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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Gastroprotection during the administration of non-steroidal anti-inflammatory drugs. A drug-utilization study

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Abstract There has been an increase of anti-ulcer drug consumption in Spain. A high proportion of this consumption may be due to the use of those drugs as gastroprotective agents when co-prescribed with non-steroidal anti-inflammatory drugs (NSAIDs). The aim of this study was to learn how these treatments are being used: the prevalence of use, the type of drug and the main features of patients. A sample of patients going to pharmacies with a NSAID prescription, with or without a gastroprotective agent, was obtained. A survey questionnaire was distributed to learn clinical and demographic data of the patients. Of the 942 patients interviewed, 41.6% were co-treated with a gastroprotective agent in addition to the NSAID. Most of these patients received proton-pump inhibitors and, to a lesser extent, histamine-2-receptor antagonists, antacids and prostaglandin analogues. The use of gastroprotective agents increased with age, treatment duration and illness chronicity; specialists prescribed a higher proportion of those co-treatments than did general practitioners. There was a high prescription rate of gastroprotective agents; in general, these were used according to recommendations. However, the type of gastroprotective agents being used does not seem to be justified by the current guidelines: histamine-2-receptor antagonists and antacid drugs have not proved their efficacy in this indication. The fact that one in four treatments with gastroprotective drugs was issued to patients without associated risk factors identifies a possible problem where an intervention could be appropriate.

Keywords Gastroprotection · NSAIDs · Drug-utilization study

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Introduction

The so-called gastroprotection that accompanies non-steroidal anti-inflammatory drug (NSAID) prescription is usually performed with anti-ulcer or antacid drugs. Thus, gastrointestinal damage caused by anti-inflammatory drugs is intended to be prevented. Various studies agree that NSAID utilization in Spain and other countries has markedly increased during the last decade [1, 2, 3, 4, 5, 6, 7]. It is estimated that in Spain approximately 4 million persons take NSAIDs more or less regularly to treat mild or moderate pain and inflammation [8, 9]. However, their use is occasionally limited by the frequency and severity of their adverse effects, which can affect up to 25% of treated patients [10]. Among these effects, gastrointestinal ones should be highlighted, ranging from mild digestive discomfort or dyspepsia to bleeding ulcers and perforations.

In the hospital setting, the usual practice is to administer anti-ulcer drugs to prevent the gastric impact of certain aggressive factors, such as stress caused by the hospital stay or the administration of some drugs. It has been estimated that 46% of inpatients from various Spanish hospitals received anti-ulcer or antacid drugs [11]. In the last years, this practice is being extended to the primary care setting, although there are no clearly established criteria on treatment regimens or the type of patient to be protected [1, 12]. In addition, several studies have been published that show that anti-ulcer drug use does not seem to suit to current scientific knowledge. Burrull et al. [1] in 1995 reviewed a total of 205 clinical charts from an urban basic health area of Barcelona. According to previously fixed criteria, only 7.4% of NSAID-treated patients were candidates to receive concomitant therapy for gastrointestinal protection; however, of those patients, only 40% did receive

it. Jiménez Plata et al. [13] analyzed 713 prescriptions of anti-ulcer drugs from 195 primary care physicians in Andalusia, considering their suitability to a therapeutic protocol. They found that about half of the prescriptions of anti-ulcer drugs were unjustified, the most common reason of the excessive prescription rate of anti-ulcer drugs being non-investigated dyspepsia and prophylaxis of gastrointestinal lesions induced by NSAIDs.

Interestingly, both in primary care and hospital settings, an increase in the prescription rate of anti-ulcer drugs has been detected, particularly proton-pump inhibitors and histamine-2 (H2)-receptor antagonists. Also, it has been reported that the consumption of anti-ulcer drugs in Spain had increased from 5 defined daily doses per 1000 inhabitants per day in 1988 to 19 in 1997 [14]. Some of these studies reported that one of the causes of this increase was their use in the prophylaxis of NSAID-induced gastrointestinal lesions [8, 15].

