Cardiovascular Safety of Non-Steroidal Anti-Inflammatory Drugs. Lights and Shadows

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The cardiovascular safety profile of non-steroidal anti-inflammatory drugs (NSAID) is being questioned since the publication of the results of several clinical trials and observational studies. True, at the beginning research focused exclusively on selective inhibitors of cyclo-oxygenase 2 (COX-2, also known as coxib, but the results of some recent studies indicate that the increase in the risk of cardiovascular disease could more or less be shared with some traditional NSAID (NSAIDt).

The use of NSAID has been associated with a larger risk of hipertension[1] and heart failure,[2,3] and its possible association with the development of atherothrombotic disease emerged towards the end of the nineties. In 2000 the first epidemiological study that showed a small increment in the risk of myocardial infarction (MI) associated with the chronic use of NSAIDt was published.[4] Around the same time, coxibs started to be commercialized worldwide. The unexpected rise in the cardiovascular risk observed in patients that had been treated with high doses of rofecoxib in the VIGOR[5] study, together with the results of 2 other previous pharmacologic studies on coxibs[6,7] seemed to point at a class effect regarding cardiovascular damage, as a consequence of the suppression of prostacyclin in the absence of thromboxane A_2 (TXA_2) inhibition. In this way, a selective inhibition of COX-2 could reduce the cardioprotective effects of prostacyclin in the vascular endothelium, whose synthesis of mediated by this enzyme, without inhibiting the proaggregation effects of TXA_2, whose production is primarily controlled by the isoenzyme cyclo-oxygenase 1 (COX-1). Nonetheless, there where those who postulated that the observed result did not correspond to a rofecoxib-associated increment in the risk, but to a hypothetical cardioprotective effect of the drug it was being compared to, namely naproxen, because this NSAID has a long half-life and a greater affinity for COX-1 in a reversible manner, different from aspirin which irreversibly acetylates the enzyme and secondly, not even the protective effect of aspirin, that in clinically controlled trials was found to have a maximal reduction close to 30%, could explain the magnitude in the excess risk for MI observed in those exposed to rofecoxib in VIGOR.

The withdrawal of rofecoxib in 2004 was motivated by the results of another study, APPROVe, which was not specifically designed to evaluate cardiovascular safety of the drug, but to study its hypothetical protective effect against the recurrence of intestinal polyps.[8] This study was prematurely stopped due to an excess in the atherothrombotic events in the group with rofecoxib, compared to the placebo group. Nonetheless, another clinical trial in patients with Alzheimer did not show an increase in the cardiovascular risk associated with this drug.[9]

The clinical trials carried out up to date with other selective inhibitors do not answer all of the questions on their security profile. One of the 4 large clinical trials carried out with celecoxib (APC) detected an important increase in the number of cardiovascular events, as well as an increment in the parallel risk when the dosage was increased.[10] But the other 3 trials did not show a repetition of these results.[11-14] On the other hand, from among a dozen observational studies published up to date, only 2 of them have shown a significant increase in the cardiovascular risk associated to the use of this drug.[15] The contrast of these results with those of rofecoxib could be explained because of the infrequent use in the dose of celecoxib over 400 mg/day in the general population and also because celecoxib seems to have selectivity for the COX-2 enzyme comparable to that shown by some NSAIDt and less than rofecoxib.[16]

Among the selective inhibitors of COX-2 authorized in Spain, one can also find etoricoxib, valdecoxib, and parecoxib (prodrug of valdecoxib, used parenterally). The results of the MEDAL program have been recently published. This program analyzes 3 clinical trials jointly with the objective of comparing the frequency of atherothrombotic episodes in patients treated with etoricoxib or diclofenac. In general terms, both the incidence of atherothrombotic events and the rate of appearance of complicated ulcers and lower gastrointestinal tract toxicity were relatively constant during the whole treatment and similar in both groups. In the same study,

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the number of withdrawals due to edema or hypertension and the incidence of heart failure where more noticeable in the etoricoxib group, while the incidence of uncomplicated ulcer and withdrawal due to liver failure where more frequent in the group taking diclofenac.[17,18] On the other hand, in 2 observational studies recently published, an increase in the risk of MI of more than twice in patients treated with etoricoxib.[19,20]

