

Hypersensitivity to nonsteroidal anti-inflammatory drugs: From pathogenesis to clinical practice

Hipersensibilidade a anti-inflamatórios não esteroides: Da patogénese à prática clínica

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the leading causes of hypersensitivity reactions, which affect a considerable percentage of the general population. These drugs can induce a wide spectrum of reactions with distinct timing, organ involvement and severity, including either immunological or nonimmunological mechanisms. A proper diagnosis can be particularly challenging since most reactions result from the pharmacological mechanism of the drug and might be dose-dependent. The clinical classification of NSAIDs-induced reactions has changed over time. Accurate diagnosis depends on strict clinical history and proper understanding of underlying mechanism. Skin testing and in vitro testing have limited usefulness. Drug challenge tests with the culprit or alternative drugs are the gold standard for the diagnosis, and provide information about drug avoidance and safe therapeutic options. In selected cases drug desensitization might be a therapeutic option. In this review, we will attempt to highlight the main aspects to be taken into account for a proper management of patients with NSAIDs hypersensitivity.

Key-words: Acetylsalicylate acid, alternative drugs, desensitization, diagnosis, hypersensitivity, nonsteroidal anti-inflammatory drugs.

RESUMO

Os anti-inflamatórios não esteroides (AINEs) são uma das principais causas de reações de hipersensibilidade, afetando uma percentagem considerável da população em geral. Estes fármacos podem induzir um amplo espectro de reações que variam quanto ao tempo de aparecimento, órgãos envolvidos e gravidade, incluindo tanto mecanismos imunológicos como não imunológicos. O diagnóstico pode ser particularmente desafiante, dado que a maioria das reações resulta do respetivo mecanismo farmacológico dos fármacos e pode ser dosedependente. A classificação clínica das reações induzidas pelos AINEs tem sofrido alterações ao longo do tempo. O diagnóstico apropriado depende de uma história clínica rigorosa e da compreensão do mecanismo envolvido. Os testes cutâneos e os testes *in vitro* têm uma utilidade limitada na abordagem diagnóstica. As provas de provocação com o fármaco implicado ou com os alternativos constituem o *gold standard* para confirmar o diagnóstico e fundamentar as orientações sobre os fármacos a evitar e as opções terapêuticas seguras. Em casos selecionados a dessensibilização a fármacos pode ser uma opção terapêutica. Nesta revisão, os autores pretendem destacar os principais aspetos para a abordagem de doentes com hipersensibilidade a AINEs.

Palavras-chave: Ácido acetilsalicílico, anti-inflamatórios não esteroides, dessensibilização, diagnóstico, fármacos alternativos, hipersensibilidade.

INTRODUCTION

Aspirin/acetylsalicylate acid (ASA) and other non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used pharmacological groups. Their efficacy to relieve pain and ameliorate inflammation results in its widespread use, mostly by patients who suffer from orthopedic and rheumatologic diseases¹. NSAIDs provide analgesic, antipyretic, and anti-inflammatory effects. ASA can also be used to prevent cardiovascular disease.

Owing to their growing use, NSAIDs are one of the most frequently pharmacological groups involved in adverse reactions, including hypersensitivity reactions²⁻⁴. These reactions consist of reproducible signs and/or symptoms, resulting from drug exposure to a dose that is usually tolerated by the general population. The reactions can be considered as allergic, if there is an underlying immunological mechanism (IgE-mediated or cell-mediated) and non-allergic. Regarding the hypersensitivity reactions to

NSAIDs, most of them are non-allergic, mediated by non-immunological mechanisms, namely by the inhibition of the cyclooxygenase pathway. However, some cases result from IgE-mediated mechanisms, such as immediate reactions to pyrazolones^{2,5}.

Hypersensitivity reactions can lead to a spectrum of clinical manifestations, ranging from cutaneous symptoms (urticaria and/or angioedema) or respiratory symptoms (rhinitis, dyspnea, and severe bronchoconstriction) to anaphylactic reactions, and can occur few minutes after drug exposure. Beyond immediate reactions, late reactions may occur within a period of up to 48 hours after NSAID intake².

EPIDEMIOLOGY

Previously considered as the second cause of hypersensitivity reactions, following antibiotics, some recent reports have considered NSAIDs to be nowadays the

most frequent cause of drug-induced hypersensitivity, regardless the severity of the reactions^{2,3,6}.

