem to cause undesirable effects and medicinal interactions probably

serious and badly known, especially for the elderly person often fragile and exposed to a polypharmacy [4]. On the other hand, it is a very expensive therapeutic class and frequently used in an inappropriate way [2–4]. In Tunisia, the use of these medicines to the old subject, in the public structures, by specialists, was not studied. So, we have led this study to realize an evaluation of the professional practices concerning the prescription of these molecules, by gastroenterologists, in a teaching hospital (CHU) of the Tunisian South, to the geriatric population.

The objectives of our study were:

1. Specify the main indications and the modalities of the long-term prescription of the PPI to the old subjects and compare them with the international recommendations.
2. Evaluate the observance, the tolerance, and the possible medicinal interactions of the prescribed PPI in the long term to the elderly subjects.
3. Specify, through our results and review of the literature, the difficulties were met and the risks incurred during the prescription of these medicines to the elderly and proposed strategies to overcome them in our current practice.

2. Material and methods

It was about a retrospective study including 45 subjects of more than 65 years old followed in the external consultation of the gastroenterology department of Hédi Chaker hospital of Sfax, having consulting between July 01st, 2015 and December 31st, 2015. The PPI indication, the results of a possible initial endoscopic exploration, and their tolerance were specified by the data of the file. During the consultation, we realized an interrogation with the aim of checking the molecule's type, the dose, and the quality of the PPI observance. The criteria of inclusion were as follows: an upper age or equal to 65-year-old during the beginning of PPI treatment and PPI consumption at least three times a week during a duration of more than 12 months. The criteria of noninclusion were represented by the absence of an exhaustive list of the personal histories of patients and their medicines. The evaluation of the best use of the PPI was realized by referring to the current recommendations of the High Authority of Health and the French Agency of sanitary safety of the products of health (Afssaps) in 2007 [5]. The data were analyzed by using the statistical software SPSS 20.0.

3. Results

The average age of our patients was of ±75 7 years (65–92). About 1/3 of the patients were less than 70 years old (**Figure 1**). In our study, a clear feminine predominance was noted with a sex ratio H/F of 0.4 (**Figure 2**). The majority of our patients were of urban origin (60%) (**Figure 3**). The distribution of the patients according to antecedent is specified as in **Table 1**. Excepting the

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pathology that justifies the PPI use, 25 patients (55.4%) had at least 3 medical antecedent with a daily average number of medicine consumption of 4.8 ± 4.3 (0–17). Six patients had osteoporosis, diagnosed before the establishment of the PPI in a case and after the establishment of the PPI in the five remaining cases. The average deadline separating the beginning of taking the PPI and the discovery of the osteoporosis was of 2.5 years (1–4). No control of the bone densitometry was asked during the follow-up of our patients who have a normal initial examination. Two patients (4.4%), with antecedent of ischemic heart disorder with angioplasty, were treated by clopidogrel (Plavix®) neither with any precaution's closed view to the type of the molecule nor with the schedule of taking PPI. During our interview, we recommended them to keep an interval of 12 hours between the consumption of the PPI and that of the clopidogrel. The main indication of the PPI at our patients was the gastroesophageal reflux (GER) (75.6%) (**Figure 4**). Before the prescription of the PPI, 41 patients (91%) underwent upper digestive endoscopy FOGD. The results of this examination were dominated by the association of a peptic esophagitis and a hiatal hernia (**Table 2**). Among the four remaining patients:

- The FOGD was refused by two patients having abdominal pain
- The FOGD was made after a deadline of using of the PPI (2 years and 6 months respectively) in two patients having typical clinical signs of GER.

Five patients having a normal FOGD had:

- Typical symptoms of GER in three cases
- Abdominal pain in a case
- A long-term treatment by nonsteroidal anti-inflammatory drug (NSAID) in a case.

