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REVIEW ARTICLE

Nonsteroidal anti-inflammatory drugs: cyclooxygenase 2 inhibitors

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Abstract

Objectives: To analyze selective COX 2 inhibitor nonsteroidal anti-inflammatory drugs (NSAID) in terms of their mechanism of action, principal indications, posology and most common adverse effects.

Sources: MEDLINE and LILACS databases and Food and Drug Administration (FDA) and National Agency for Sanitary Vigilance (ANVISA - Agência Nacional de Vigilância Sanitária) websites. The most important articles were selected and preference was given to articles published within the last 5 years.

Summary of the findings: The principal indications for NSAID are for control of pain and acute and chronic inflammation. There is no overwhelming evidence that demonstrates the superiority of one NSAID over another in terms of effectiveness. To date none of the COX 2 inhibitors has been liberated for use in the pediatric age group. Only meloxicam and etoricoxib can be prescribed for adolescents (13 and 16 years, respectively). Selective COX 2 inhibitors are indicated for patients with adverse effects that have proven to be associated with nonselective NSAID use. Selective COX 2 inhibitors can be prescribed in some cases of allergy to aspirin, but they must be used with care. Principal adverse effects include cardiovascular events and thrombotic phenomena.

Conclusions: Selective COX 2 inhibitors are medicines that have been used in certain well-defined clinical situations and which may offer certain advantages over nonselective NSAID. Nevertheless, taking into consideration the higher cost involved and the potential for adverse cardiovascular effects, they should be employed only in accordance with strict criteria.

J Pediatr (Rio J). 2006;82(5 Suppl):S206-12: Nonsteroidal anti-inflammatories, COX 2 inhibitors, indications, adverse effects.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) comprise a heterogeneous group of medications, the majority of which are organic acids with analgesic, antipyretic and anti-inflammatory actions. These drugs are widely used to control fever and acute or chronic pain.[1] They are the most sold medications worldwide and, together with analgesics and antipyretics, account for approximately 30% of all medicines used (prescribed by physicians or otherwise).[1]

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Synthesis of prostaglandins and leukotrienes

When there is damage to the cell membrane, which is basically made up of phospholipids, the enzyme phospholipase A2, which is present in leukocytes and platelets, is activated by proinflammatory cytokines, such as interleukin (IL)-1. This enzyme leads to the degradation of phospholipids, resulting in production of arachidonic acid . This, when metabolized, forms leukotrienes through the action of the enzyme lipoxygenase, and prostaglandins, prostacyclins and thromboxanes, through the action of the cyclooxygenase enzyme (COX).

COX is the first enzyme involved in producing prostaglandins from arachidonic acid.[2-4] It converts, by oxygenation, the arachidonic acid into two unstable components: prostaglandin G2 and prostaglandin H2. These prostaglandins are later transformed by isomerases into prostacyclin, thromboxane A2, and prostaglandins D2, E2 and F2α. Prostaglandin E2 is important because of its pyrogenic action and in increasing sensitivity to pain. Arachidonic acid also leads to production of leukotrienes, via lipoxygenase enzyme (Figure 1).

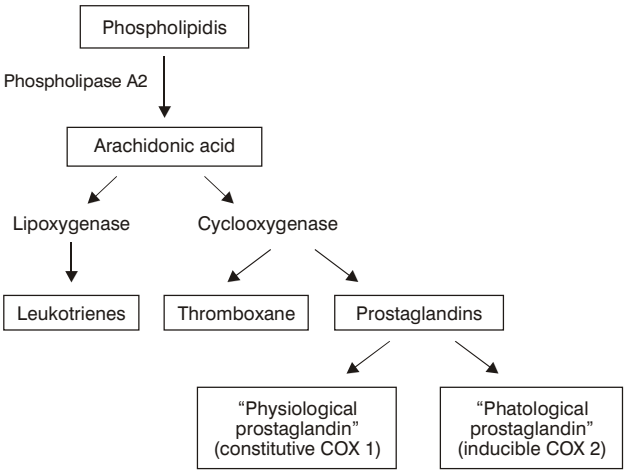

Figure 1 - Mechanism of action of nonsteroidal anti-inflammatories

An important advance in anti-inflammatory therapy was the discovery of two isoforms of COX (also known as synthetase prostaglandins): COX 1 and COX 2. Whereas COX 1 has 17 amino acids at the terminal amino section, COX 2 has 18 amino acids at the terminal carboxyl section. Although they are very similar in terms of their protein structure, these enzymes are coded by different genes. Genetically, COX 1 and COX 2 are approximately 60% homologous and their genes are located at chromosomes 9 and 1, respectively.[2]