The overall prevalence of NSAIDs hypersensitivity ranges from 0.6 to 6%, depending on the analyzed population, method of assessment and type of reaction². An epidemiological study performed in Portugal, revealed that 2% of the general adult population has self-reported hypersensitivity to NSAIDs⁷. NSAIDs have been considered as the most common cause of anaphylaxis induced by drugs. Considering a drug-induced anaphylaxis survey during a 4-year period in Portuguese allergy departments, NSAIDs were responsible for 48% of all cases (aspirin, diclofenac and ibuprofen are the main culprits)³. Similar results were found in a 6-year observational study performed in a Spanish tertiary hospital, in which NSAIDs were responsible for 49% of the anaphylactic reactions (dipyrone, aspirin and diclofenac as main culprits)⁸. Comparing to a previous study describing a decade review of reactions reported to the Portuguese Pharmacovigilance Authority, NSAIDs were the culprit drugs in 13% of cases (after antibiotics)⁹. In the same study, a subgroup analysis in the pediatric population showed that NSAIDs/acetaminophen accounted for 7% of the reported cases⁹. Additionally, and according to the Online Latin American Survey on Anaphylaxis (OLASA), NSAIDs were the culprit agents in 73% of the drug-induced anaphylaxis¹⁰.

Hypersensitivity reactions to NSAIDs appear to be more prevalent among asthmatic patients ranging from 4 to 21%. Chronic rhinosinusitis with nasal polyps, severe asthma, female gender and/or atopy are associated with higher prevalence of NSAIDs hypersensitivity².

Cutaneous manifestations are less frequent (0.3%) in the general population without allergic disease¹¹. On the other hand, in chronic urticaria, NSAIDs might cause a disease exacerbation in up to 40% of patients. This is a dose-dependent effect, more prone to occur in cases with poorly controlled chronic urticaria. Despite most of patients suffering from spontaneous chronic urticaria, other types of urticaria might be affected, such as cholinergic urticaria².

Cross-reactivity between NSAIDs occurs frequently in patients with cutaneous reactions. Nevertheless, one third of patients are single-reactors (selective reaction). The NSAIDs commonly involved in this pattern are the pyrazolones (metamizole), ibuprofen, diclofenac, AAS and paracetamol/acetaminophen².

The prevalence of late reactions is barely known, including maculopapular exanthema (MPE), fixed drug eruption (FDE), contact dermatitis and photosensitivity reactions. Severe and potential life-threatening skin reactions, such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) are extremely rare².

All NSAIDs can be involved. Owing to their chemical structure, some groups (naproxen, diclofenac, ketorolac and ibuprofen) have been more frequently implicated in anaphylactic reactions.

Although rare, cases of paracetamol hypersensitivity have been reported, including anaphylaxis, namely in children^{12,13}. Ibuprofen is the most frequent elicitor of urticaria/angioedema or anaphylaxis in children, although paracetamol and pyrazolones have also been implicated¹⁴. Despite the low frequency of delayed reactions in children, FDE has been reported with ibuprofen, naproxen, dipyrone, oxicams, nimesulide, and other NSAIDs¹⁴.

In adults, the drugs more frequently involved in IgE-mediated/immediate reaction are pyrazolones, followed by ibuprofen and diclofenac¹⁴.

In a large study with 659 adolescent/adult patients, it was described that 76% had cross-intolerance and the remaining were selective responders¹⁵. Among patients with cross-intolerance, urticaria and angioedema were the main symptoms and in a less extent airway involvement, whereas in selective responders there was a predominance of urticaria and/or angioedema, followed by anaphylaxis¹⁵.

In extremely rare occasions (0.008%) cyclooxygenase 2 selective inhibitors (coxibs) might also be implicated¹¹.

CLASSIFICATION

Hypersensitivity reactions to NSAIDs can be classified in different clinical phenotypes, according to clinical manifestations, the presence of an underlying allergic disease, cross-reactivity pattern with other COX-I inhibitors and distinct immunological or pharmacological mechanisms.

According to the last proposed classification², there are three types of nonimmunological reactions (NSAIDs-exacerbated respiratory disease; NSAIDs-exacerbated cutaneous disease; NSAIDs-induced urticaria/angioedema) and two types of immunological mediated reactions (Single-NSAID-induced urticaria/angioedema or anaphylaxis; Single-NSAID-induced delayed reactions).

NSAIDs-exacerbated respiratory disease (NERD): Hypersensitivity reactions induced by aspirin or other NSAIDs with predominant respiratory manifestations (bronchial obstruction, dyspnea, and nasal congestion/rhinorrhea), occurring in patients with an underlying chronic airway respiratory disease (asthma/ rhinosinusitis/ nasal polyps). This clinical association was previously known as the aspirin triad or Widal syndrome. It is more prevalent in female gender (more than 2 to 1) and at least one third of patients are atopic. Typically, these patients develop chronic rhinitis during the third or fourth decade of life, refractory to medical management. The chronic rhinitis evolves into chronic eosinophilic rhinosinusitis with nasal polyposis. Multiple sinus surgeries result in only limited temporary benefit. During the evolution of the sinus disease, asthma appears and persists. Lastly, NSAID-induced respiratory reactions appear, after exposure to these medications. Despite subsequent avoidance of NSAIDs, the disease persists, and often requires therapy with systemic corticosteroids. Adequate asthma control can only be accomplished with the simultaneous control of the associated rhinosinusitis. With few exceptions, there is a progressive worsening of the clinical manifestations over time¹⁶.