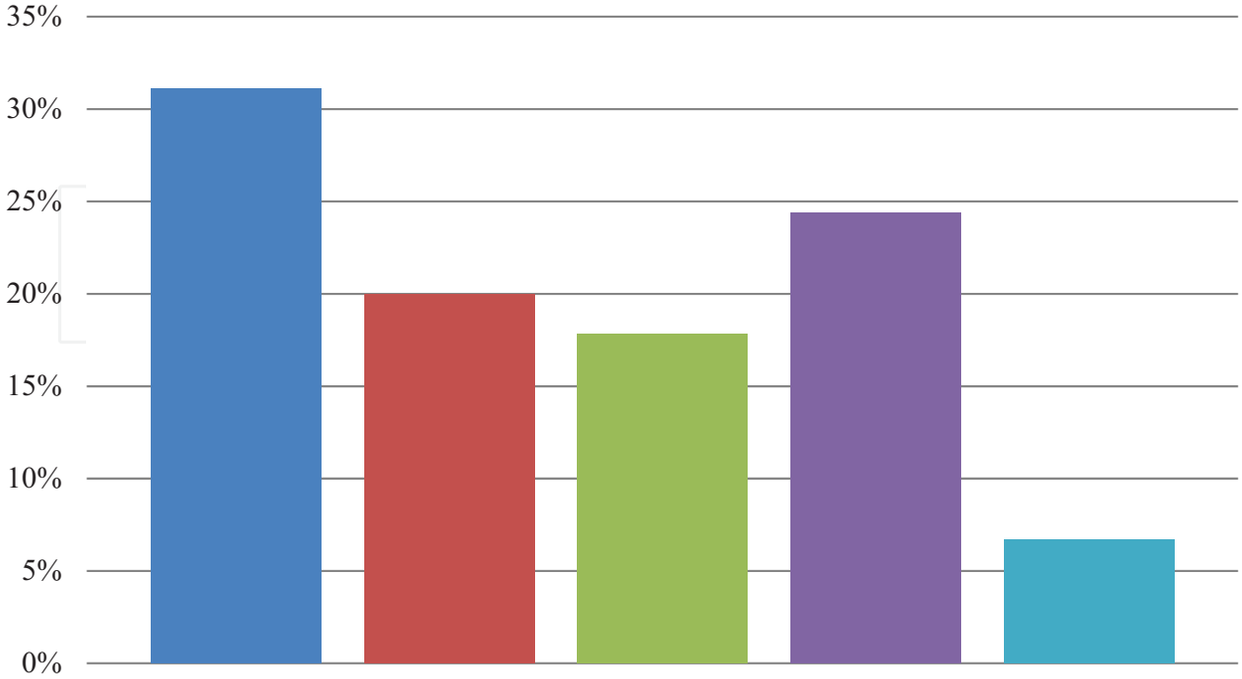

Figure 1. Dividing patients according to the age.

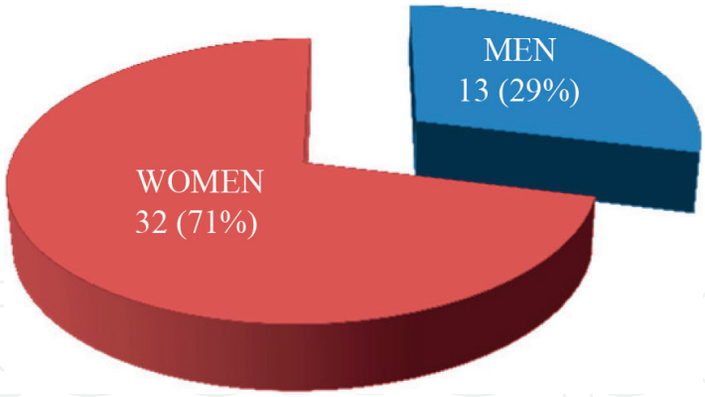

Figure 2. Dividing patients according to sex.

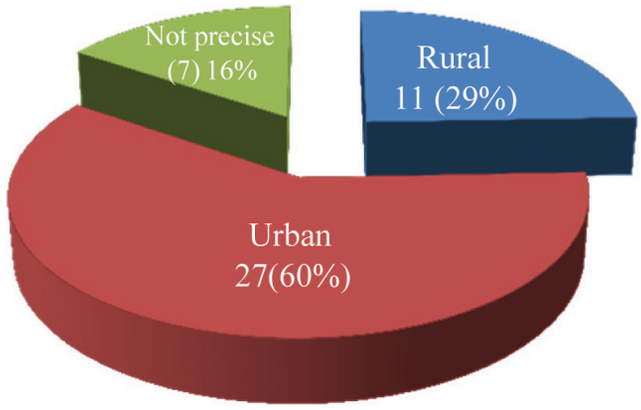

Figure 3. Dividing patients according to their geographic origin.