COX 1 and COX 2 exhibit minor differences, which confer distinct functions on them. COX 1 is present in almost all tissues (blood vessels, platelets, stomach, intestine, kidneys) and, for this reason, is defined as a constitutive enzyme. Cyclooxygenase 1 is associated with prostaglandin production and results in a variety of physiological effects, such as gastric protection, platelet aggregation, vascular homeostasis and maintenance of renal blood flow.

In contrast, COX 2 is present at the site of inflammation, and because of this is defined as an inducible enzyme. It is primarily expressed by cells that are involved in the inflammatory process, such as macrophages, monocytes and synoviocytes. Nevertheless, it is known that COX 2 can also be found in other tissues and organs, such as kidneys, brain, ovaries, uterus, cartilage, bones and vascular endothelium. COX 2 is induced by cytokines (IL-1, IL-2 and tumor necrosis factor [TNF]) and other mediators (such as growth factor and endotoxins) at the site of inflammation. It is probably also expressed in the central nervous system and plays a role in central mediation of pain and fever. Expression of COX 2 can, however, be suppressed by glucocorticoids, IL-4, IL-10 and IL-14. More recently a third COX type has been described, called COX 3.[5]

Prostaglandin functions

Prostaglandins are involved in several physiological and pathological processes, including vasodilation or vasoconstriction, contraction and relaxation of bronchial or uterine musculature, hypotension, ovulation, bone metabolism, increase in renal blood flow (resulting in diuresis, natriuresis, caliuresis and stimulation of renin secretion), suppression of gastric acid secretion, immunoresponse, hyperalgesia, regulation of chemotactile cellular activity, endocrine response and angiogenesis, among others.

In the gastrointestinal tract, prostaglandins I2 and E2 are cytoprotective of the gastric mucosa – because they suppress acid secretion, increase local blood flow, provoke mucus production and increase synthesis of glutathione (and consequently the capacity to eliminate free radicals) and because they increase bicarbonate synthesis and blood flow to the surface layers of the gastric mucosa. In the kidneys they increase glomerular filtration because of their vasodilator effect. Finally, within the cardiovascular system, they can cause several hemodynamic effects, such as vasodilation. They also provoke smooth muscle relaxation. Thromboxane A2 (a substance that promotes coagulation) is produced from platelet COX, and acts as a potent aggregant agent.

Prostaglandins also have pathophysiologic effects such as erythema and increased local blood flow, hyperalgesia, probably due to sensitization of pain receptors, and increased body temperature at the hypothalamus through cytokine stimulation. When prostaglandin production is increased, there is increased sensitivity to pain and fever and increased inflammatory response. Nevertheless, prostaglandins are also capable of anti-inflammatory action due to suppression of IL-1 and TNF synthesis.

Mechanism of action

The mechanism of action of NSAIDs consists in suppression of COX enzymes, resulting in reduction of the production of prostaglandins, thus controlling inflammation, pain and fever.

There are some anti-inflammatories that selectively or specifically inhibit wither COX 1 or COX 2.[6] Only COX 1 inhibits thromboxane formation. COX 1 inhibition is associated with increased risk of gastrointestinal bleeding and damage. Selective and specific COX 2 inhibitors were developed in an attempt to reduce the incidence of adverse effects of COX 1 inhibition.[2] These inhibitors include piroxicam, meloxicam, diclofenac, naproxen and nimesulide (first-generation selective COX 2 inhibitors), and celecoxib, etoricoxib, valdecoxib, parecoxib and lumiracoxib[7] (second-generation, more specific, selective COX 2 inhibitors).