In summary, various problems related to the utilization of gastroprotective medication, including doubts about its effectiveness, use suitability, safety or high cost, can result in an inadequate consumption of this medication. We think that their study can contribute to a better use of these drugs and, consequently, a greater benefit to patients. Therefore, we intended to learn the utilization profile of the so-called gastroprotective drugs (antacids, H2-receptor antagonists, proton-pump inhibitors and misoprostol) associated with the treatment with NSAIDs in outpatients. Other objectives were to learn the therapeutic groups and active ingredients used as gastroprotective, describe clinical and demographic characteristics of the population to which these drugs are prescribed and estimate the incidence of the association of gastroprotective drugs with NSAIDs.

Materials and methods

This was a drug-utilization study (prospective, cross-sectional) carried out by means of a structured survey administered in a group of pharmacies to the patient to whom the medication had been prescribed or to a relative who had gone to get the drug and knew the patient's clinical condition. When considered necessary, the questionnaire was complemented by a telephone interview. Several pharmacies of Valladolid and León provinces, through their license holders, agreed to participate in the study. The subjects included were patients of either sex, older than 14 years, who were prescribed a NSAID treatment. Through the survey, information on history of gastrointestinal disorders, as well as the patient's medication, was obtained, including prescription of NSAIDs, gastroprotective drugs and other associated medication (corticosteroids, anticoagulants and antiplatelets) as well as indication, dose and duration of treatment. Socio-demographic and other clinical characteristics of patients prescribed a NSAID with or without a gastroprotective agent were also collected. Likewise, information on personal characteristics such as sex, age, education level, cigarette smoking and social security status was collected.

To avoid selection bias (administering questionnaires preferably to those patients having no co-prescription), clear and repeated explanations were given to pharmacists on the main objective of the study. In addition, they were asked to administer the questionnaires to previously defined patients, e.g., the first three to arrive, those who came during the last hour of the business day and so on.

The estimated sample size was 598 subjects; for the estimate we assumed an α-error of 0.05, a precision of 4% and for the worst situation concerning use prevalence of a gastroprotective agent, 50%. The patient recruitment took place between September 2001 and July 2002.

A descriptive data analysis was carried out: use prevalence of gastroprotective agents, type of agents and a patient profile. Also, chi-square tests and means (Student's t-test) were performed. A univariant analysis of factors associated with the prescription of gastroprotective agents was also done: estimation of the odds ratio (OR), confidence interval (CI) and a multivariate analysis to learn the weight of potential determinants of gastroprotective agent prescription depending on the physician, health care setting and patient characteristics.

Results

During the period November 2001–July 2002, 942 questionnaires from 33 different pharmacies participating in the drug-utilization study were collected, of which 920 were valid; the mean number of questionnaires per pharmacy was 27.9 (SD, 19.4).

Gastroprotective medication, in addition to NSAIDs, was received by 41.6% of patients ($n = 383$); the estimation for the reference population ranged between 39.4% and 43.8%. Most of the patients received proton-pump inhibitors and, to a lesser degree, H2-receptor antagonists, antacids and prostaglandin analogues (Table 1). The mean age of the patients to whom gastroprotective agents were prescribed was 61.7 years; the patients who did not receive this co-medication were 4.7 years younger (Table 2). The use of gastroprotection increased with age, treatment duration and the chronic nature of the disease. Also, in the specialized care setting, these gastroprotective drugs were prescribed in a higher proportion. A history of gastrointestinal disorders and the concomitant use of antiplatelets were also associated with more prescriptions of gastroprotective agents.

The adjusted weight of various factors in relation to gastroprotection is shown in Table 3: the history of gastrointestinal disorders was associated with a high probability of being prescribed a gastroprotective drug (OR = 9.0; 95% CI, 6.0–13.5). However, an acute condition such as transient headache was associated

Table 1 Utilization pattern of gastroprotective drugs associated with non-steroidal anti-inflammatory drug treatment ($n = 383$)

Gastroprotective agent	Frequency (%)
Proton-pump inhibitors	221 (57.7)
Lansoprazole	56 (14.6)
Omeprazole	146 (38.1)
Pantoprazole	15(3.9)
Rabeprazole	4 (1.0)
H2-receptor antagonists	107 (27.9)
Ranitidine	75 (19.6)
Famotidine	32(8.4)
Antacid drugs	40 (10.4)
Zinc acexamate	2 (0.5)
Algeldrate	1 (0.3)
Almagate	34 (8.9)
Dihydroxyaluminium aminoacetate	1 (0.3)
Magaldrate	2 (0.5)
Prostaglandin analogues	10(2.6)
Misoprostol	10(2,6)
Non-specified/other	5(1.3)

with a high probability of not being prescribed a gastroprotective drug (OR = 0.4; 95% CI, 0.1–1.0). After adjustment for various confusion factors, diclofenac, aceclofenac, naproxen and ibuprofen, in this order, were associated with a higher probability of being prescribed a gastroprotective agent, although significant differences were not detected (Table 4).