Antecedents	N (%)
HTA	24 (53.3)
Rheumatologic pathology	16 (35.6)
Dyslipidemia	11 (24.4)
Heart disease	9 (20)
Diabetes	8 (17.7)
Osteoporosis	6 (13.3)
Anemia	2 (4.4)

Table 1. Dividing patients according to antecedents.

The FOGD data at five patients who had abdominal pain motivating the endoscopy were the following ones:

- A bulbar ulcer in one patient
- Bulbar ulcerations in one patient

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- Ulcerated antral gastropathy associated with a bulbar ulcer in one patient
- A congestive gastropathy in one patient
- Normal FOGD in one patient

Gastric biopsies were realized in all the patients who had a bulbar ulcer or bulbar ulcerations. These biopsies were concluded with the absence of the helicobacter pylori in all cases. It was probably caused by the intermittent consumption of AINS in these patients. During the follow-up, only three patients had undergone an endoscopic control, having two peptic stenosis and one Barrett esophagus (BO). It revealed the disappearance of the stenosis in both patients and the absence of dysplasia in the third.

During the period of study (in July 01st, 2015–December 31st, 2015), the PPI availability in the pharmacy of the hospital and in the health centers was omeprazole in the form of 20 mg capsules. Concerning the years preceding the study's period, the molecules availability in the hospital list were either the omeprazole in the form of tablets or 20 mg capsules, or the lansoprazole in the form of 30 mg capsules.

However, these medicines were not always available in this pharmacy and\or in the pharmacies of health centers (frequent breaks of the stock). As a result, some patients would have used other molecules, which they had bought from nearby pharmacies. The interrogation of the patients and their parents was not able to specify the type of these molecules. The average duration of the PPI treatment was of 6 ± 4 years (1–16) with a duration of more than 2 years in 34 cases (75.6%). The PPI was prescribed at the rate of a simple daily dose for 29 patients (64.4%) and of a double daily dose for 5 patients (11.1%). For the rest of the patients, the treatment was prescribed:

- At first, in simple daily dose, during an average duration of 39.1 months (2–96) and then in double daily dose for 9 patients (20%) during an average duration of 4.5 years (1–10).
- At first in double daily dose and then in simple daily dose for two patients (4.4%). The duration of taking the simple dose was of 2 months for a patient and 9 months for the second and that of the double dose was of 6 years and 18 months respectively.

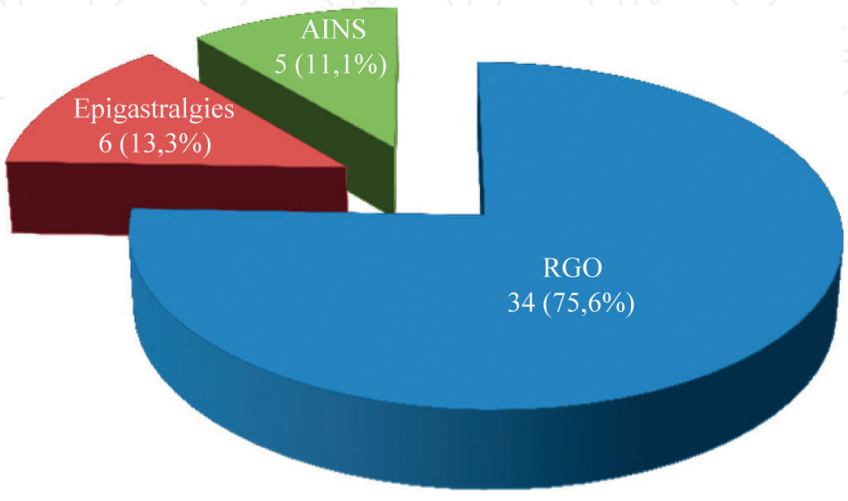

Figure 4. Dividing patients according to PPI indications.