The NSAID dose necessary to reduce inflammation is larger than that needed to inhibit prostaglandin formation, suggesting that other mechanisms mediate the anti-inflammatory effects. In addition to suppressing prostaglandin production, current anti-inflammatories inhibit specific proteases involved in breaking down proteoglycans and collagens in cartilage, and inhibit the generation of oxygen free radicals, particularly superoxide.[8] These medications also interfere with the liberation of bradykinin, with the lymphocyte response to antigen stimulus, with phagocytosis and with chemotaxis of granulocytes and monocytes.[8]

Pharmacokinetic

The following are characteristics of NSAIDs:

- rapid absorption;
- the majority of absorption takes place in the stomach and the upper portion of the small intestine;
- absorption is reduced when taken at night;
- the majority binds with plasma proteins;
- the pharmacological effect comes from the drug in its free state (unbound);
- metabolism is predominantly hepatic and is faster in children;
- excretion is renal;
- elimination is faster in children than in adults, requiring more frequent doses.

A study of 11 children with neoplasias assessed the pharmacokinetics of celecoxib.[9] The authors observed significant differences in terms of the availability of celecoxib in children compared with in adults, such as elimination that is twice as fast and a half-life that is half as long. They also observed that absorption of the medication is optimized when taken with a fat-rich meal.

In a study undertaken with 18 patients with juvenile rheumatoid arthritis, the pharmacokinetics of meloxicam suspension was evaluated, with greater elimination of the medication being observed in the younger children, although with a similar half-life to other age groups.[10]

Indications

The most common indications for NSAIDs in childhood and adolescence are control of fever, acute and chronic pains and inflammation. Acetylsalicylic acid, naproxen, ibuprofen and tolmetin are the only ones approved for pediatric use by the Food and Drug Administration (FDA). Despite not being licensed for the pediatric age group, indomethacin is used to control fever and pain in children and adolescents with juvenile idiopathic arthritis (JIA).

Selective COX 2 inhibitors are indicated for patients who exhibit adverse effects that are confirmed to be related to nonselective NSAID use, such as gastric intolerance that cannot be controlled by combination with gastroprotective medication. In the pediatric age group, the use of COX 2 is limited since a majority of these medicines are contraindicated before 18 years of age. Table 1 lists dosage, posology and minimum age recommended for NSAIDs by the FDA and the Brazilian National Agency for Sanitary Vigilance (Agência Nacional de Vigilância Sanitária – ANVISA).

Table 1 - Dose and posology of nonsteroidal anti-inflammatories (information obtained from labels)

Medication*	Daily dosage	Number of doses per day	Minimum recommended age (years)†
Acetylsalicylic acid‡	80-100 mg/kg	3 to 4	12
Naproxen	10-20 mg/kg	2	2
Ibuprofen	20-40 mg/kg	3 to 4	6 months
Indomethacin§	1.5-3 mg/kg	3	14
Meloxicam	7.5-15 mg	1	13
Celecoxib	200-400 mg	2	18
Valdecoxib	40 mg	1	18
Parecoxib‖	40 mg (IM or IV)	1	18
Etoricoxib	60-120 mg	1	16
Lumiracoxib	100-400 mg	1	18

* The selective COX 2 inhibitor rofecoxib (12.5 – 50 mg/day in a single dose) was withdrawn from the market in 2004 by the manufacturer.
† Ages recommended by the Food and Drug Administration (FDA) in the United States of America and by the National Agency for Sanitary Vigilance (ANVISA - Agência Nacional de Vigilância Sanitária) in Brazil.
‡ In clinical practice acetylsalicylic acid is used in children with inflammatory diseases of all ages, but it is not recommended in cases with suspected viral etiology because of the increased risk of Reye syndrome.
§ Indomethacin is used to treat persistent ductus arteriosus in newborns and to control of fever and pain in children and adolescents with juvenile idiopathic arthritis (systemic type) and arthritis related to enthesitis.
‖ Parecoxib is metabolized into valdecoxib in less than 1 hour and is contraindicated in cases of sulfonamide allergy.

Nonsteroidal anti-inflammatories are routinely employed by many specialties. Pediatricians, otorhinolaryngologists, rheumatologists, gynecologists and orthopedists prescribe these medicines the most often. Habitual indications for NSAIDs are shown in Table 2.[11-17]

Specific COX 2 inhibitors and atopic disease

We should be cautious when prescribing NSAIDs for atopic patients with sensitivity to acetylsalicylic acid (ASA), since there is a possibility of exacerbating the allergic condition. In these cases, selective COX 2 inhibitor NSAID could be a treatment option since the response mechanism of sensitivity to ASA particularly involves the COX 1 enzyme. It is important to point out that this recommendation is based on the results of few studies involving small numbers of patients, and there are reports of sporadic cases with significant worsening of asthma with the use of selective COX 2 inhibitors.

