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Safety and efficacy of low doses of diclofenac on acute pain in the emergency setting

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Abstract. – Diclofenac is the most widely prescribed non-steroidal anti-inflammatory drug worldwide. Data collected during the last 10 years reported a dose-duration dependent increasing of cardiovascular risk associated with the use of diclofenac, supporting the evidence of a close association with the degree of COX-2 inhibition achieved in vivo. Nevertheless, the amplitude of cardiovascular risk associated with the administration of diclofenac at low doses and for the short-term duration is still poorly defined. Indeed, data did not show a clear and strong increasing of the risk for daily doses of 75 and of 50 mg. Concerning duration, while the identification of a safe temporal window is less defined, some studies reported an absence or a very low risk when the exposure is shorter than 30 days. Today, new low-dosage diclofenac formulations are available, allowing to reduce the systemic exposure, the degree of COX-2 inhibition and possibly the risk of occurrence of cardiovascular events. This is the reason why those new formulations may represent the ideal drug for the management of pain in the emergency setting.

Key Words:
Diclofenac, Cardiovascular risk, Mortality.

Introduction

Diclofenac is the most widely prescribed non-steroidal anti-inflammatory drug (NSAID) worldwide[1]. It was synthesized by Alfred Sallmann and Rudolf Pfister as diclofenac sodium and after its introduction in 1973, a number of different formulations have been developed aimed at improving efficacy, tolerability and safety[2]. The best known mechanism of action, common to all NSAIDs except for acetylsalicylic acid (ASA), is the competitive and reversible inhibition of the cyclooxygenase (COX) activity of 2 major isoforms of prostaglandin (PG) G/H synthase, known as cyclooxygenase 1 and 2 (COX-1 and COX-2) and reduced biosynthesis of respective prostanoids, which in turn are implicated in the modulation of a wide range of different and often opposing physiological and pathological processes, by binding to cell and tissue-specific receptors[3-7].

Diclofenac shares a wide spectrum of therapeutic and adverse effects typical of other NSAIDs[3,4]. In this article, we analyze all aspects related to the cardiovascular (CV) risk associated to the use of diclofenac and highlight the importance of the new low-dosage formulations specifically created to increase safety with a preserved analgesic activity.

Pharmacological Features of Diclofenac

Diclofenac is classified among traditional NSAID (t-NSAID), but differently from some of them, shows *in vitro* a higher selectivity for COX-2, almost as celecoxib[5]. COX-2 selectivity is displayed also for therapeutic concentrations achieved *in vivo*, to which inhibition of platelet COX-1 is too weak (< 97%) to translate into platelet functional impairment[2,5]. Furthermore, diclofenac is among the most effective inhibitors of PGE2 production[2,5].

Diclofenac is a phenylacetic acid, characterized by a partial solubility in both aqueous and hydrophobic environments, a short biological half-life and a rapid oral absorption[8]. It is available, as sodium salt, potassium salt or epolamine salt, as well as in formulations complexed with hydroxy-propyl-beta-cyclodextrin or in free micronized acid particles[2]. Oral formulations, also associated to misoprostol and omeprazole, or topical and injectable formulations are currently available, with different dosages and pharmacokinetic properties[2]. Due to its weak acid nature and the high degree of plasma proteins binding,

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diclofenac accumulates and persists in inflamed tissues and synovial fluid even longer than in plasma, ensuring a prolonged analgesic and anti-inflammatory effect regardless of a short half-life[5,9]. On the other hand, short half-life may increase diclofenac safety compared to long half-life NSAIDs, due to a more rapid clearance and a full recovery of COX activity in other sites[5,9]. Since the target for a therapeutic efficacy is achieved when the drug plasma concentration inhibits about 80% of COX-2 activity, diclofenac is often administered at higher doses than necessary, then increasing the probability of inducing side effects[10]. This may contribute to explain the association between the use of diclofenac and the occurrence of cardiovascular events reported in the literature, especially when the dosage is higher than 100 mg daily[11,12].