Localization and types of lesions	N (%)
Isolated esophageal lesions	8 (19.5)
Peptic esophagitis OP	4
Peptic stenosis	2
Mycosic esophagitis	1
Barrett esophagus	1
HH/G isolated	1 (2.4)
OP + HH	10 (24.4)
Isolated gastric lesions:	7 (17.1)
Congestive antral gastropathy	3
Ulcerated antral gastropathy	2
Nodular antral gastropathy	1
Pyloric big folds	1
Isolated duodenal infringement:	2 (4.9)
UB	1
Bulbar ulcerations	1
Multiple locations of the lesions:	8 (19.5)
HH + congestive antral gastropathy + bulbar ulcer	1
OP + HH+ bulbar ulcerations	2
OP + HH+ congestive antral gastropathy	1
OP + bulbar ulcerations	1
Ulcerated antral gastropathy + UB	2
HH + bulbar ulcerations	1
FOGD normal	5 (12.2)
Total	41 (100)

OP: peptic esophagitis; HH: hiatal hernia.

Table 2. Dividing patients according to the data of initial FOGD.

The change of the PPI dose was indicated by the evolution of the symptoms motivating their prescription. So, the increase in doses was secondary in the persistence of the symptoms in spite of a good observance of a simple dose, whereas the decrease in doses was motivated by the decrease in the frequency of the symptoms under a double dose of treatment.

The characteristics of seven patients treated straightaway by an PPI double dose are detailed in **Table 3**. The recommendations of the HAS were not respected within the frameworks of:

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- The indication of the FOGD in four cases (9%): because of the absence of realizing an FOGD before prescribing the PPI for four patients having abdominal pain or symptoms of GER with an age > 60 years.
- The PPI indication in two other cases (4.4%): having a prescription of the PPI in front of abdominal pain with a normal FOGD, for one case and a congestive gastropathy in another case, without prescribing long-term AINS in two cases. These two situations do not establish an indication for a treatment by a PPI according to the HAS recommendations.
- the PPI posology:
  - Seven cases (15.5%) were treated straightaway by an PPI double dose. Indeed, according to the HAS recommendations, the interest of a double dose was not even demonstrated in RGO case with a severe esophagitis (except in not healing case and subject to a good observance of the treatment, where an increase in the posology can be proposed). So, no indication, among those of our patients, justifies an IPP treatment with one double dose straightaway. For the other cases, it was difficult to judge the concordance of posology with the recommendations against the difficulties of specifying the molecule's type of the prescribed IPP (omeprazole or lansoprazole), because the recommended posology, within the framework of our study's indications, is the full dose (or simple dose) for the omeprazole and the half-dose for the other molecules. The average duration of using PPI with our patients was of 6 ± 4 years (1–16). During the follow-up of our patients, the evaluation of PPI tolerance and the efficiency of the PPI, realized every 6 months, were based on anamneses data without any complementary examination. Furthermore, updating the antecedent list and the patients' treatments was not realized in a systematic way at every consultation. Among our patients, 31 (75.6%) had a good observance for the PPI. The nonavailability of the PPI in the public sanitary structures was the cause of the limited observance.

No.	Age (years)	Sex	Indication of the IPP	Duration of the DD of the PPI (months)	Endoscopic data
1	72	F	Abdominal pain	12	Congestive antral gastropathy
2	84	M	+ NSAID GER	2	Ulcerated antral gastropathy
3	76	F	Abdominal pain	9	+ bulbar ulcer
4	78	F	GER	60	Congestive antral gastropathy
5	82	M	GER	48	HH/G, OP type 2
6	78	F	GER	24	Peptic stenosis
7	68	M	GER	12	Normal

HH: hiatal hernia, GER: gastroesophageal reflux, NSAID: regular consumption of non steroidal anti inflammatory drugs OP type 2: peptic esophagitis type 2.

Table 3. Characteristics of patients treated by double dose (DD) of PPI.

