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The Special Case of Diclofenac

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Abstract

Since rofecoxib was withdrawn from the market in 2005, the controversy keeps going on about the cardiovascular risk of Non Steroidal Anti-Inflammatory Drugs (NSAIDs). With their analgesic, anti-inflammatory, antipyretic and anti-thrombotic properties, NSAIDs are among the most widely used therapeutic agents. They are also known for their side effects: dyspepsia, peptic ulcerations, fluid retention, high blood pressure … The recent revelation of thrombotic events due to the use of coxibs (selective COX-2 inhibitors) has led to a thorough study of this risk with every NSAID. The results have shown that the vascular risks of diclofenac were comparable to coxibs. In 2013, new recommandations have been announced to warn patients and healthcare professionals about the safe use of diclofenac. Beyond these European recommendations, the use of diclofenac should be revised on a worldwide scale since its use is very common in countries such as China and India.

Keywords Non Steroidal Anti-Inflammatory Drugs; Diclofenac; Cardiovascular risk

Abbreviations NSAID: Non Steroidal Anti-Inflammatory Drug; COX-1: Cyclooxygenase-1; COX-2: Cyclooxygenase-2

Introduction

Summer 2013 brought new recommendations on the use of diclofenac. Diclofenac is a Non Steroidal Anti-Inflammatory Drug indicated for treating painful chronic pathologies and/or painful acute pathologies [1]. This recent piece of information comes directly from the European Medicines Agency, who, in 2011, had started surveying how safe the molecule was. Since rofecoxib, a selective inhibitor of COX-2, was withdrawn from the market in 2005, the potential cardio-vascular risks of NSAIDs were examined. Indeed, the APPROVE study had shown that the use of this anti-inflammatory drug increased risks of cardiovascular accidents [2]. An independent research project on « the safety of NSAIDs » was then implemented. Since 2006, the results of the project, along with a number of other studies, put forward more proofs on the links between non selective NSAIDs and strokes and myocardial infarctions. Collected data also indicated a higher risk of thrombotic events with diclofenac than with the other non selective NSAIDs [3]. This increase was similar to that observed with COX-2 inhibitors. Therefore, the Pharmacovigilance Risk Assessment Committee started in November 2012 a new study on diclofenac, which led to the aforementioned recommendations.

Methods and Materials

Diclofenac belongs to the Non Steroidal Anti-Inflammatory drug class. With their analgesic, anti-inflammatory, antipyretic and anti-thrombotic properties, NSAIDs are among the most widely used therapeutic agents. They are indicated for a wide range of ailments, such as osteoarthritis, arthritis, headaches, back pains and dysmenorrhea [1]. That is why more than 30 million people throughout the world use it daily [4]. A growing and aging population combined with free access to drugs and larger indications are the causes for the constant increase of the use of these molecules.

There are various families of molecules among the NSAIDs, based on their chemical structures (Table 1). Diclofenac belongs to family of carboxylic acid derivatives.

Carboxylic acid derivatives	Salicylates	*Acetylsalicylic Acid*
	Propionics	*Ibuprofen, ketoprofen, naproxen, flurbiprofen*
	Anthranilics	*Niflumic acid*
	Acetic acid derivatives	*Diclofenac, indomethacine, sulindac and ketorolac*
Enolic acid derivatives	Oxicams	*Meloxicam, piroxicam, tenoxicam*
	Pyrazoles	*Phenylbutazone*
Coxibs	*Celecoxib, etoricoxib, parecoxib*	
Nimesulide		

Table 1: *Classification of the NSAIDs according to their chemical structure*

The mechanism of NSAIDs is based on the inhibition of cyclooxygenases COX-1 and COX-2. COX-1 is an enzyme found in most tissues. It enables platelets to produce A2 thromboxane, with pro-aggregating effects. It also enables the secretion of the prostaglandins that protect the gastro-intestinal mucosa [4]. COX-2 is a non constitutive enzyme inducible by pro-inflammatory factors [5]. It modules the synthesis of prostaglandins involved in inflammatory reactions and platelets aggregation, with anti-aggregation effects [4]. NSAIDs are also classified on their action on cyclooxygenases. Schematically speaking, there are two kinds of NSAIDs: conventional NSAIDs, that are COX-1 and COX-2 inhibitors, and coxibs, that are only COX-2 inhibitors. However, the inhibition effect of these enzymes is more or less selective depending on each anti-inflammatory drugs. The selectivity is defined by *in vitro* tests that measure the inhibitory activity of COX-1 (platelets producing thromboxane during platelet aggregation) and COX-2 (polysaccharides-stimulated monocytes producing PGE_2). The inhibitory concentration (IC) ratios such as IC50-COX 1/IC50-COX2 can thus be measured. (Figure 1) The higher this ratio is, the greater anti-COX-2 selectivity will be. Traditional NSAIDs may show a pattern of COX-2 selectivity similar to that of COX-2 inhibitors, coxibs, as is the case of diclofenac when compared with celecoxib, or may be more active as COX-1 inhibitors, as for naproxen and ibuprofen. [6].

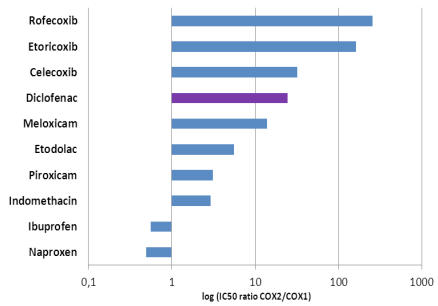

Figure 1 : Biochemical selectivity, assessed as COX-1/COX-2 IC50 values of several NSAIDs [7].