Diclofenac and Cardiovascular Risk

After the first reports of a role of selective COX-2 inhibitors (COXIBs) in increasing the incidence of atherothrombotic events[11], further studies[11,12] reported a similar effect for some t-NSAIDs, including diclofenac. While the mechanisms are still not fully elucidated, they appear strictly dose and duration dependent, and widely related to the degree of COX-2 inhibition achieved *in vivo*[13]. As elegantly expressed in a retrospective cohort study by Garcia Rodriguez et al[14] in 2008, who analyzed the THIN (The Health Improvement Network) database in the UK, NSAIDs such as diclofenac, which able to inhibit COX-2 without a complete COX-1 platelet inhibition, may increase the risk of myocardial infarction (MI) in the general population and this effect is proportionate to the extent of COX-2 inhibition. In fact, individual NSAIDs with a degree of COX-2 inhibition lower than 90% achieved at therapeutic concentrations, showed a relative risk (RR) for MI of 1.18 (1.02-1.38, CI 95%), whereas those with a higher degree of COX-2 inhibition reported a RR of 1.60 (1.41-1.81, 95% CI). The risk increased proportionally to daily dose and treatment duration and with the use of slow release formulations[14].

There are two main hypotheses, not mutually exclusive, to explain why some NSAIDs may increase the CV risk. The first is that this may result by an imbalance between inhibition of the two main COX isoenzymes, by favoring COX-2, resulting in a reduced biosynthesis of endothelial PGI-2 associated with ineffective platelet inhibition and thromboxane (TX) A2 biosynthesis[15]. According to this hypothesis, the net pro-thrombotic effect may also show an immediate onset in otherwise susceptible individuals[15]. The other hypothesis is that the increased CV risk may result from the renal COX-2 inhibition, with decreased local PG biosynthesis, resulting in blood hypertension and subsequent development of endovascular atherothrombotic alterations[16]. This mechanism is common to several chronically administered NSAIDs, except for low dose ASA[16], but is not the case of NSAIDs administered administered at low-doses and for short-term exposures[17]. Among all mechanisms involved in the increasing of the CV risk, the most relevant step seems to be the of COX-2 inhibition and the corresponding reduced prostanoid synthesis[15-17].

Limits of Current Data

Before exploring the results obtained by different authors on this issue, we have to start from the assumption that there are no randomized controlled trials (RCTs) in the literature specifically designed to investigate the effect of NSAIDs on general and individual CV risk[18]. Many studies currently available are often lacking of critical data allowing to draw any definite and significant conclusion about the CV risk of individual NSAIDs administered at diverse doses and for different durations. Particularly, the main source of information from where data may be obtained is observational studies, extremely heterogeneous in terms of design, outcomes, population features, doses and duration of therapy[19]. Furthermore, some scholars did not consider very important concomitant factors, such as body mass index (BMI), smoking, lipid levels, blood pressure, left ventricular ejection fraction, NYHA classification of heart failure, simultaneous administration of ASA and/or over the counter (OCT) NSAIDs, which may affect the results of the studies. Moreover, none of the authors even considered that some conditions requiring analgesic therapy, such as illness/inflammatory events or painful conditions may independently increase the CV risk or precipitate acute coronary syndromes[20,21]. As a consequence, even the results of meta-analysis or review articles published on this issue are affected by the poor quality of the available data[22]. Finally, in order to better define the amplitude of the problem, while the RR for GI complications related to the use of NSAIDs is estimated to be around 4, the same for CV events is usually between 1 and 2[23].

Effect of the Dosage on Cardiovascular Risk

Current knowledge plays in favor of a dose-dependent effect of diclofenac on the CV risk; as a consequence, low doses may be the key to reduce diclofenac-related side effects. Nevertheless, the definition of "low-doses" is still far from satisfactory, as in many studies the authors defined as "low" a daily dosage up to 100 mg, while in others dosages below or equal to 150 mg, which represents the highest allowed in many Countries[24]. Since the incidence of side effect of diverse dosages of diclofenac may differ[24] currently available data are still confusing and inconclusive.

Only the cohort study performed by Garcia Rodriguez et al[14] in 2008 has investigated the impact of a broad spectrum of available doses of diclofenac, ranging from 50 to 150 mg on myocardial infarction (MI) in the general population. They found a weak association either with 50 mg [1.12 (0.60 to 2.20; 95% CI)] or 75 mg [1.31 (0.80 to 2.16)], while the RR became more consistent by increasing the dosage to 100 mg [1.65 (1.26 to 2.18) and 150 mg daily [1.80 (1.49 to 2.18)].

In a recent study, Odom et al[23] performed a meta-regression analysis by using data coming from 11 observational studies, demonstrating a linear relationship between the dosage of diclofenac and the RR for CV events. The RR was 1.13 (1.08-1.18) for doses of 50 mg, 1.26 (1.17-1.35) for 100 mg and 1.39 (1.25-1.53) for 150 mg compared with no use.