The PPI did not cause any symptoms in 44 patients (97.7%). The remaining patients were presented after the consumption of lansoprazole double dose during 1 year (in front of a refractory GER) with profuse diarrhea. The colonoscopy revealed a normal colonic mucous membrane, but the colonic biopsies had revealed a microscopic colitis of colitis collagen type. Stopping the use of PPI has entrained the disappearance of the diarrhea. Because of the absence of treating the GER by famotidine in the dose of 40 mg/d, the patient was treated by the omeprazole in the dose of 20 mg/d). A few days after the beginning of the treatment, the evolution was marked by the reappearance of the diarrhea. So, the PPI was stopped. For the GER treatment, the patient was treated by a double dose of famotidine associated with the sodium alginate with a satisfying control of symptoms without diarrhea.

4. Discussion

The PPI are an expensive medicinal class and widely prescribed in the world. Indeed, they represented more than 16 million of prescriptions in France in 2008 and about 101 million prescriptions in the United States in 2006 [5, 7]. A recent study, led in Denmark, has revealed a greater increase in the prescription of the PPI during the last decade [8]. In Tunisia, the PPI prescription was not evaluated on the national scale, but the development of several generic medicines since 2013 (10 for omeprazole, 6 for esomeprazole, 4 for lansoprazole, and 1 for pantoprazole) suggests an increasing in the prescription during these last years [9].

The overuse of the PPI is a notorious problem in the world. Numerous studies were interested in the evaluation of the good use of this therapeutic class by basing itself on the recommendations. In the United States, in 2007, a study showed that 54% of the prescriptions of IPP were not adapted [10]. In France, a report from the accounts commission of the Social Security in October, 2009 reported that 15% of the IPP would prescribe out the planned indications. According to this report, 65% of the IPP prescriptions for GER in 2008 were concerned with patients more than 65 years old [11]. Furthermore, in retirement homes, this medicinal class was prescribed for the old subjects in 21.8–37.8% of cases according to the studies [3, 12] However, few studies were interested in the harmlessness of the PPI in the long term, and particularly to the elderly [13].

In spite of its retrospective and monocentric character, with a limited number of patients and impossibility to study the effect of every PPI molecule alone, this study has allowed us to evaluate, for the first time in Tunisia, the tolerance of these medicines, in short and medium terms, as well as the current modalities of their prescription, to old subjects, by gastroenterologists, in a Tunisian CHU.

In our study, the PPI indications were not in agreement with the recommendations in 4.4% of the cases. This percentage was lower than that found in a study led in an American urban geriatric university health center, which was 29% [2]. This fact could be related to the more limited number of patients in our study (45 vs. 100 in the American study) and to the use of different recommendations concerning the good use of the PPI.

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Concerning the PPI dose prescribed in our study, it was higher than the dose recommended in at least 15.5% of the cases. This fact could be partially explained by the unavailability, in our public sanitary structures, of some PPI molecule dosages (such as tablets or capsules of lansoprazole of 15 mg), which could impose to the prescriber an increase in doses, because of the economic problems of patients who cannot get themselves treated on their own responsibility in the private pharmacies. However, the increase in the PPI doses was found in a prospective French study evaluating the practices in general medicine to the patients of 75 years old and more, where the full dose represented 53% of the prescriptions in prevention of the gastroduodenal lesions or for the EGR without esophagitis, whereas the recommended dose, in these indications, was half of the dose [14].

In our study, the duration of the prescribed PPI was more than 2 years in 34 cases (75.6%). This result was found in another study where two-third of the old subjects was treated by PPI during more than 2 years [14]. However, the indications of the extended treatment by IPP are limited in the symptomatic periods of EGR or in case of treatment by long-term AINS after 65 years, or in case of a bulbar ulcer Hp (−). This prolonged duration was related to a strong adherence of the patients who felt a bounce effect of the symptoms while stopping the PPI and insisting by consequence on extending the prescription in near the prescribers.