NSAIDs-exacerbated cutaneous disease (NECD): Cutaneous hypersensitivity reactions induced

by aspirin or other NSAIDs (urticaria and/or angioedema) occurring in patients with underlying chronic spontaneous urticaria. Symptoms usually appear from 0.5 to 6 hours after NSAID intake, although both immediate (within 15 minutes) and late (within several hours) reactions can occur. Skin lesions may last from few hours to several days. The severity of symptoms is dose-dependent and greater when chronic urticaria is active; being less frequent and less intense when chronic urticaria is in remission or under control. Chronic spontaneous urticaria in patients with NECD can also be exacerbated by other triggers (infections, antibiotics, physical factors, and stress), further complicating the clinical picture and diagnosis⁴.

NSAIDs-induced urticaria/angioedema (NIUA): Hypersensitivity reactions induced by aspirin or other NSAIDs with cutaneous manifestations as urticaria and/or angioedema, occurring in otherwise healthy subjects (symptoms induced by at least two NSAIDs belonging to different chemical groups).

Regarding immunological mediated reactions, they can assume two different clinical patterns:

- 1. Single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)** consists of an immediate hypersensitivity reaction (usually IgE-mediated) to a single NSAID (or to a similar one belonging to the same chemical group), with tolerance to other chemically nonrelated NSAIDs. It occurs in subjects without history of asthma or chronic urticaria.
- 2. Single-NSAID-induced delayed reactions (SNIDR)** consists of hypersensitivity reactions (usually T-cell mediated) to a single NSAID (or to a similar one belonging to the same chemical group) that appear usually within 24 to 48 hours after drug administration. They can assume cutaneous manifestations (maculopapular exanthema, fixed drug eruption), organ-specific symptoms (as renal and pulmonary involvement) or severe cutaneous adverse reaction (SCAR).

CLINICAL MANIFESTATIONS

Hypersensitivity reactions to NSAIDs can display a wide spectrum of symptoms, from rhinitis, conjunctivitis, bronchospasm, urticaria, angioedema and anaphylaxis. The reactions occur generally within 30 to 60 minutes after drug administration but can be delayed up to 4 hours. Beyond these immediate reactions, late reactions may occur and delay up to 48 hours².

The overall incidence is greater after the third decade of life, with predominance of respiratory symptoms in adults and cutaneous symptoms in children. In adults, greater incidence is found in females, whereas in pediatric age males are more frequently affected (2:1)^{17,18}.

There are different clinical patterns, with respiratory or cutaneous predominance, according to the last clinical classification (NERD, NECD, NIUA).

In NERD, rhinorrhea and nasal obstruction used to appear first, in the fourth decade of life. Therapy-resistant rhinosinusitis and recurrent nasal polyps combined with asthma appear typically some years before. These patients suffer from severe asthma with near-fatal outcome,

and fifty percent of them have corticosteroid-dependent asthma^{16,17}.

PATHOGENESIS

The underlying pathophysiological mechanisms of NSAIDs hypersensitivity are usually non-immunological, related to pharmacological properties and/or to dose amount of NSAID. NSAIDs act in the arachidonic acid (AA) metabolic pathway, reducing prostaglandin synthesis through inhibition of cyclooxygenase (COX)-1 with increased release of cysteinyl leukotrienes (LTs). These mediators induce inflammation, bronchoconstriction (LTC₄, LTD₄, LTE₄) and have a chemiotactic action (LTB₄, LTE₄). Concomitant decrease in prostaglandin synthesis (PGE₂, PGI₂) amplifies bronchoconstriction^{17,19}.

Two cyclooxygenase isozymes (COX-1 and -2) were identified: COX-1 (constitutive; involved in prostaglandin synthesis) and COX-2 (inducible in pathologic circumstances, such as inflammation). The AA metabolites produced by COX-1 protect the gastric mucosa, regulate renal blood flow and induce platelet aggregation²⁰. Anti-inflammatory effects of NSAIDs results from COX-2