Since many patients use diclofenac OCT, two authors have investigated its effect of CV risk, reporting different results. In fact, while Moore et al did no found a clear increased risk[24], other authors showed an overall RR for CV events of 1.22 (1.12-1.33)[25].

Concerning the CV effect of dosages of diclofenac up to 100 mg, Fosbøl et al[26] evaluated the dose-related risk of various NSAIDs in a cohort of healthy individuals, extrapolated from the Danish national register. Notably, they did not find any significant association for daily doses of 100 mg or lower; indeed, RR was 0.62 (0.45-0.86) for CV death, 0.88 (0.69-1.12) for the composite endpoint coronary death or non-fatal MI, and 0.93 (0.71-1.73) for fatal or non-fatal stroke. Conversely, for doses of diclofenac higher than 100 mg the RR increased for all the above-mentioned endpoints [1.28 (1.08 to 1.53); 1.28 (1.10 to 1.50) and 1.59 (1.35-1.88), respectively][26].

Other authors have also evaluated the effect of different doses of diclofenac on CV threat of "high risk" patients. Gislason et al[27] in 2006 determined the CV risk induced by NSAIDs, including diclofenac, on a cohort of Danish patients with previous MI, showing a RR of 0.89 (0.66 to 1.20) for CV death and 1.27 (0.92 to 1.76) for re-MI, for doses below 100 mg. Conversely, RR increased to 4.44 (3.79-5.19) and 1.89 (1.40-2.55) for dosages of 100 mg or greater. The same authors, in a further study, have investigated the NSAIDs-related CV risk in a cohort of Danish patients with a previous hospitalization for heart failure (HF). For doses of diclofenac up to 100 mg, the RR was 1.31 (1.20-1.42) for death, 1.34 (1.21-1.48) for re-hospitalization for HF and 1.14 (0.9-1.43) for MI. RR increased for doses higher than 100 mg, reaching 5.54 (5.08-6.03), 1.42 (1.17-1.73) and 2.43 (1.74-3.40) respectively[28]. In a nested case-control cohort study using the General Practice Research Database (GPRD), Andersohn et al[29] reported a RR for MI of 1.31 (1.6-1.61) for diclofenac doses up to 100 mg and 1.35 (1.13 to 1.61) for doses higher than 100 mg, while using the Dutch database PHARMO, Van der Linden et al[30] showed a RR of 1.13 (0.79 to 1.61) for MI for doses of diclofenac up to 100 mg.

Of interest is the meta-analysis sponsored by EMA (European Medicines Agency), under the SOS project (Safety of NSAIDS), involving observational studies published from 1990 to 2011 on the risk of MI in a patient treated with NSAIDs[31]. The pooled RR for doses of diclofenac up to 100 mg was 1.26 (1.03-1.53) showing only a weak association with further CV events[31]. Despite some discrepancies in the study[32], it's surprising as EMA has issued the PRAC (Pharmacovigilance Risk Assessment Committee) recommendations 353084/201332, also considering these metanalysis results[32].

Likewise, McGettigan et al[25] in 2011 reported only a week association between diclofenac dosage up to 100 mg and CV risk [RR 1.22 (1.12-1.33)], while it was 1.98 (1.40-2.82) for doses higher than 100 mg. Conversely, two studies have surprisingly reported a minor and, in some way, a cardio-protective effect for high doses of diclofenac compared to low dosages. Ray et al[33] in 2009, analyzed the Tennessee Medicare, Saskatchewan and GPRD database for the use of NSAIDs in patients with a recent hospitalization for a severe coronary artery disease. They found higher RR for severe coronary artery

disease [1.65 (1.13 -2.42)] and serious CV disease [1.43 (1.14-1.78)] for daily doses of diclofenac up to 150 mg. Conversely, RR for doses higher than 150 mg was 0.99 (0.66 to 1.50) and 1.34 (1.09-1.65) respectively; interestingly, authors did not provide any explanation concerning such a phenomenon[33]. Varas-Lorenzo et al[31] reported similar results in 2009, by analyzing the Saskatchewan database; they showed a RR of 1.29 (0.78-2.13) for doses up to 100 mg and 0.63 (0.37-1.08) for doses higher than 100 mg, justifying those unexpected result with the small number of cases included in the study.

Effect of Duration on Cardiovascular Risk

Given all the above-mentioned limitations, current inclination is that the risk of developing CV adverse events associated with the use of diclofenac, increases proportionally with the duration of treatment[18]. But what is the safe temporal window?