With the data collected, a predictive model of logistic regression has been built, with which we can estimate probabilities as a function of the various patient characteristics or the health care setting where the prescription was done (logit = $-1.901 + 0.015\times$age$- 0.974\times$headache $+ 0.725\times$specialist $+ 1.133 \times$ corticosteroids $+ 2.205\times$history); thus, a patient younger than 25 years, who goes to a primary care physician due to a headache, has no history of gastrointestinal disorders and is not being treated with corticosteroids has a 7.6% probability to be prescribed, in addition to the NSAID, a gastroprotective agent (Table 5). Gastroprotection use percentage according to the number and type of risk factors considered is shown in Fig. 1.

Discussion

The main finding of this study is the high percentage of prescription rate of gastroprotective drugs together with NSAIDs. A gastroprotective agent in combination with a NSAID was prescribed to 41.6% of the analyzed sample. The sample seems to be representative of the population having a NSAID, since it is quite large ($n = 920$)—more than that estimated for a use prevalence lower than the one we found—and because it includes a very varied geographical spectrum, including urban and rural areas. Although the Castilla y León population is slightly older than those of other Spanish regions, we do not think that this difference would significantly change the results if the estimation were done in other regions.

Table 2 Use of gastroprotective agents associated with non-steroidal anti-inflammatory drugs according to various socio-demographic and clinical factors

	Gastroprotection Frequency (%)[a] $n = 383$ (41.6)	P value
Age (mean; SD)	61.7 years; 15.8 years[b]	< 0.001
Age groups		
< 40 years	38 (25.7)	< 0.001
41–65 years	160 (43.1)	
> 65 years	185 (46.1)	
Gender		0.470
Male	232 (40.8)	
Female	151 (43.3)	
Education level		0.013
None[c]	56 (41.2)	
Primary	243 (45.1)	
Secondary	52 (30.2)	
University	30 (42.9)	
Non-specified	2 (66.6)	
Smoking habit	70 (39.3)	0.487
Cause of prescription[d]		
Rheumatic condition	167 (48.5)	0.001
Headache	6 (20.0)	0.015
Trauma	33 (44.0)	0.476
Muscular pain	74 (37.0)	0.382
Other	151 (38.0)	–
Duration		0.001
< 15 days	79 (31.6)	
15–30 days	85 (43.4)	
> 30 days	219 (46.3)	
Concomitant medication		
Corticosteroids	25 (75.8)	< 0.001
Anticoagulants	5 (35.7)	0.651
Antiplatelets	9 (81.8)	0.007
Health care setting		
Specialized	159 (55.4)	< 0.001
General	224 (35.4)	
History of gastrointestinal disorders	151 (80.3)	< 0.001

[a]Percentages refer to all individuals in the corresponding category, those who received gastroprotective medication plus those who did not

[b]For patients without a gastroprotective agent, 57.1 years (SD, 18.7 years)

[c]"None" is the category for those who did not finish primary education

[d]More than one cause of prescription was possible

Table 3 Determinant factors in the utilization of gastroprotective drugs associated with non-steroidal anti-inflammatory drug treatment

Factor	Adjusted odds ratio (95% confidence interval)[a]
Cause of prescription: headache	0.4 (0.1–0.99)
Specialized care	2.1 (1.5–2.9)
Age > 65 years	2.4 (1.5–3.8)
Associated corticosteroids	3.0 (1.2–7.2)
Associated antiplatelets	4.5 (0.9–23.0)
History of gastrointestinal disorders	9.0 (6.0–13.5)

[a]Age-adjusted odds ratio, categorized into three categories: type of medical care, headache as a cause of non-steroidal anti-inflammatory drug prescription, history of gastrointestinal disorders, associated corticosteroids and associated antiplatelets

