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Research Article
Cardiovascular Risk Associated with the Use of Non Steroidal Anti-Inflammatory Drugs, Cases and Controls Study in a Health Care Area in Spain

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Abstract

Purpose: The purpose of this study is to evaluate cardiovascular impact related to the use of non steroidal anti-inflammatory drugs in a Health Care Area in Castilla La Mancha (Spain). **Methodology:** A retrospective observational study of clinical cases and controls during 5 years (2008-2012) is done, in which patients older than 18 years (n = 9.880) was included with acute coronary syndrome and randomly selected controls with pneumonia mathed for age, sex and calendar year. The statistical analysis was done estimating the incidence of acute coronary syndrome in relation to the exposure time. **Results:** The NSAID consumption is generally not associated with a risk of acute coronary syndrome (odds ratio = 1.07, IC95% 0.9-1.25, p<0.001). However, this risk is observed with diclofenac (odds ratio = 1.88, IC95% 1.6-2.22, p<0.001), higher doses than 1800 mg daily of ibuprofen (odds ratio = 1.60, IC95% 1.31-1.97, p<0.001) and celecoxib (odds ratio = 1.32, IC95% 1.11-1.46, p<0.001). With other anti-inflammatory drugs an increase of cardiovascular risk is not observed. **Conclusion:** Diclofenac, high doses of ibuprofen and celecoxib have been related to a risk of acute coronary syndrome, so it should be recommend taking low doses and for a short time of these drugs, especially in patients with a high cardiovascular risk.

Key words: Anti-inflammatory agents, non-steroidal, acute coronary syndrome, cases and controls studies

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAID) are among the most prescribed and consumed groups drugs in the world, with figures that reaching up 10% of the total of prescriptions[1], without the percentage that represent self-medication, being that in many countries as Spain, this drugs can be dispensed without a prescription.

A recent report by the Spanish Agency for Medicines and Health Products (AEMPS) shows that prescriptions of these drugs in the period from 2000-2012 have increased notable until 2009 with a slight decline in the last 3 years (2010-2012)[2]. The NSAID may have cardiovascular effects that are produced by their ability to inhibit the synthesis of cyclooxygenase, an enzyme that has a fundamental role as a modulator of the haemodynamic function, ion transport and renal hormonal synthesis.

Several studies analyzed from meta-analysis of clinical trials[3-5] and observational studies[6-10] have shown that NSAID can increase the risk of cardiovascular events, such as Acute Coronary Syndromes (ACS) and stroke. These studies have included patients with important concomitant diseases. There are no reliable studies in which have analyzed the association of NSAID use with risk of ACS in the Spanish population, so it can not be assured that previous findings may be extrapolated to this population characteristics. Therefore, the aim of this study is to know in what extent can NSAID increase cardiovascular risk thereupon conducted a population-based study of cases and controls.

MATERIALS AND METHODS

Study design: A retrospective case-control study ranged from 1 January, 2008 until 31 December, 2012 based on a cohort study on the incidence of ACS and its association with the use of NSAID[11], which served as the starting point for this case-control study. It was carried out in the Health Care Area of Alcázar de San Juan with a population of 195.321 habitants living in 22 towns[12].

Selection of cases and controls: Subjects were 18 years of age or older and with a first episode of ACS, treated at the General Hospital Mancha Centro, centre of reference in the Health Area (Fig. 1). The ACS was diagnosed by the basic minimun data set using the international classification of diasease 10th revision, clinical modification codes 410-414. The cases were paired by sex, aged (±3 years) and year recruitment (±2 years) of the controls. These latter were selected by diagnosis of pneumonia also using the international classification of diasease 10th revision, clinical modification codes 480-486.

Variables and sources of information: Pharmaceutical consumption data were processed with the information system of the pharmaceutical delivery through prescription Health Service of Castilla La Mancha (DIGITALIS®) and through electronic billing files prescriptions provided by the Official College of Pharmacists, while classification of NSAID was carried out according to the Anatomic Therapeutic Chemical scheme.

Statistical anályis

Descriptive analysis: The variables were summarised with appropiate statistical descriptions with central tendency measures (mean or median according the distribution (Gaussian/non-Gaussian) and the dispersión (standard deviation or interquartile range with the mean or median, respectively).