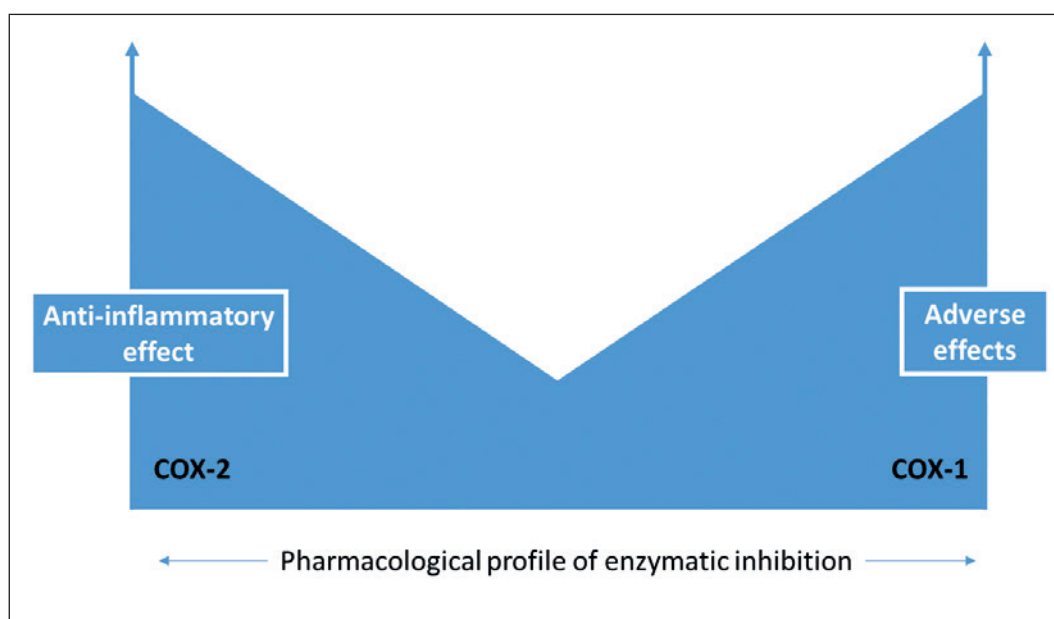


Figure 1. Relation between the profile of enzymatic inhibition and the pharmacological effect

inhibition, whereas their adverse gastrointestinal and renal effects occur through blockage of COX-I activity, with subsequent decrease of protective prostaglandins (Figure 1)²⁰.

It has been described a third distinct COX isoenzyme, COX-3, that might explain the mechanism of action of acetaminophen. Unlike other isoenzymes, COX-3 inhibition is not related to an increase of pro-inflammatory mediators, but its selective inhibition explains its analgesic and antipyretic properties. At therapeutic doses, the acetaminophen has only a weak inhibitory effect on COX-I and COX-2 with lack of anti-inflammatory effects considering its selective target²¹.

In patients with aspirin hypersensitivity, there is a positive correlation between the potency of the drug to inhibit *in vitro* COX-I activity and asthma worsening. It is also known the role of leukotriene antagonists in prevention of bronchoconstriction related to aspirin intake¹⁷. In patients with NERD, chronic viral infections might explain the development and persistence of airway inflammation, promoted by specific cytotoxic lymphocytes. Several genetic polymorphisms have been associated with NERD².

The pathogenesis of cutaneous inflammatory response to NSAIDs is controversial, and arachidonic acid mediators are not eventually involved. In susceptible subjects, NSAIDs can induce urticaria, angioedema and/or anaphylactic reactions by activation of mast cells and eosinophils. Unlike NERD, the mechanism IgE-mediated might have more relevance. In this case, the reactions are selective (compounds within the same chemical group), regardless the COX inhibition. IgE-mediated mechanism has been described in immediate reactions to diclofenac, acetaminophen, aspirin and pyrazolones^{5,11}.

A recent study, including only patients with immediate reactions to ibuprofen and other arylpropionic acid derivatives, showed that 17% of them were classified as selective reactors by both clinical history and drug challenge, with good tolerance to ASA²².

CROSS-REACTIVITY

Most of reactions occur with exposure to more than one group of NSAIDs. The classical NSAIDs (ASA, diclofenac, ketorolac, ibuprofen and naproxen) belong to distinct chemical groups, even though they share the same pharmacological mechanism of action – preferable COX-I inhibition. Indeed, this pharmacological effect, non-immunological, explains the occurrence of cross-reactivity among chemically distinct groups. On the other hand, some patients developed symptoms only when exposed to a single NSAID, from a specific group, and tolerate the remaining chemical groups.

Classical NSAIDs such as ASA, ibuprofen and indomethacin are preferential COX-I inhibitors, whereas diclofenac is considered almost equipotent to COX-I and COX-2. Among NSAIDs with preferential COX-2 inhibition are nimesulide and meloxicam. At low doses, meloxicam does not have cross-reactivity with remaining NSAIDs, showing selective COX-2 inhibition. At higher doses this selective profile can change, occurring also COX-I inhibition²³.

COX inhibition depends on drug concentration. Relative COX-I/COX-2 specificity varies among NSAIDs commonly used in clinical practice, with a more than 50-fold COX-2 selectivity to etoricoxib, from 5 to 50-fold COX-2 selectivity to celecoxib, meloxicam, nimesulide, etodolac and diclofenac, and a less than 5-fold COX-2 selectivity to indomethacin, ibuprofen, naproxen, aspirin, ketoprofen and ketorolac (Figure 2)^{20,24}.