Conclusion

The most common side effects of NSAIDs -among which diclofenac- are digestive: dyspepsia, gastritis and genesis of gastric or duodenal ulcer with possible perforation and bleeding [8]. NSAIDs selective of COX-2 have thus been developed in order to reduce the risk of adverse effects, with a maintained activity of COX-1 (which production of prostaglandins protects the gastro-duodenal mucosa).

However, the post Marketing Authorizations (MA) studies on coxibs showed that the risk of gastro-intestinal lesions had not decreased as much as planned by the CLASS and VIGOR studies, which led to the MA. Between 2000 and 2002, the national pharmacovigilance follow-up collected notifications of serious accidents when celecoxib and rofecoxib were administered (ulcers, perforation and gastrointestinal bleeding). These complications were mainly observed in patients aged over 70 years old with a digestive history, and who were concomitantly following an aspirin-based treatment, or a treatment based on anti-aggregants or anti- coagulants [9]. Furthermore, data stemming from randomized tests, among which the APPROVE study, along with data from observational studies carried out in 2004, showed that coxibs increased cardiovascular risks (myocardial infarctions, strokes), especially rofecoxib, thus justifying its withdrawal from the market in 2005.

After the « rofecoxib case », diclofenac was much studied to determine its cardiovascular risk. Two recent studies were carried out based on Danish data to assess the risk of thrombotic events (myocardial infarctions, strokes) in patients with a cardiovascular history. The first study used treatment periods to compare the cardiovascular risk of various NSAIDs in patients aged over 30 years old who had had a myocardial infarction between 1997 and 2006 [9]. The obtained results showed that the highest risk came from diclofenac, whether in the short term (0 to 7 days) or in the long term (over 90 days [10]). In comparison, naproxen, another NSAID non selective of COX-2, seemed to be the least deleterious [10]. The second study assessed the risk of recurrence or death according to how long it had been since the myocardial infarction occured, and NSAIDs were prescribed. Again, the highest risk was linked with diclofenac, and the lowest, with naproxen [11]. In 2011, Mc Gettigan et al. [12] updated the meta-analysis of observational studies carried out in 2006, and assessed the cardiovascular risk of NSAIDs in patients with no cardiovascular history. Rofecoxib (withdrawn in 2005), etoricoxib and diclofenac were the three NSAIDs with the highest cardiovascular risk. This risk can be observed even with small doses (100 mg), and increases with higher dosages (150 mg). The risk associated with celecoxib also increases with dosage. However, the risk associated with ibuprofen increases only with high dosages (1.6 to 1.8 grams). Finally, the risk associated with naproxen remains the same whichever the dosage [12].

Results and Discussion

Various mechanisms are mentioned to explain these cardiovascular side effects. One hypothesis involves the degree of inhibition of cyclooxygenases. Indeed, COX-1 and COX-2 both have a role to play in vascular homeostasis. Prostacyclin (PGI2) is a molecule with anti-thrombotic properties, produced via COX-2 near the endothelial cells. Thromboxane (TXA2) is a pro-aggregant secreted by COX-1 in the platelets. The selective inhibitors could then increase the risk of thrombosis by unbalancing COX-2 inhibition and COX-1 activity. When COX-2 is inhibited, the production of anti-aggregant prostacyclin PGI2 is reduced. Coupled with the incomplete inhibition of COX-1, generating enough TXA2 with pro-aggregant effects, the PGI2-TXA2 balance is then altered [12]. In other words, the higher the degree of inhibition of COX-2 is, the less COX-1 will be blocked, and therefore the higher the risk of thrombotic events will be. Although diclofenac and naproxen are both non-selective NSAIDs, the difference in preferential inhibition for COX-1 and COX-2 of each molecule could explain the variability of cardiovascular risks [13].

Moreover, NSAIDs induce a hypertensive effect, linked to prostaglandins inhibition, which can lead to fluid retention. This hypertensive effect is all the more important in hypertensive subjects, and is higher with coxibs than with NSAIDs [14].

In August 2013, the French National Agency for Medicines and Health Products Safety (NAMHPS) sent a letter to all health professionals on diclofenac use restrictions [15]. The Summary of Product Characteristics (SPC) of diclofenac-based specialties will be updated, along with the user instructions. We suggest that the same use recommendations given for selective inhibitors of COX-2 be applied to diclofenac [15]. Diclofenac is now contraindicated in patients suffering from:

- confirmed congestive heart failure (stage II to IV of New York Heart Association's classification)
- ischemic heart disease
- peripheral arterial disease and/or
- cerebrovascular disease

Therefore, patients treated with diclofenac and suffering from cardiovascular pathologies will need to have their doctor review their treatments. Treatments with diclofenac must be implemented only after the benefits and the risks have been assessed in patients with cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus and smoking). Diclofenac should be used only with the smallest efficient dosage and during the shortest period of time guaranteeing symptoms monitoring. Health professionals must regularly review whether it is necessary that their patients continue their treatment.

Many doctors and researchers are also questioning the presence of diclofenac on the national lists of essential medicines in numerous countries. Indeed, this drug appears on the list of essential medicines in 74 countries, whereas naproxen only appears on 27 [13]. Moreover, none of these two NSAIDs appear on the WHO List of Essential Medicines, which is used as a reference worldwide. It should be reminded that these national lists have a strong influence on the molecules used in each country. For instance, diclofenac is on China, India, and Pakistan's list of essential medicines, whereas naproxen is not [13]. In these countries, where diclofenac is available without a prescription, sales rates of diclofenac represent 30 to 40% of the world market [16]. Moreover, these countries's populations, which add up to almost 40% of the world population, suffer from an increase in cardiovascular diseases. That explains why the risk of thrombotic events is now very strong, given the increased use of diclofenac. Thus, beyond European recommendations, the use of diclofenac should be revised on a worldwide scale.

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