Inferential analysis: The contrasts were performed between cases-control groups by student's t-test (quantitative indicators) and chi-square statistic (qualitative indicators). The

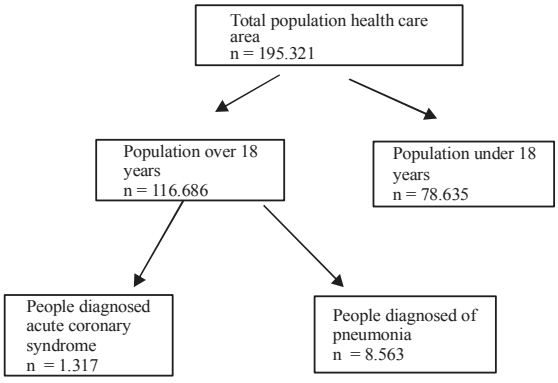

Fig. 1: Algorithm of cases and controls

magnitude of the association is estimated as incidence Odss Ratio (OR) and with 95% Confidence Interval (IC95%). It was calculated Odds Ratio (OR) as measure of association with IC95%.

Using a conditional logistic regression model (by nature pared of their design), it was identified the independent variables associated to the event of interest (Hospital admission for cardiovascular pathology). Statistical analysis was performed with stata satistical analysis software (Stata corp).

RESULTS

During the study period (January, 2008-December, 2012), 9880 patients were selected, of which 1.317 (13.32%) were cases and 8.563 (86.68%) were controls. Their average age was 65.65±19.66 years and 3.480 (35.22%) were women. Diabetes with chronic complications and congestive heart failure were the most prevalent comorbidities in the studied sample (Table 1).

During the 5 years of the study, 835.360 containers were consumed in the health area with a defined daily dose defined per thousand habitants (DHD) of 46.47. The most prescribed were propionics, mainly ibuprofen 28.91 (62.21%) and acetic derivates, especially diclofenac 9.77 (21.02%) (Table 2).

There have been identified 1.317 patients with a SCA and admitted in the Hospital Mancha-Centro, 1.090 (83.76%) patients in the NSAID exposed group and 217 (17.23%) in the not NSAID exposed group.

The NSAID use is not associated with an increased risk of acute coronary syndrome (OR 1.07, IC95% 0.90 a 1.25, p<0.001). The NSAID type was related in a different way with the risk of a cardiovascular event (Table 3). The association was positive and statistically significant for diclofenac (OR 1.88, IC95% 1.6 a 2.22, p<0.001), high doses of 1800 mg daily of ibuprofen (OR 1.60, IC95% 1.31 a 1.97, p<0.001) and celecoxib (OR 1.32, IC95% 1.11 a 1.46, p<0.001) (Table 3). In other NSAID no increased cardiovascular risk was observed.

DISCUSSION

This study places thirdly COX-2 inhibitors, behind diclofenac and ibuprofen at high doses (greater than 1800 mg). The drugs that presumably have a higher cardiovascular risk as coxibs do not increase their cardiovascular risk over time, it is according to these results[5,13,14]. However, regarding to propionic acids, which are the most NSAID consumed in Spain, ibuprofen is the only that increases the cardiovascular risk over time. It would be appropiated to recommend as a result of this study to take this medicine with caution and with medical prescription, assessing the benefit-risk, especially when is taken chronically and at high doses.

Clinical practice guidelines[15,16] and technical specifications take it into account to establish the indications, to set the maximum daily dose, to set the maximum time of use recommend and to advise against its use in patients with cardiovascular disease. The NSAID use in patients with chronic heart failure is associated with a significant increase in the cardiovascular morbidity and mortality[17]. However, despite the warnings, the use of these drugs is so broad that patients end up taking them.

Several previous studies[14,18-20] demonstrated the association between the NSAID use and cardiovascular disease, positioning COX-2 selective inhibitors like the most associated with cardiovascular risk. These data are opposite to these results, the fact that these drugs are prescribed with more caution in patients with cardiovascular risk could be the cause that minimizes the correlation between the comsumption of NSAID and ACS.

