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Prescriptions of Proton-Pump Inhibitors Non-Compliant with Recommendations

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Abstract

Context: In 2013, reimbursements for Proton-Pump Inhibitors (PPIs) amounted to nearly 530 million euros in France. PPI usage was subject to official recommendations in France in 2007 and 2009. Six years later, however, they are being prescribed primarily for off-label uses. This study sought to further light the prevalence of noncompliant PPI prescriptions at our institution.

Patients and methods: Transversal, descriptive, observational 1-day study including all patients receiving at least one PPI, in all conventional hospitalization and intensive care wards at a university hospital centre. The study excluded day- and week-stay hospitalization wards, the emergency department, as well as the short-term hospitalization and care ward. Besides demographic data, comorbidity was assessed based on the Charlson index. Medications that could potentially interact with PPIs were recorded.

Results: In total, 26 wards participated and 519 patients were assessed, 198 of which (38%), aged 67 ± 13 years on average, were receiving a PPI treatment, were including 113 men (57%). The average Charlson score was 1.7 ± 2. Amongst these 198 patients, 50 (25%; IC95%: [19-32%]) were taking PPIs in compliance with official recommendations for best clinical practice, and 126 (63%) were additionally undergoing at least one treatment known to cause drug interactions with PPIs. For all included wards, expenditures for PPIs amounted to 31.57 Euros for the study day.

Conclusion: Over one out of three hospitalized patients (38%) were receiving a PPI (23% had a PPI at arrival). Whilst over half of prescriptions exhibited potential drug interactions, only 25% of them complied with good clinical practice recommendations. The significant number of such prescriptions may be explained by their low cost, the image of good tolerance they enjoy, a lack of information regarding side-effects and drug interactions, fear of ceasing PPI administration with ensuing peptic ulcers, as well as unwillingness to question a prescription lacking proper scientific basis. Prescribers must, therefore, be better informed.

Keywords: Proton-pump inhibitor; Prescription; Prevalence; Overuse; Side-effect; Iatrogenesis

Introduction

The category of medications acting upon stomach acidity saw the fourth-highest sales in terms of quantity and fifth-highest in terms of turnover in town in 2013 [1]. Proton-Pump Inhibitor (IPP) prescriptions peaked in 2009 at nearly 970 million euros of annual costs in France [1-2]. Expenditures subsequently underwent a progressive drop to just over 530 million euros in 2013 [3]. That said, although costs to health insurance have dropped sharply, the number of boxes distributed rose from 42 million to 50 million between 2009 and 2013 [3]. Therefore, although PPI costs borne by society are displaying a downward trend, and despite the fact that such medications are often well-tolerated, the rise in volume of PPIs being administered exacerbates exposure to potentially serious side-effects, thereby entailing likely repercussions for public health. Several recent studies have shown a significant link between PPI administration and the occurrence of digestive infections by *Clostridium difficile* [4-8]. This risk appears to raise with the duration of PPI administration [9] and increased dose levels [10]. Furthermore, PPI administration during treatment of *Clostridium difficile* may increase the risk of its reoccurrence up to 42%, as the altered gastric pH may affect gut flora [11]. PPI usage is also associated with increased risk of contracting community- and hospital-acquired pneumonia [12-14]. Other non-infectious diseases are significantly associated with PPI administration: Rise in risk of myocardial infarction and cardiovascular mortality [15]; hyponatremia via potentiation of the hyponatremia-causing effect of other concomitant treatments [16]; bone fractures, particularly of the femoral neck through an increased osteoporosis risk [17,18], and hypo-magnesemia in the event of associated diuretic administration

[19-21]. Such effects must act as red flags for prescribers, especially in light of additional, potentially serious drug interactions. In particular, these interactions include modifications to serum concentrations of immunosuppressive treatments, antiretroviral drugs (up to threefold rise in raltegravir serum levels) [22,23], clopidogrel (up to 60% drop in serum levels), [24] as well as effects on the INR balance in patients on vitamin K antagonists (VKA) [25].