Garcia Rodriguez et al[34] in 2005 analyzed data form the United Kingdom GPRD and found that the use of diclofenac for durations shorter than 1 month was not associated with any increased CV risk, with an estimated RR 0.99 (0.73-1.35). Conversely, for durations ranging from 31 to 365 days, the RR increased to 1.19 (0.92-1.53), reaching 1.38 (1.00 to 1.90) for lengths longer than 1 year. Similar results emerged from another study[14] performed by the same authors in 2008, where the RR for CV events was 1.13 (0.92-1.39) for durations up to 30 days, 1.34 (1.15 to 1.56) for durations from 31 to 365 days, 1.39 (1.16-1.67) for durations from 1 to 3 years and 1.53 (1.28-1.82) for those more than 3 years.

On the contrary, in a study performed by Varas-Lorenzo et al[35], the RR for daily doses of diclofenac of 100 mg for durations up to 30 days was 1.38 (0.59-1.98), falling at 0.90 (0.62-1.30) when the therapy lasted longer than 30 days. Andersohn et al[29] found only a weak association between increased CV risk and daily diclofenac doses below or equal to 100 mg for treatment durations lower than 3 months [1.27 (1.0-1.55)] with a little progressive increase by prolonging treatment to 3-12 months [1.20 (0.95-1.53)] or more than 12 months [1.73 (1.31-2.28)]. Ray et al[33] showed an increased CV risk for daily doses up to 150 mg for up to 90 days [RR 1.86 (1.2-2.9)], which decreased for durations higher than 1 year [RR 0.91 (0.5-1.6)].

Others studies, such as that performed by Schjerning Olsen et al[36] in 2011, who enrolled patients with a previous history of MI, showed that the CV risk (death/MI or early recurrent MI) significantly increased immediately after the starting of the treatment, from 0 to 7 days [RR 3.26 (2.57-3.86)] and decreased after 90 days [RR 1.92 (1.66-2.22)]. Naturally, those results should be interpreted with caution, since only very "high risk" patients were enrolled. The results of the Coxib and traditional NSAID Trialists' (CNT) Collaboration meta-analysis, collecting data from 754 RCTs COXIBs/t-NSAIDs, which is currently the most comprehensive and reliable source of information about NSAIDs CV safety were also evaluated. This study doesn't allow us to draw any definite conclusions whether specific NSAIDs increase CV risk immediately after the starting of the treatment. Moreover, the authors[11] concluded that the increased vascular risk for diclofenac is for high-doses. McGettingan et al[1] and Varas-Lorenzo et al[31] have tried to investigate the association between CV risk and duration of diclofenac administration. However, data are too limited to draw any definite and reliable conclusion.

In conclusion, the effect on CV risk of different durations of treatment with diclofenac remains then not yet defined. Nevertheless, current impression is for a progressive negative effect on the CV risk, possibly starting after the first month of therapy.

Interaction with Acetylsalicylic Acid

An important aspect to be considered before starting a therapy with NSAIDs is the potential interference with the antiplatelet effect exerted by low-dose of ASA (75-100 mg/daily), commonly prescribed to prevent ischemic events[37]. For its unique pharmacokinetic and pharmacodynamic features, low dose ASA irreversibly and cumulatively inhibits platelet COX-1, with a quite complete suppression of its ability to synthesize TXA2 throughout a 24 hours dosing interval[12]. This complete and permanent suppression of platelet COX-1 is necessary to translate into cardio-protection, as even small concentrations of TXA2 may cause platelet activation[38]. The irreversible platelet COX-1 inhibition by ASA requires an affinity for the arginine-120 residue of the COX-1 channel[39], which is also recognized by others NSAIDs[38,39]. This is the case of naproxen, which competes with this docking site, thus preventing ASA antiplatelet action[40]. On the contrary, this effect is not observed for other drugs displaying a high selectivity for COX-2 isoenzymes, such as celecoxib, or those showing intermediate selectivity for the

same, including diclofenac[41,42]. Although further studies are needed to explore the clinical relevance of these pharmacodynamic interactions, the absence of interference with ASA could be an advantage in patients concomitantly treated with this drug but needing analgesics for acute pain in the emergency setting.