According to our study, the PPI was tolerated well, during an average follow-up of 6 years, with a single unwanted effect (2.3%), a type of diarrhea was related to a microscopic colitis. The well-tolerated character of PPI with long term, to the elderly, was found in other studies [15]. In a study, a type of case witness, by comparing old subjects treated by PPI versus others without PPI, the diarrhea was independently related to the PPI use with an odds ratio of 1.60 [1.20–2.15] [12]. The PPI incrimination in the induction of microscopic colitis is also well documented in the literature with an odds ratio of 6.4 for the collagenous colitis [16]. Other potential unwanted effects of the PPI were described in the literature, in particularly the elderly, such as:

- The consequences of the malabsorption: hyponatremia [17, 18], deficiency in vitamin B12 [19] and hypomagnesemia [20, 21] (which could have serious consequences such as confusion [22, 23])
- The infections, particularly, the bacterial pneumopathies [24] and the intestinal infections, especially to *Clostridium difficilae* [25]
- Osteoporotic fractures [26, 27]
- On the other hand, medicines decreasing the acid gastric secretion such as the long-term PPI would be theoretically capable of leading the genesis of gastric tumors, and even colorectal; in fact, the hypergastrinemia is led by these treatments [28, 29].

In our study, six patients (13.3%) had an osteoporosis without arisen pathological fracture during the follow-up. The PPI incrimination in the genesis of this disease cannot be realized in this study, caused by the absence of a comparison with a witness group, especially that the osteoporosis is frequent in the Tunisian old subject with 23.4% prevalence in Tunisian woman aged more than 50 years old [30]. No control of the densitometry bone and no

supplementation by the association vitamin D + calcium were realized during the follow-up of our patients. This decision could be explained by the controversial character of the results of the studies. Indeed, several observational studies and meta-analyses evaluated the PPI effect, alone or in association with biphosphonates, concerning the risk of fractures. In these studies, the PPI use was associated with a higher risk of pathological fractures (particularly of the hip and the vertebras) favored by an osteoporosis, but the association strength was low most of the time. The PPI impact would be higher in case of a good adhesion to high daily doses [31]. In fact, the role of the multiple confusing factors (represented by the age, the female, body mass indexes, the alcoholism, the smoking, the antecedent of falls or previous fractures, the neurological and hematological diseases and the use of antidepression, anxiolytics, antipsychotics, antiepileptics, diuretics, and antidiabetics) could explain the weak character of this association. Moreover, Kaye et al. showed the absence of PPI association at a higher risk of pathological fractures, to a population of 1098 patients having no risk factor of osteoporosis [32]. Also, the supervision results in the long-term tolerance of treated patients by PPI, within the framework of two clinical trials (followed forward looking until 12 years), and hazardous pathological fractures [33] did not appear. Finally, only 1–5% of fractures on osteoprotic bone would be attributed for the PPI use [31].

So, in the United States, the administration of food and medicine (FDA) considered the low clinical impact, neither justifying a calcium supplementation nor a regular supervision of the osseous density [34]. The mechanisms at the origin of changing of the osseous density by PPI are represented by the decrease in the ionization and the absorption of the calcium and the inhibition of the osteoclastic activity, compulsory for the norm progress of the physiological osseous reshaping [13]. Concerning hypomagnesemia risk, no patient in our study benefited from a magnesium plasmatic dosage. This attitude is debated in the literature, due to the absence of a forward-looking study with a long-term follow-up. However, in 2012, after a literature review, Hess et al. recommended a dosage of magnesemia plasmatic rate before the introduction of an PPI long-term treatment, particularly with the patients treated with other hypomagnesemiants medicine (such as the digoxine, the diuretics), with a regular follow-up. In case of discovering a hypomagnesemia, these authors recommended a stop of PPI with an addition of calcium and magnesium [35]. In this case, according to these authors, the substitution of the PPI by the anti- histaminic receptor (anti-H2), which does not lead to a hypomagnesemia risk, could not be recommended. If the symptoms related to the hypersecretion acid were not controlled by the anti-H2, occasional cures by PPI can be prescribed by a biological supervision [35]. In front of the potentially serious complications of the hypomagnesemie, especially with elderly (vomiting, diarrhea, hypokalemia, hypocalcemia, muscular tetanizes, rhythm disorders, the extension of the interval QT, the convulsions, the confusion) and through the frequent undesirable effects, which is considered rare if the PPI was prescribed by recommended doses, the FDA recommended a magnesemia dosage before the introduction of a PPI treatment:

- If the treatment duration would be extended.
- Or in case of association with other hypomagnesemiants medicine.