Table 1: Main characteristics of study population

Characteristics of study population	Total study population (n = 9.880)	Cases (n = 1.317)	Controls (n = 8.563)
Men	6.400 (64.78%)	834 (63.3%)	5.566 (65%)
Women	3.480 (35.22%)	483 (36.7%)	2.997 (45%)
Middle age±Standard Deviation	65.65±19.66	71.4±12.7	65.2±21.10
Congestive heart failure	1.804 (18.25%)	263 (20%)	1.541 (17.9%)
Peripheral vascular disease	400 (4.04%)	66 (5%)	334 (3.9%)
Cerebrovascular disease chronic	468 (4.73%)	48 (3.6%)	420 (4.9%)
Pulmonary disease	764 (7.73%)	39 (3%)	725 (8.4%)
Peptic ulcer disease	1.030 (10.42%)	163 (12.4%)	867(10.1%)
Mild liver disease	141 (1.42%)	16 (1.2%)	125 (1.4%)
Mild diabetes	288 (2.91%)	21 (1.6%)	267 (3.1%)
Diabetes with chronic complications	2.233 (22.60%)	409 (31.1%)	1.824 (21.3%)
Renal disease	784 (7.93%)	55 (4.2%)	729 (8.5%)
Cancer	94 (0.95%)	5 (0.4%)	89 (1%)
Severe liver disease	958 (9.69%)	104 (7.9%)	854 (9.9%)

Table 2: Consumption of NSAID group in the study population

NSAID	DHD consumption (%)
Coxibs	4.67 (10.04%)
Propionoics	28.91 (62.21%)
Acetic derivatives	9.77 (21.02%)
Enolics	2.83 (6.08%)
Alkanones	0.26 (0.55%)
Others	0.03 (0.064%)
Total	46.47 (100%)

NSAID: Nonsteroidal anti-inflammatory drugs and DHD: Daily dose per thousand inhabitants

Table 3: Cardiovascular risk associated with the use of NSAID

NSAID	OR (IC95%)	p-value
General		
No Consumption	1	
Consumption	1.07 (0.90 a 1.25)	<0.001
High doses	1.24 (0.997-1.45)	0.12
Ibuprofen		
No Consumption	1	
Consumption	1.3 (0.98-1.57)	<0.001
High doses (>1.800 mg day^{-1})	1.60 (1.31-1.97)	<0.001
Diclofenac		
No Consumption	1	
Consumption	1.88 (1.6-2.22)	<0.001
High doses (>150 mg day^{-1})	2.05 (1.74-2.31)	<0.001
Celecoxib		
No Consumption	1	
Consumption	1.32 (1.11-1.46)	<0.001
High doses (> 400 mg day^{-1})	1.37 (0.983-2.15)	0.004
Eterocoxib		
No Consumption	1	
Consumption	1.27 (0.96-1.68)	0.10
High doses (>120 mg day^{-1})	0.996 (0.962-1.031)	0.81
Piroxicam		
No Consumption	1	
Consumption	0.97 (0.84-1.57)	0.004
High doses (>10 mg day^{-1})	0.98 (0.72-1.23)	0.004
Indomethacin		
No Consumption	1	
Consumption	0.95 (0.86-1.41)	0.004
High doses (>100 mg day^{-1})	0.87 (0.61-1.33)	0.004
Naproxen		
No Consumption	1	
Consumption	1.1 (0.89-1.45)	<0.001
High doses (>1.000 mg day^{-1})	1.55 (0.95-1.92)	<0.001

NSAID: Nonsteroidal anti-inflammatory drugs, OR: Odds Ratio, IC95%: Confidence interval of 95%, all estimates were adjusted for age and sex

A recent meta-analysis[5] shows that diclofenac, ibuprofen and coxib produce the same cardiovascular risk. However, in these study, it was found higher cardiovascular risk with diclofenac followed by ibuprofen and finally coxib in the last place.

According to this meta-analysis, naproxen did not show cardiovascular risk. However, the Food and Drug Administration (FDA), through the Advisor Drug Safety and Risk Management Committee decided to continue with the cardiovascular warning. This naproxen cardiovascular risk is consistent with these study. With these data, it can stood out that the most cardiovascular safety NSAID are oxicams (as piroxicam) indolacetic (as indomethacin) and naproxen, so those would be recommend in patients with high cardiovascular risk, naproxen is also identified as the lowest cardiovascular risk drug in several studies[17,21].

The main limitation of this study is that is not accessed the patients medical history. It was worked with databases of prescriptions and billing diagnostics, by set the basic minimum data. However, the results were especified using comorbidities, so it was avoided these limitations. Data have not been obtained from self-medication but from billed prescriptions retired in the pharmacies.

CONCLUSION

The NSAID use is not associated with an increased risk of ACS, however diclofenac, high doses of ibuprofen and celecoxib have been related to a ACS, so it should be recommend taking low doses and for a short time of these drugs, especially in patients with a high cardiovascular risk.

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