Selective COX-2 inhibitors (coxibs) provides a similar efficacy, but with less adverse reactions. Pharmacological studies have demonstrated a relation between *in vitro* selective COX-2 inhibition and better gastrointestinal and renal tolerance²⁵. Despite potential cardiovascular risk related to these drugs, clinical practice has confirmed its good tolerance. Considering a reasonable lack of cross-reactivity with remaining NSAIDs, they appear to be good alternative drugs in most patients with hypersensitivity to classical NSAIDs.

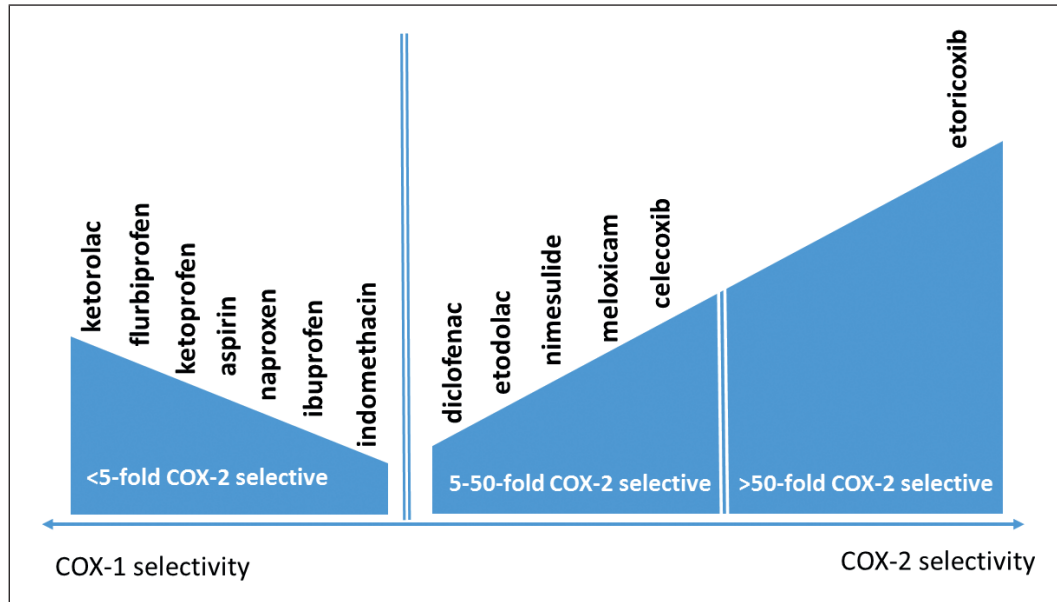


Figure 2. *In vitro* selectivity COX-1/COX-2

DIAGNOSIS

The diagnosis of NSAIDs hypersensitivity is based on a detailed clinical history.

Considering the underlying physiopathology mechanism, skin testing is not routinely performed. Its usefulness is limited to some circumstances, which are infrequent, such as immediate reactions of urticaria and/or angioedema and anaphylaxis, suspected to be IgE-mediated (such as pyrazolones). For pyrazolones (metamizole), the value of skin tests is clearly documented. Despite available in some centers, *in vitro* diagnostic tests, such as BAT (Basophil Activation Test) or CAST (Cellular Allergen Stimulation Test), have low sensitivity, and therefore are hardly useful in clinical practice^{2, 26}. BAT displays insufficient sensitivity to diagnose immediate hypersensitivity reactions to NSAIDs. Only a minority of reactions seems to be reliable IgE-mediated, and these patients are susceptible to a single NSAIDs group. Available studies using BAT in selective hypersensitivity to pyrazolones²⁶, have reported a sensitivity of 42–70% and a specificity of 86–100%.

Oral challenge test (OCT) remains the gold standard to confirm or exclude the diagnosis and is generally open, or eventually single or double-blinded. OCTs allow to confirm or to rule out the hypersensitivity, as well as to investigate alternative drugs which can be safely used. This procedure consists on the administration of increasing doses up to the therapeutic dose. The adverse reactions, particularly severe reactions, occur usually during the first four hours after drug intake (immediate response). OCT is not recommended in case of severe anaphylactic reaction, severe medical or surgical condition, uncontrolled underlying chronic disease (asthma, urticaria), airway obstruction, pregnancy, severe delayed type reactions (only patients with MPE and FDE can be tested)².

Due to its risk OCT should always be performed at an experienced center, under cardiorespiratory surveillance and with lung functional assessment.

OCT is considered to be positive when a drop of at least 20% of FEV₁ from baseline value occurs or resulting in respiratory and/or cutaneous symptoms.

There are other routes of challenge tests: inhaled, intranasal, conjunctival, and intravenous (the usefulness of the last two has not been sufficiently documented). Bronchial challenge with inhaled lysine acetylsalicylate is useful in patients with bronchial symptoms after drug intake and history of asthma²⁷. Intranasal challenge with lysine acetylsalicylate can be employed in patients with nasal symptoms or bronchial symptoms in whom other routes are not recommended due to asthma severity².