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A regular supervision of the magnesemia was also recommended by the FDA in the quoted situations, without specifying the monitoring methods [34]. In a recent literature review, besides the authors had recommended this conduct to the elderly or those having chronic diseases (diabetics, kidney insufficiency, or having a cardiovascular pathology) [31].

No patient of our series presented an intestinal or lung infection during the follow-up, but the retrospective character of our study does not eliminate this fact, because the patients could forget or neglect to mention these infections to the consultant physician of the IPP, during the various consultations. The PPI was different in the increase of infectious risk that caused the decrease in the gastric acidity, which is considered as an antimicrobial natural barrier. A meta-analysis demonstrated the PPI association with an increasing risk of Salmonella infection, Campylobacter, and other bacteria except *Clostridium difficilae* (CD) (odds ratio = 3.33 [1.84–6.02]) [36].

The increasing risk of the infection by the CD was demonstrated by three meta-analyses published in 2012 (odds ratio between 1.48 and 2.31) [37–39] with an increase of this risk in case of IPP association with an antibiotic treatment [37]. However, the other confusing factors such as the elderly and the comorbidity were not specified in most of these studies [31]. On the other hand, a recent retrospective study recommended avoiding the PPI use with the patients having antecedent of repeated infections with CD [40].

Because of these data, the FDA recommended considering the infection diagnosis with CD in case of persistent diarrhea under PPI and limiting the use of these molecules to the effective minimal dose during the shortest possible duration, to avoid this risk [41]. The upper age to 65 years constitutes an individual factor risk for the infections with CD [42]. Furthermore, the consequences of this infection (diarrhea, colitis, megacolon, colonic perforation) are more serious in the elderly. Moreover, in England and in WALES, the death rate related to these infections is concerned mainly with elderly more than 65 years old [43]. So, this risk justifies the limitation of the IPP prescription, particularly to the elderly.

Concerning the pneumonia's risk under PPI, the pathophysiological mechanisms of this association were not clearly established, but they are essentially represented by the gastric bacterial colonization, the change of the bacterial oropharyngeal flora, and the lung microinhalation of these bacteria [31]. The results of the case-witness studies and meta-analysis suggest a moderate increase in the arising out of community-acquired pneumonia by using the PPI [31]. The odds ratio found in a recent literature review was 1.49 (1.16–1.92) [44]. The community-acquired pneumonia risk by using the PPI is related to the treatment duration with a more important risk after a month of starting the treatment (odds ratio = 2.1 (1, 39–3, 16)) independently of the posology and of the patient's age [31]. Though there is the absence of forward-looking studies and the intervention possibility of confusing factors, these data suggest the importance to limit the IPP prescriptions to the validated indications.

In conclusion, the responsibility of the PPI in the happening of events, which is unwanted and sometimes serious, was demonstrated, but the studies were often retrospective and sometimes biased and the strength of the association was low most of the time with an odds ratio 2 [31]. However, you should not consider these medicines as simple "gastric defenders"

without any risk and to limit their prescription to the validated indications, to the recommended posology, during a well-determined duration, especially to the fragile elderly subject treated by a lot of drugs.

The PPI use may increase the risk of medicinal interactions (by modifying the absorption of medicine by acting on the gastric pH or by competition on the cytochrome P450 (CYP)) being able to make tilt the balance profit/risk negatively, at the elderly person. Indeed, by increasing the gastric pH, the PPI decreases the dissolution and the solubilization of some administered medicines per bone, such as antifungals (for example, the itraconazole [45]) or the immunosuppressors (such as the mycophenolate mofetil [46]). On the contrary, they can increase the reduction of some medicines such as the saquinavir [47]. On the other hand, the taking of a PPI could theoretically improve the bioavailability of medicines for which an important part of the ingested dose is normally hydrolyzed in acid area (such as penicillin) [48]. Finally, it was demonstrated that the omeprazole increased the bioavailability of the digoxine [49] and the nifedipine [50] by inhibiting at the intestinal level of the isoenzyme 3A4 of the CYP450 and the glycoprotein P.