Use of PPIs has been subject to recommendations by the French National Authority for Health (Haute Autorité de Santé [HAS]) since 2009 [26] and the French Agency for the Safety of Health Products (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSAPS] now called ANSM) [27] since November 2007. They authorities lay out the indications, dosages, and duration of PPI treatment, whilst adhering to marketing authorizations in order to limit PPI prescription to a favorable risk-benefit ratio. Nonetheless, recent studies [28] tend to show that, 6 years later; these drugs are being prescribed primarily for off-label uses.

The objective of this study was to demonstrate the prevalence of non-compliant PPI prescriptions at our university hospital establishment. Secondary study objectives were to assess the main drug interactions, along with additional costs to the university hospital [29,30].

Methods

Patients and data

This was a transversal, descriptive, observational, 1-day study including all patients from all conventional hospitalization and resuscitation wards at Gabriel Montpied Hospital (Clermont-Ferrand, Auvergne, France). The study excluded day- and week-stay hospitalization wards, the emergency department, as well the short-term hospitalization and care ward. The study was carried out on April 28, 2015, without a particular epidemiological context. Data was collected by means of a questionnaire filled out using information retrieved from each patient's paper and digital file. The questionnaires were completed by either a doctor from the ward or by one of the authors.

Each patient's overall condition was assessed based on the Charlson index [31]. This index constitutes a comorbidity score that predicts survival at 10 years. Valid PPI indication was defined based on recommendations by the HAS from 2009 and by the AFSSAPS from November 2007 on using PPIs, with the dosage and duration of prescribed treatment likewise taken into account [26,27]. The study was registered at the French National Commission on Informatics and Liberty (Commission Nationale de l'Informatique et des Libertes [CNIL]) under number 0120.

Statistical analysis

Statistical analyses were performed using Stata software, version 13 (StataCorp, College Station, TX, US). The tests were two-sided, with α=0.05. Patient characteristics were described for each group as mean ± standard-deviation (SD) or median and interquartile range [IQR] for continuous variables, according to statistical distribution (normality assessed using the Shapiro-Wilk test), and as the number of patients (%) for categorical variables. Comparisons between groups (compliance and non-compliance with prescription recommendations) concerning patient's characteristics were performed using Chi-squared or Fisher exact tests for categorical variables and Student t-test or Mann-Whitney test if assumptions of t-test not met ((i) normality and (ii) homoscedasticity studied using the Fisher-Snedecor test) for quantitative parameters.

Results

In total, 26 wards participated in the study and 519 patients were assessed, 198 of which (38%) were receiving a PPI treatment. Patient's age was 67.9 ± 13.2 and 57% (n=113) were men. The average Charlson score was 1.7 ± 2.0 (Charlson score ≤2: 74%). Of the 198 patients included, 50 (25%; 95% CI [19.4-31.9%]) were taking a PPI in compliance with official good clinical practice recommendations, 94 (47.5%) of patients were receiving a PPI dosage of 20 mg, and 97 (49.0%) were taking 40 mg.

The characteristics of both groups of patients (adherence or non-adherence to PPI prescription recommendations) are provided in Table 1. Higher was the dosage, greater was the tendency for prescriptions to comply with official recommendations. Overall, 60% (119) of patients receiving PPIs were on treatment for over 2 months. For 20% (39) of these, an initiation date was found. The median duration of PPI administration was 2.5 years [2-11 years] for prescriptions compliant with recommendations and 3 years [1-10 years] for non-compliant prescriptions (p=0.48).

Assessment of PPI indications

The adherence or non-adherence to recommendations depending upon indication is described in Table 2. For ulcer treatment, five prescriptions did not comply with recommendations: One patient was receiving PPI due to suspicion of a gastro duodenal ulcer (GDU) without signs of severity, whilst a fiberoptic endoscopy was to be performed within the next 24 h. Another patient was continuing PPI administration past the treatment end date. A third patient was on PPI for suspected bleeding in the digestive tract, with no fiberoptic endoscopy requested.

The remaining two patients were receiving improper dosages. Regarding the indication for preventing GDUs caused by non-steroidal anti-inflammatory drugs (NSAID) administration, six patients were receiving an insufficient NSAID dosage to justify PPI prescription. In the group initiated on PPIs whilst in intensive care (ICU), four patients were no longer in an ICU, while fifteen others did not meet the criteria justifying PPI treatment. In the epigastralga group, only two treatments had been validated as trial treatments, whereas PPI treatment was never re-assessed for the others.