ALTERNATIVE DRUGS

NSAIDs that are weak COX inhibitors, including acetaminophen and non-acetylated salicylates, like magnesium choline salicylate, sodium salicylate, and salicylsalicylate, are usually well tolerated, but less effective as anti-inflammatory or analgesic drugs. Furthermore, salicylates are not available in the Portuguese market, except for topical use and, although rare, reactions with acetaminophen have been described. Considering these constraints, selective (coxibs) and preferential (meloxicam and nimesulide) COX-2 inhibitors are suitable alternatives in case of hypersensitivity reactions to classical NSAIDs, with a satisfactory tolerance profile in most patients.

During investigation of an alternative drug, concomitant intake of leukotriene antagonists in atopic patients and under specialized surveillance, can enable to achieve tolerance in case of mandatory drug consumption²⁸.

1. Acetaminophen

Acetaminophen (paracetamol), which is widely used in clinical practice for all ages, is associated to a limited number of adverse reactions. Despite being the first alternative in case of NSAIDs hypersensitivity, in some patients (ASA-susceptible), there is a potential cross-reactivity when acetaminophen is taken in higher doses (dose-dependent effect)²⁹. Low frequency of cross-reactivity (up to 6%) was described with doses of 650mg

or less. Different results, around 30%, were found with doses from 1000mg to 1500mg. It seems to occur a relation between reactivity with low dose of ASA and the possibility of cross-reactivity with acetaminophen.

At therapeutic doses, acetaminophen is a preferential COX-3 inhibitor, and a weak COX-1 and COX-2 inhibitor³⁰. Considering this dose-dependent mechanism and the possibility for a COX-1 inhibition, patients should be advised to avoid acetaminophen's daily consumption higher than 1500mg.

2. Preferential COX-2 inhibitors

2.1. Nimesulide

Nimesulide belongs to sulphonanilides and have anti-inflammatory, antipyretic, and analgesic properties. Several mechanisms of its action have been proposed: preferential COX-2 inhibition; inhibition of neutrophilic oxidative metabolism; recruitment of reactive oxygen species; prevention of alpha-1-antitrypsin inactivation; inhibition of leukotrienes and platelet-activating factor (PAF) synthesis; inhibition of histamine release from mast cells and basophils. Preferential COX-2 inhibition explains its anti-inflammatory activity and slighter incidence of gastrointestinal effects.

Published studies have shown that nimesulide is well tolerated from 80 to 90% of patients with hypersensitivity to classical NSAIDs³¹⁻³³. Asthmatic patients with ASA intolerance rarely react to nimesulide, compared to patients with cutaneous reactions (8.6-21.3%)³³. A Portuguese study reported tolerance in 72% of ASA-susceptible patients³⁴.

In 2007, reports of nimesulide-associated hepatotoxicity led to the temporary withdrawal of this drug from several European countries and thereafter safety data have been revised. Restrictions were introduced, after considering the confirmed risk of hepatotoxicity. Nimesulide should be used as a second-line therapy and with the lowest possible effective dose. In patients with hypersensitivity to NSAIDs, it is recommended to prescribe

nimesulide up to 5mg/kg/day (cumulative daily dose up to 200mg). This drug is approved in pediatric patients 12 years of age and older, and for no longer than a 15-day course treatment.

2.2. Meloxicam

Meloxicam is a preferential COX-2 inhibitor at lower doses (7.5 mg). However, when taken at higher doses it can also inhibit COX-1 (dose-dependent mechanism). Meloxicam 7.5-15 mg/day is as efficient as conventional NSAIDs (like diclofenac), in osteoarthritis, rheumatoid arthritis and other rheumatologic diseases which require chronic anti-inflammatory and analgesic therapy, but studies have reported its superior gastrointestinal tolerability comparing to conventional NSAIDs³⁵.

Many studies assessed tolerance to meloxicam, either with low dose of 7.5mg or 15mg³⁶⁻³⁸. According to published studies, 91 to 99% of patients with NSAIDs hypersensitivity are tolerant to meloxicam. In a Portuguese study, in patients with NSAIDs hypersensitivity, where 68 oral challenges with meloxicam have been performed, 19% of patients reacted³⁹. Gathering all these results, at lower doses meloxicam has proven to be associated to a low rate of allergic reactions (about 5%), being the majority only cutaneous⁴⁰. Meloxicam is a better alternative, comparing to nimesulide. However, patients should be advised to avoid doses higher than 15mg daily in order to prevent a potential COX-1 inhibition.

Few studies were accomplished in pediatric age; thus the prescription of meloxicam is not recommended under 16 years old.

A parenteral formulation of meloxicam is available, which offers an advantage, in case of surgery for instance. Based on the patient's needs, meloxicam might be considered the first alternative in these patients.