On the other hand, all the PPIs, except the rabeprazole, are mainly metabolized by isoenzymes 2C19 and 3A4 of the CYP, [51]. At the same time, the PPI inhibit these enzymes. The omeprazole is also a moderate inductor of the CYP 1A2 [52]. Thus, pharmacokinetics interaction risk exists with medicines that are major substrata of these isoforms. The particular case of the interaction between the IPP and the clopidogrel, a platelet antiaggregant in which the efficiency depends on its bioactivation by the CYP 2C19, was widely studied, without formal proof of its clinical impact. The clopidogrel belongs to the class of thienopyridines. It is a prodrug, absorbed by the intestine and then transformed into an active metabolite by the liver via two successive reactions of oxidation by cytochromes P450, and more exact isoforms CYP2C19, CYP3A4/5, CYP2C9, and CYP2B6. By inhibiting the CYP 2C19, the PPI (except for a very weak action for the pantoprazole) decreases the clopidogrel activation and thus its efficiency, hence exposing the patients to ischemic accidents. Numerous retrospective studies confirmed this interaction [53]. According to the FDA's to the healthcare professionals of November 17th, 2009, the association of the omeprazole with the clopidogrel is not advisable. The FDA, presented the pantoprazole as a possible alternative in case of necessary association of an IPP with clopidogrel, because of its slightest inhibitive potential on the CYP 2C19 [54]. As far as the inhibition of the CYP 2C19 by the PPI is reversible and considering the short half-life of the PPI, some authors suggested minimizing the clinical consequences of this interaction by prescribing the PPI in the morning and the clopidogrel in the evening with an interval of 12 hours by separating both the takings [55]. However, the published randomized forward-looking studies did not find this interaction and confirmed the beneficial effects of the PPI on the digestive bleedings [31, 56, 57, 58]. In 2012, these data allowed Afssaps (become ANSM: National agency of Safety of the Medicine) to remove, the PPI-clopidogrel interaction from the thesaurus of the medicinal interactions [59].

However, the ANSM has issued a reserve in its recommendations of 2012 advising to avoid the clopidogrel-omeprazole and clopidogrel-esomeprazole associations [60]. In our series, two patients were treated with the clopidogrel in association with the PPI and they did not receive any information concerning the possibility of a medicinal interaction. Though

a formal proof of the clinical impact of this association was absent, we preferred to recommend our patients to space out the taking of both medicines for 12 hours, because of the pantoprazole's unavailability in our public pharmacies.

By taking into account the data of our series, which confirms the concomitant use of several medicines by elderly besides the IPP with the possibility of medicinal interactions, it is important to update the medicines' list taken by the patient at every consultation as well as to recommend him stopping the PPI if this treatment is not anymore indicated. Indeed, one of the main obstacles in stopping the PPI is the rebound effect that is generated. It is established from now on that the stop of a treatment by PPI can lead relapses by rebound effect on the gastric acidity. So, since 1996, an increase of 50% of the gastric acid secretion has been highlighted at nine patients for 14 days after the stop of a three-month treatment by omeprazole to the 40 mg/d posology [61]. In 2009, a randomized trial, with double blind versus placebo, realized at 120 asymptomatic healthy volunteers, confirmed the clinical impact of this rebound effect by showing that only after 8 weeks of a treatment with esomeprazole to the 40 mg/d posology, 44% of the exposed subjects presented the symptoms of rebound effect (heartburns, gastroenteritis ebb: esophageal or dyspepsia) against 15% in the witness group [62] These symptoms arose from the second week following the PPI stop, and they were still described till the end of the follow-up period, that is 4 weeks after the stop. Other studies showed that the rebound effect on the acid secretion lasts beyond 8 weeks after the stop [63, 64]. To the naive subjects for the pylori helicobacter, this effect rebound seems to be proportional in the rise of pH during the treatment, while it tends to be masked by the persistent hypochlorhydria observed at the infected patients by the pylori helicobacter [63]. Other multicentral trials, randomized, in double blind showed that less than a third of patients receiving a long-term IPP, succeeded to stop the treatment without an effect on the control of the symptoms and the quality of life, whereas another third passed to a treatment "in the request" [65, 66]. Several pathophysiological hypotheses were envisaged to explain this rebound effect on the acid gastric secretion, such as a hypergastrinemia [61] or a hypertrophy and a hyperplasia of the cells of the gastric wall [63].

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