	Compliance with prescription recommendations (n=50)	Non-compliance with prescription recommendations (n=148)	Total % (n=198)	p
Age (years), mean ± SD	67.8 ± 12.4	67.9 ± 13.5	67.9 ± 13.2	0.9
Gender male, n (%)	27 (54.0)	86 (58.1)	113 (57.1)	0.6
Charlson score, mean ± SD	2.2 ± 2.3	1.5 ± 1.9	1.7 ± 2.0	0
Prescription in international nonproprietary names (INN), n (%)	11 (22.0)	40 (27.0)	51 (25.8)	0.5
Doses, n (%)				
10-20mg	18 (36.0)	76 (51.4)	94 (47.5)	0
30-40mg	28 (56.0)	69 (46.6)	97 (49.0)	
>80mg	4 (8.0)	3 (2.0)	7 (3.5)	
Unit, n (%)				
Intensive care units	6 (12.0)	15 (10.1)	21 (10.6)	0.1
Surgical departments	11 (22.0)	60 (40.6)	71 (35.9)	
Medical departments	33 (66.0)	73 (49.3)	106 (53.5)	
Administration, n (%)				
Oral route	46 (92.0)	137 (92.6)	183 (92.4)	0.9
Voie IV	4 (8.0)	11 (7.4)	15 (7.6)	
PPI intake duration (years), median [IQR]	2.5 [2; 11]	3 [1; 10]	3 [1; 10]	0.5
PPI initiation during hospitalization, n (%)	22 (44.9)	58 (39.5)	80 (40.8)	0.5

Table 1: Patient distribution depending on adherence to PPI prescription recommendations.

	All population n=198 (%)	No conform indication n=148 (%)	Conform Indication n=50 (%)	p
Ulcer treatment	14 (7.1)	5 (3.4)	9 (18.0)	0.002
Treatment of NSAID-induced ulcers	0 (0)	NA	NA	-
Helicobacter pylori eradication following gastro-duodenal ulcer	2 (1.0)	0 (0.0)	2 (4.0)	0.06
Prevention of gastro-duodenal ulcer recurrences	3 (2%)	0 (0.0)	3 (6.0)	0.02
Prevention of gastro-duodenal ulcers whilst on NSAIDs	13 (6.6)	6 (4.1)	7 (14.0)	0.02
Management of esophageal-reflux	12 (6.1)	0 (0.0)	12 (24.0)	< 0.001
Zollinger-Ellison syndrome	1 (0.5)	0 (0.0)	1 (2.0)	0.25
PPI initiation in ICU	25 (13)	22 (14.9)	3 (6.0)	0.1
Corticosteroid-therapy alone	13 (6.6)	12 (8.1)	1 (2.0)	0.13
Aspirin (<300 mg) alone	7 (3.5)	5 (6.6)	1 (1.6)	0.11
Clopidrogel/aspirin association (without NSAIDs >300 mg)	12 (6.1)	6 (7.9)	6 (4.9)	0.39
Epigastralgia	12 (6.1)	10 (6.8)	2 (4.0)	0.73
No known indication	75 (37.0)	61 (41.2)	14 (28.0)	0.1

Table 2: Adherence to PPI prescription recommendations depending on PPI indications.

Description of main associated treatments

Out of the 198 patients, 126 (63%) were receiving at least one additional treatment (mean of 1.52, with three patients undergoing a maximum of four associated treatments) known to cause drug interactions with PPIs. Overall, 67 (33%) patients were receiving low aspirin dosages, but the indications for only 13 out of 67 prescriptions complied with good clinical practice recommendations. The major associated treatments exhibiting notable drug interactions are shown in Table 3.