Valdecoxib, which in spite of having authorization for its use, has never been employed in Spain, was recently withdrawn from the European market in part due to skin hypersensitivity reactions caused by it.[21] Parecoxib and its active metabolite, valdecoxib, is commercialized in Spain. Unfortunately, there are no clinical trials with these drugs that have followed patients for a prolonged time. In spite of this, 2 studies that administered parecoxib intravenously, followed by valdecoxib orally compared to placebo after a coronary bypass Intervention noted an increment in the appearance of severe cardiovascular events.[22,23] But a study concerning general surgery did not show an increment in any risk associated to the administration of both these drugs.[22]

Even though the attention was initially centered on the coxibs, the results of the ADAPT, a trial planned to compare the incidence of Alzheimer's disease in patients older than 65 years of age treated with celecoxib or naproxen, was suspended prematurely due to non-scientific data after the appearance of the results of the APC trial, adding to the confusion.[24]

The preliminary results of this study, published in late 2004, indicated an increase in the number of cardiovascular events (stroke, MI, and death) in patients treated with naproxen when compared to those receiving celecoxib or placebo. The idea that naproxen, thought by some to have cardioprotective effects similar to those of aspirin, would have a relationship to the appearance of atherothrombotic events was surprising to say the least. In spite of the scarce validity of ADAPT, this study generated a certain degree of alarm when it pointed out that, for the first time in a clinically controlled trial an association between the consumption of NSAIDt and cardiovascular risk had been observed.

In contrast to the selective inhibitors of COX-2, no placebo-controlled clinical trials exist that permit an evaluation of the safety of NSAIDt; the evidence is limited to observational studies or indirect comparisons with coxibs in clinical trials. In a meta-analysis of observational studies, of the 3 NSAIDt individually studied, only diclofenac was clearly associated to an increase in the cardiovascular risk, compared in magnitude to the ones associated to coxibs.[25] In this same study there was no evidence of an increase in the risk associated to ibuprofen or naproxen. Little can be said of the rest of the NSAIDt because they are used less frequently or due to lack of evidence. One aspect to review, with respect to the relationship between NSAIDt and cardiovascular risk is the hypothetical pharmacodynamic interaction described by Catella-Lawson et al[26] during the concomitant use of ibuprofen and aspirin. Due to the great affinity of ibuprofen for COX-1, which it reversively inhibits, the chronic administration of aspirin and ibuprofen could partially impede aspirin from binding to the enzyme, both drugs competing for the binding site. Therefore, the use of ibuprofen in this type of patients could diminish the cardioprotective of aspirin. Though the interaction has been demonstrated in laboratory studies, there is not enough evidence on the impact that it could have in the general population and, in fact, studies published on this subject show contradictory results.[27,28]

Faced with this situation, health authorities have not been indifferent; the FDA (Food and Drug Administration) decided last year to demand that the technical data and prospectus of all NSAIDt contain warnings on their possible relationship to atherothrombotic events similar to those described for selective inhibitors of COX-2. EMEA (European Agency for the Evaluation of Medicinal Products), the European homologue of the FDA and the Spanish Agency for Drugs have established wide ranging evaluation commissions for NSAID after these events. Recently, EMEA published the conclusions of this review in which a small increase in the risk for MI associated to the use of NSAIDt is not discarded, especially when large doses are used or the time of use is prolonged. In spite of this, the report concludes that the risk-benefit balance of these drugs is still favorable.[29]

Recently, the Spanish agency made public an informative letter sent to health professionals in which, on the basis of studies carried out, estimated the excess of atherothombotic episode cases around 3 for each 1000 persons/year when treated with coxib.[30] On the other hand, a final report is expected to be published soon from the Spanish agency's commission evaluating NSAID use.

NSAID are a pharmacological group of drugs with extensively used and growing within the population, making any increase in the cardiovascular risk, no matter how small, of great impact on the health of the population. The gastrointestinal safety profile of these drugs has concentrated a lot of media attention and research efforts. The perception of the gastrointestinal risks has modified therapeutic practice and has derived in the generalized use of proton bomb inhibitors and the appearance of coxib, introduced into the market with an apparently more advantageous gastrointestinal security profile than NSAIDt. Paradoxically, since the introduction of these drugs, the cardiovascular safety of the coxib has been called into question and has later been extended to NSAIDt. Everything seems to point to, as occurred in the case of the gastrointestinal safety profile, not all of the drugs in the group have the same cardiovascular risk in the way in which they are used in daily clinical practice, even though to conclude this with certainty will require more studies.

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