3. Selective COX-2 inhibitors

Selective COX-2 inhibitors (coxibs) are assumed to be a safe alternative in patients susceptible to non-selective NSAIDs.

Studies suggested that coxibs can be safely used in patients with previous hypersensitivity reactions to COX-1 inhibitors NSAIDs⁴¹. However allergic reactions, including severe reactions, have also been described^{42, 43}. These new drugs are considered to be promising, with equivalent anti-inflammatory efficacy and lower rate of gastrointestinal effects.

Celecoxib was the first COX-2 inhibitor approved by the FDA (1998), followed by rofecoxib (1999). However, rofecoxib was withdrawn from the market after a clinical trial, since it has been associated with an increased risk of myocardial infarction. Subsequently, parecoxib, valdecoxib, etoricoxib and lumiracoxib were developed. The lack of adequate data on the cardiovascular safety, along with the increased risk of adverse cardiovascular events and reports of serious and potentially life-threatening skin reactions lead to voluntarily withdraw of valdecoxib from the market in 2005. In 2007, lumiracoxib was suspended due to severe hepatotoxicity. Currently, only celecoxib, parecoxib and etoricoxib are available. Celecoxib is approved in adults and etoricoxib for adults and adolescents over 16 years old.

In most patients COX-2 inhibitors are considered to be suitable and safe alternative drugs. Weberstock *et al.*⁴⁴ reviewed 84 studies about the severity and the type of adverse reaction to coxibs, and 13 of them described double-blind COX-2 inhibitor challenges to determine the probability of adverse reactions to coxibs; 119 patients (3.6%) reacted with COX-2 inhibitors from a total of 3304 patients. Asero *et al.*⁴⁵ described a higher rate of coxibs hypersensitivity up to 33%. A high percentage of positive challenges (21%) was also found by Malskat *et al.*⁴³, whose study demonstrated that a second challenge with a different COX-2 inhibitor can provide a safe alternative. A study performed in 47 patients with cross-intolerance to NSAIDs and intolerance to paracetamol showed that 25% were intolerant to etoricoxib, whereas among those with cross-intolerance to NSAIDs and good tolerance to paracetamol (n=50) only 6% showed to be intolerant to etoricoxib⁴⁶.

Given the relatively increasing rate of positive challenges with COX-2 inhibitors and multiple drug intolerance, it is necessary to perform an oral challenge under medical surveillance prior to a prescription of an alternative drug⁴⁷.

Based on 13 studies (n=749) which addressed celecoxib tolerability, a 4% rate of positive reactions has been documented, being the majority urticaria and angioedema⁴⁰.

Regarding etoricoxib, tolerability was similar. Ten studies (n=823) showed the same rate (4%) of positive reactions, mainly described as non-severe, but there were 4 subjects who had moderate to severe reactions⁴⁰. In a study performed in 104 aspirin-sensitive patients, 3 patients (2.9%) developed a positive asthmatic reaction with etoricoxib (cumulative dose from 45 to 105mg)⁴⁸. In 118 patients with history of urticaria or angioedema triggered by one or more NSAIDs, only 2 had positive challenges with etoricoxib 60mg⁴⁹.

Patients with hypersensitivity to non-selective NSAIDs should be advised to avoid dosage higher than 60mg daily of etoricoxib.

The safety and efficacy of selective COX-2 inhibitors under 18 years have not been established. A recent study⁵⁰ performed in 41 children aged 9-14 years with hypersensitivity to NSAIDs confirmed by oral challenge with the culprit drug and ASA, found that 100% tolerated acetaminophen and etoricoxib and only 2 (5%) reacted with meloxicam. According to these data, both etoricoxib and meloxicam seem to be suitable alternatives in children over 8 years, even though these drugs are not recommended in this age group, which means an off-label use.

DESENSITIZATION

The desensitization is reserved to exceptional situations. It is a high-risk procedure that should always be performed in hospital setting. Increasing doses are given within a short period of time (from several hours to few

days) until the cumulative therapeutic dose is achieved with tolerance and followed by daily intake. Desensitization is a suitable option only in patients in whom alternative drugs are less effective or unavailable. Hypersensitivity to involved drug must be clearly confirmed, as well as the absence of an alternative drug.

Desensitization is not recommended in case of systemic vasculitis and severe cutaneous reactions.

The main indications for aspirin desensitization are anti-aggregative therapy with AAS in coronary disease with indication for chronic dual antiplatelet therapy, antiphospholipid syndrome, aspirin hypersensitivity associated to upper and/or lower airway disease despite multiple nasal/sinus surgical procedures and aggressive anti-inflammatory treatment (inhaled and/or systemic corticosteroids)^{51, 52}. Moreover, for those needing chronic NSAIDs treatment due to osteoarticular diseases without satisfactory alternative drug.

Several desensitization protocols were proposed according to different cumulative doses of aspirin to achieve control of the above-mentioned diseases.