Table 4 Use of gastroprotection by non-steroidal anti-inflammatory drug (NSAID) type

NSAID	Adjusted odds ratio (95% confidence interval)[a]
Rofecoxib	1
Aspirin[b]	1.2 (0.5–2.6)
Piroxicam	2.1 (0.8–5.1)
Celecoxib	2.1 (0.9–4.8)
Ibuprofen	2.9 (1.3–6.6)
Naproxen	3.4 (1.5–7.7)
Aceclofenac	3.5 (1.5–7.8)
Diclofenac	3.9 (1.8–8.3)

[a]Age-adjusted odds ratio, type of medical care, headache as a cause of prescription and history of gastrointestinal disorders
[b]Dose ≥300 mg/day

In a study carried out in a basic health area of Hospitalet de Llobregat, Barcelona (Spain), in 1994, a clinical chart review found that 16.6% of patients who were prescribed a NSAID received also a gastroprotective agent [1]; in this case, the H2-receptor antagonists were the most used (41.1%) and, to a lesser degree, misoprostol and omeprazole (6% each). Obviously, both the use percentage of gastroprotection and the pattern of drugs used have changed markedly. According to the use pattern observed in the present study, proton-pump inhibitors would be currently the gastroprotective agents used more often—nearly 60% of all cases. It is worthwhile to emphasize, however, that H2-receptor antagonists and antacids, which have not proved their efficacy in clinical trials nor in observational studies [16], are used in quite high percentages. In our study, they represented nearly 40% of the total; in addition, their safety should be considered [17, 18, 19].

Similarly, other studies carried out in different countries have addressed the use of gastroprotective medication. The percentage of people aged 65 years and higher who received a gastroprotective agent different from misoprostol was 22.9 in 1992 in Quebec (Canada) [3] and 17.1 in Nova Scotia (Canada) during 1993 and 1994 [4]. This figure was 21.7% in patients admitted to medical wards through an emergency department in Ireland in 1996 (median age, 70.5 years) [5]. In France, with a sample of 791 prescriptions from general practitioners from the Côte d'Or, co-prescription was found in 29.5% in 1999 [6]. More recently, in the USA, in a cohort of patients with arthritis treated with NSAIDs, 42% had a co-prescription [7].

The use of gastroprotective medication increased with risk factors known to cause gastrointestinal lesions: age, history of gastrointestinal disorders, use of corticosteroids or concomitant use of antiplatelets (Fig. 1). Antiplatelet use was associated with more prescriptions of gastroprotective agents, although this was not so with anticoagulants. Also, the setting in which medical care took place influenced markedly on prescriptions: after adjusting for all possible confusion factors, the probability of being prescribed a gastroprotective agent in

Table 5 Predictive model for the estimation of the likelihood to be treated with a gastroprotective agent by various factors

			History of gastrointestinal disorder, no				History of gastrointestinal disorder, yes			
			Headache, no		Headache, yes		Headache, no		Headache, yes	
			Corticosteroids, no	Corticosteroids, yes	Corticosteroids, no	Corticosteroids, yes	Corticosteroids, no	Corticosteroids, yes	Corticosteroids, no	Corticosteroids, yes
Age (years)	25	Primary care	17.9	40.3	7.6	20.3	66.3	85.9	42.7	69.8
		Specialized care	31.0	58.2	14.5	34.5	80.3	92.7	60.6	82.7
	40	Primary care	21.4	45.8	9.3	24.2	71.9	88.5	48.2	74.3
		Specialized care	35.0	63.6	17.5	39.7	83.6	94.1	65.8	85.7
	55	Primary care	25.4	51.4	11.4	28.6	75.6	90.6	53.9	78.4
		Specialized care	41.3	68.6	21.0	45.2	86.5	95.2	70.7	88.2
	70	Primary care	29.9	57.0	13.9	33.4	79.5	92.3	59.4	82.0
		Specialized care	46.9	73.2	25.0	50.8	88.9	96.1	75.1	90.4
	85	Primary care	34.8	62.4	16.8	38.5	82.9	93.8	64.7	85.0
		Specialized care	52.5	77.4	29.4	56.4	90.9	96.9	79.1	92.2