New Low-Dose Formulations

Considering the dose-duration dependent effect of NSAIDs on the CV risk, both EMA and the Food and Drug Administration (FDA) have issued a recommendation to use the lowest effective dose of NSAIDs for the shortest time necessary to control symptoms[43,44]. To fulfill those recommendations, today pharmaceutical technology has made available new products characterized by significantly reduced diclofenac dosages, allowing to reduce the systemic exposure, the degree of COX-2 inhibition and potentially the probability of occurrence of adverse CV event, but with a preserved therapeutic efficacy[2].

In 2013, FDA approved for the management of mild to moderate acute pain in adults with arthritis new diclofenac capsules of 18 or 35 mg, containing submicroscopic particles of the drug developed using the SoluMatrix technology. This new formulation improves drug dissolution, bioavailability and absorption, then allowing to reduce the dosage by at least 20% compared to diclofenac potassium tablets[45]. In a randomized, phase III, placebo-controlled trial in patients with acute pain following bunionectomy, treatment with this new formulation of diclofenac 35 mg ($p < 0.001$) and 18 mg ($p < 0.010$) tid determined a significant reductions in pain intensity 48 hours after administration ($p < 0.001$ and < 0.010, respectively) compared to placebo[46]. In another study conducted on patients with osteoarthritis of the hip or knee, pain was significantly improved after treatment with SoluMatrix diclofenac 35 mg tid compared to placebo ($p < 0.0024$), with a 12 week of follow-up, while administration of the same dosage twice a day did not achieve statistical significance ($p < 0.0795$)[47]. Despite the shortness of the follow-up, this new formulation was well tolerated and no adverse events, even CV, were reported[47].

A novel formulation of diclofenac sodium complexed with hydroxypropyl-beta-cyclodextrin (HPBCD diclofenac) has been approved by FDA[48]. This formulation is now available in solution for intramuscular (i.m.) or subcutaneous (s.c.) injection with three different doses of 25, 50 and 75 mg. Main indications are acute painful episodes, such as renal colic, exacerbations of osteoarthritis and rheumatoid arthritis, acute back pain, acute attacks of gout, acute trauma and fractures and post-operative pain requiring analgesic therapy for 2 days[48]. Besides an improved facilitation of the self-administration due to the pre-filled syringes, the availability of a very low dose of diclofenac, such as 25 mg, allows to customize the therapy according to patient BMI and comorbidities, including sarcopenia. Beta-cyclodextrins are hydrophilic molecules incorporating in their core the lipophilic active principle, allowing the improvement of solubility, bioavailability and absorption of diclofenac. This plays in favor of a significant reduction of the dosage of the drug, diluted in a very small amount of total volume of injection (1 mL). The final result is the creation of a low dosage of diclofenac with a very high rapidity of action, achieving full pain relief just 5-10 minutes after the administration[48]. Several studies have been done on efficacy and safety of this new formulation. In a randomized, double-blind, placebo-controlled multicenter phase III clinical trial, Dietrich et al[48] evaluated efficacy and safety of all diclofenac HPBDC doses administered as a single injection in the treatment of moderate or severe pain following dental surgery. Notably, a significantly greater pain relief compared to placebo was obtained for all groups ($p < 0.001$), with no significant differences between different doses. Moreover, the new 50 mg dose was equivalent to the 75 mg in terms of efficacy[48]. Moreover, the DIRECT study showed a very powerful effect of HPBCD diclofenac 75 mg administered s.c. or i.m. compared to the traditional i.m. formulations in patients with minor orthopedic surgery[49] while a recent observational study reported a significant reduction of moderate to severe neuropathic pain by using s.c. injection of diclofenac HPBCD 75 mg, with a follow-up of 2 months and two weeks[50]. Diclofenac HPBCD was generally well tolerated in all clinical trials and no serious side effects have never been reported[48-50].

Conclusions

Data collected during the last 10 years showed a dose-duration dependent increasing of CV risk in patients treated with diclofenac[1,18,25], supporting the evidence of a close association of NSAIDs CV-risk with the degree of COX-2 inhi-

bition achieved *in vivo*[12,14]. Concerning diclofenac, according with the current knowledge, the use of low doses for a very short duration significantly reduce the systemic exposure to this drug, the degree of COX-2 inhibition and, as a consequence, the risk of occurrence of CV events with a preserved therapeutic efficacy[45-50]. On the other hand, diclofenac does not interfere with the antiplatelet effect exerted by ASA, commonly used by many patients[41,42]. Today, new low-dose formulations of diclofenac are available, allowing to reduce side effects and to customize the dosage to the clinical characteristics of the patients. All those features make these new diclofenac low-dose formulations a safe and effective choice for the management of acute pain in the emergency setting.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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