Medications	Number of patients receiving such treatment among the 198 patients on PPI n (%)	Frequency of validated indication n (%)	Type of interaction
Major interaction			
Raltegravir	1 (1)	1 (1)	Increase in serum raltegravir levels up to threefold, [23]
Clopidogrel	20 (10)	3 (2)	Decrease in active metabolite bioavailability up to 50 [24]
VKA*	39 (20)	6 (3)	INR modifications [25]
Prasugrel	5 (3)	1 (1)	
Tacrolimus	2 (1)	0	Increase in CYP 2C19 serum concentrations within P450 cytochrome
Methotrexate	2 (1)	0	
Cyclosporine	3 (2)	1 (1)	
Phenytoin	2 (1)	0	
Citalopram	1 (1)	0	
Levetiracetam	13 (7)	4 (2)	
Carbamazepin	3 (2)	1 (1)	
Minor interactions			
Loop diuretics	58 (29)	12 (6)	Addition of hyponatremic effects [16]
ACEIs**	30 (15)	7 (4)	
Thiazid diuretics	9 (5)	2 (1)	
Fluoxetine	2 (1)	0	
Paroxetine	2 (1)	0	
Sodium valporate	2 (1)	0	
Acetazolamid	3 (2)	0	
*Vitamin K antagonists			
**Angiotensin converting enzyme inhibitors			

Table 3: Prevalence of drugs exhibiting potential interactions with PPIs.

Economic impact

In total, on the study day, 99 tablets of INEXIUM 20 mg, 88 tablets of INEXIUM 40 mg, and 22 pouches of intravenous INEXIUM 40 mg were distributed, resulting in a total of 209 items. Expenditures for INEXIUM amounted to 31.57 Euros for the study day.

Discussion

Over one out of three patients (38%) hospitalized in our institution was treated using a PPI. The patients were relatively young (67 years old on average), and displayed low comorbidity rates (74% exhibited a Charlson score ≤2). Only 25% of PPI prescriptions complied with good clinical practice recommendations. Over half (63%) of the prescriptions could potentially cause drug interactions. Overall, 46% (92/198) of patients were receiving a PPI as part of their normal treatment at arrival at the hospital, 32% (64/198) of which were non-compliant with good clinical practice recommendations. Whilst the consequences in terms of drug interactions or side effects were potentially significant, additional costs linked to such improper prescriptions seemed marginal (24 euros a day).

The main limit of the study could be due to the lack of information in some patient files. The prevalence of PPI usage resembles that

observed in studies on hospitalized patients (25-62% depending on the studies) [32-38]. In international literature, the frequency of improper PPI prescriptions is likewise similar, displaying rates from 12-62% amongst adults, depending on the studies [8,32,33,37,39]. That said, these results should not disguise the methodological differences and heterogeneity of targeted populations.

Both at hospitals and in town, PPIs are generally viewed as innocuous medications. A recent retrospective study that included 2.9 million patients, however, suggests that exposition to PPIs is associated with an increased risk of 1.16 (95%, 1.09-1.24) of myocardial infarction [15]. Survival analysis in a prospective cohort demonstrated a doubling (HR=2; 95% CI: 1.07-3.78; P=0.031) of cardiovascular mortality [15].

The significant number of such erroneous prescriptions may be accounted for by their low cost, the image of good tolerance they enjoy, a lack of information regarding side-effects and potential drug interactions, fear of developing peptic ulcers on PPI discontinuation, as well as unwillingness to question a prescription lacking proper scientific basis. Reduction in PPI misuse must entail providing better information and awareness-building amongst prescribers. A fact sheet has been drafted to this end (Table 4). Moreover, it would prove beneficial to suggest re-assessment of PPI treatment in the discharge letter to the general practitioner. The general practitioner is, after all, the healthcare actor who is best informed of patients' medical history and in the best position to evaluate whether or not continuing PPI treatment would be appropriate.

1 - Systematic re-assessment of treatment at patient arrival and departure
2 - No indication in the event of Aspegic® administration (dosage below 300 mg), unless high gastrointestinal hemorrhages occur after administering low-dosed NSAIDs
3 - No indication for prescribing PPIs along with antiplatelet drugs, particularly clopidogrel and low-dosed aspirin, or corticosteroids, or anticoagulants (VKA or DOAC), without associated NSAID administration at a dosage exceeding 300 mg of aspirin equivalent.
4 - No indication in the event of corticosteroid therapy on its own, without associated NSAID administration at a dosage exceeding 300 mg of aspirin equivalent.

Table 4: Prescription optimization in terms of four points corresponding to 65 of on-compliant treatments causes.

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