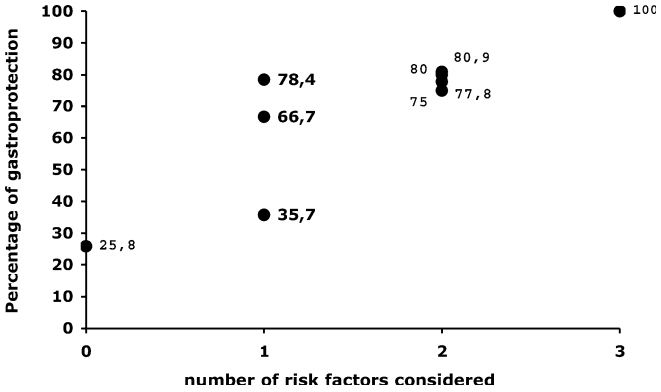

Fig. 1 Percentage of gastroprotection use by the number and type of risk factors considered (none 25.8; age 35.7; corticosteroids 66.7; previous history 78.4; corticosteroids and previous history 75; age and corticosteroids 77.8; age and antiplatelets 80; age and previous history 80.9; age, corticosteroids and previous history 100; age, antiplatelets and previous history 100). For antiplatelets as a unique risk factor, there was only one non-treated patient

combination with a NSAID in the specialized care setting was double that observed in primary care. This can be due to a greater restraint of primary care physicians, who are perhaps more sensitive to warnings on problems arisen by excessive pharmaceutical spending, to the practice of a more defensive medicine by specialists or perhaps to a spurious mechanism due to an insufficient adjustment. It could be possible that the most severe patients, as should be expected, are visited by the specialist and the adjustment performed is unable to neutralize that severity factor.

It is difficult to select clear criteria to assess prescription appropriateness. This difficulty lies in the complexity and diversity of clinical conditions not prone to be classified with necessarily rigid criteria. At any rate, it is easier to estimate what proportion of the patients that show no risk factors have been treated with gastroprotective medication. In our study, this proportion was 25%. There exists, however, a trend to use more gastroprotective drugs when the number of risk factors increases in patients (Fig. 1).

When individual NSAIDs are considered, diclofenac, aceclofenac, naproxen and ibuprofen, in this order, are associated with a higher probability of being prescribed a concomitant gastroprotective agent. However, CIs of estimated risk values overlap, and there seems not to exist significant differences in this respect.

A surprising fact observed in this study is the prescription of gastroprotective drugs combined with the selective COX-2 inhibitors, rofecoxib and celecoxib, in large proportions. These drugs have been marketed as agents with a lesser risk to produce gastrointestinal lesions and were prescribed with a gastroprotective drug in 33.9% and 45.9% of the occasions, respectively. It could be thought that they are used in patients with a higher risk, which we have been able to note in our study, and that, consequently, they are also associated with a gastroprotective agent in an apparently ''double protection.''

The consumption of anti-ulcer and antacid drugs, used for gastroprotection, has experienced a substantial increase in the last years [14]. Gastroprotection against the risk of gastrointestinal lesions produced by NSAIDs represents 41.3% of the consumption of these anti-ulcer and antacid drugs [2]; this was estimated through information derived from clinical charts of six health centers of Navarra in 1997.

One of the limitations of our study could be the fact that the participating pharmacists administered the questionnaires preferably to the patients coming with only one prescription, since by doing so, the questionnaire would become easier to complete; this would account for a selection bias that could be considered as ''laziness bias'' and was dealt with as stated above. The high prevalence of gastroprotective medication use, however, leads us to think that there has not been such a selection bias. In addition, being a cross-sectional and prospective study designed to find out the prevalence and pattern of gastroprotective drug use, its findings are more reliable than those obtained by means of retrospective studies taking advantage of data that were not collected with that purpose.

In conclusion, there seems to exist a high prescription rate of gastroprotective agents that, in general, follow recommended criteria. However, the type of gastroprotective agent used does not seem to be justified by literature data: H2-receptor antagonists and antacids have not reliably demonstrated their efficacy in this indication. The fact that one-quarter of treatments with gastroprotective agents are received by patients that do not show a priori risk factors identifies a potential problem on which an intervention could be carried out to discuss and change, if necessary, this prescription pattern.

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