In patients with aspirin/NSAIDs hypersensitivity and coronary disease, the aspirin maintenance dose commonly proposed is from 100 to 150mg.

Aspirin desensitization may be a safe alternative in women with antiphospholipid syndrome who require treatment with ASA during pregnancy⁵³. Also, women with inherited thrombophilia and recurrent miscarriage have been successfully desensitized before pregnancy⁵⁴.

The desensitization process can be done safely at the outpatient setting in less than 2 days in for the majority of patients⁵².

Regarding NERD, the maintenance dose ranges from 325mg to 1300mg daily, depending on the protocol⁵². The optimal dosage is still not clear, and the literature has shown a similar benefit with different regimens, but some patients will need to adjust the dosage. Some authors recommend to begin with higher dose (650 mg twice daily) and subsequently decrease to the lowest effective dosage⁵⁵. Older studies preconized a dose of at least 650mg

twice daily⁵⁶. In the last decade, several studies have demonstrated clinical efficacy with lower dosage (300 to 975mg daily)^{55, 57}. Available data have demonstrated that this intervention is beneficial in reducing both nasal and bronchial symptoms with subsequent reduction of systemic corticosteroids, decreasing the rate of polyp formation and as a result, lesser number of surgeries, and additionally improving the quality of life of these patients^{52, 58}.

UNMET NEEDS / FUTURE PERSPECTIVES

Currently, the NSAIDs are the pharmacological group most frequently responsible for hypersensitivity reactions. Most of these reactions result from activation of the leukotriene pathway without specific immunological recognition and potential cross-intolerance. However, there are a growing number of selective reactions, induced by immunological mechanisms (mediated by IgE antibodies or by T cells). Considering the heterogeneity of clinical patterns, the underlying mechanisms need to be better clarified. Neither skin testing nor *in vitro* tests may be used as diagnostic tools for all NSAIDs. Most of these patients undertake multiple drug challenges to confirm diagnosis or, considering the severity of the clinical history are exclusively challenged with safer alternative drugs. Further research to develop both *in vivo* and *in vitro* tests is required in order to perform an accurate diagnosis. Eventually genetic studies will enable to explore individual predispositions and improve our understanding of selective reactors.

Despite the promising emergence of coxibs as alternative drugs, safety concerns mainly due to its cardiovascular effects remain under suspicion. Cardiovascular effects are more related to the individual agent rather than the COX-2 selectivity of every drug. The underlying mechanisms are not fully explained by prothrombotic state and requires further investigation.

Several novel pharmaceutical manipulations are under development, to improve safety and efficacy of

NSAIDs. Promising formulations including a vasodilating agent naproxinod as the prototypical COX-inhibiting nitric oxide has the potential to improve the gastrointestinal safety profile and protect against to the vasoconstrictive and prothrombotic effects⁵⁹. Hydrogen sulfide (HS)-releasing compounds seem to protect gastrointestinal mucosa. Some of these compounds are currently being developed in preclinical studies including diclofenac, naproxen, indomethacin, ketorolac, and aspirin⁵⁹. For instance, HS-diclofenac caused 90% less gastric damage compared with traditional diclofenac⁶⁰. New reliable injectable formulations for perioperative and inpatient use as ibuprofen, parecoxib and tenoxicam are currently available⁵⁹. Innovative products including glycopolymers have been used to produce intra-articular extended-release NSAIDs combined with hyaluronic acid⁵⁹. Nano-formulations of submicron NSAIDs, allowing to deliver lower doses with similar efficacy, have been tested in diclofenac, indomethacin, naproxen, and meloxicam⁵⁹.

Further research in NSAIDs is required to develop enhanced formulations and delivery vehicles that can improve their safety profile.

CONCLUSIONS

The prevalence of NSAIDs hypersensitivity can reach 6% of the general population, increasing up to 20% in asthmatic patients and up to 40% in chronic urticaria. Clinical manifestations range from rhinoconjunctivitis, asthma and urticaria to anaphylaxis. The leading pathogenic mechanism results from COX-I inhibition with increasing release of inflammatory mediators, which are responsible for the occurrence of respiratory and cutaneous symptoms in susceptible patients. NSAIDs cross-reactivity is a common feature, considering the mechanism of enzymatic inhibition. Nevertheless, up to one third of patients might react to a single NSAID, tolerating the remaining groups of NSAIDs.

NSAIDs hypersensitivity diagnosis is based on a detailed clinical history. Skin tests are not routinely recommended in most of patients. Oral challenge tests are crucial to confirm the diagnosis, as well as to investigate safe alternative drugs. Acetaminophen and COX-2 selective inhibitors (coxibs) or preferential inhibitors (meloxicam) are typically well-tolerated and reasonable alternatives. Exceptionally, whether the culprit drug is considered indispensable or if it is not available an equivalent alternative, desensitization can be achieved.

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