Martin-Garcia et al. did not observe asthma exacerbation after use of celecoxib (200 mg/day for 7 days), a highly selective COX 2 inhibitor, in 33 patients with asthma induced by NSAIDs.[18] In a placebo-controlled study, Bavbek et al. assessed the safety of three NSAIDs (nimesulide, meloxicam and rofecoxib) with a group of 137 patients with history of allergy to this class of medication.[19] Cutaneous and respiratory reactions were observed in 24 patients: nimesulide 14.3%, meloxicam 8.1% and rofecoxib 2%. Only the subset given rofecoxib did not exhibit any exacerbation of preexisting asthma. Etoricoxib, another selective COX 2 inhibitor, was also shown to be safe when used on patients with urticaria and angioedema.[20]

Urticaria exacerbation related to nonselective COX inhibitors has been known for a long time. Nonselective anti-inflammatories are COX inhibitors and the theoretical explanation for this mechanism may be based on the fact that these enzymes are responsible for synthesis of

Table 2 - Habitual indications for nonsteroidal anti-inflammatories

Indication	NSAIDs	Characteristic features	References
Fever	Ibuprofen, indomethacin	– The effectiveness of ibuprofen is similar to paracetamol. – Indomethacin is the drug of choice for the control of fever in children with systemic JIA and of pain in adolescents with ERA.	Perrott et al.[11]
Acute and chronic pain	Naproxen, ibuprofen, indomethacin, selective COX 2 inhibitors	– Medicines used for the control weak to moderate pain. – Most common indications: migraine, dysmenorrhea and postoperative pain. – The effectiveness of NSAIDs is comparable with paracetamol. They can be used in combination with paracetamol.	Perrott et al.[11], Bricks & Silva[12]
Pediatric rheumatology	Acetylsalicylic acid (ASA), naproxen, ibuprofen, indomethacin, selective COX 2 inhibitors	– Acetylsalicylic acid is the NSAID of choice for the treatment of arthritis from rheumatic fever. – Used to treat patients with Henoch-Schönlein purpura, juvenile systemic lupus erythematosus. – Naproxen is the first-line drug for patients with oligoarticular and polyarticular JIA. – Meloxican has proven safe and effective in patients with oligoarticular and polyarticular JIA at doses of 0.125 and 0.25 mg/kg/day. – Chronic use demands serial urinary sediment testing (because of a risk of interstitial nephritis with hematuria).	Anthony & Schanberg[13], Ruperto et al.[14], Reiff et al.[15], Hochberg[16]
Infections of the upper respiratory tract	Ibuprofen, selective COX 2 inhibitors	– Safety and efficacy similar to paracetamol for relief from symptoms.	Weckx et al.[17]

NSAIDs = nonsteroidal anti-inflammatories; JIA = juvenile idiopathic arthritis; ERA = enthesitis-related arthritis.

proinflammatory (PGD_2) and anti-inflammatory prostaglandins (PGE_2). PGE_2 inhibits synthesis of leukotrienes (LTB_4); therefore blocking production of PGE_2 could increase production of leukotrienes, with deterioration of clinical symptoms. Selective COX 2 inhibitors preferentially block synthesis of PGD_2 and, to a lesser extent, PGE_2. This mechanism could explain improvements in the urticaria of some patients treated with a combination of antileukotrienes and COX 2 specific NSAIDs.[21]

Adverse effects

There is no overwhelming evidence that demonstrates the superiority of one NSAID over another in terms of effectiveness and, very often, the choice is based on lower frequency and intensity of side effects and on the cost of the medication.

Although age over 60 years, previous history of gastrointestinal complications and concurrent corticosteroid use are the principal risk factors for severe gastrointestinal complications from NSAID use, we must not forget that chronic use of these medicines can result in esophagitis, gastritis or duodenitis, gastric or duodenal ulcers, even if subclinical, in children and adolescents. A study carried out at our service with 14 children with juvenile rheumatoid arthritis on chronic NSAID use found that while just 27% presented gastrointestinal complaints, on endoscopy macroscopic lesions were observed in 43% and microscopic injuries in 57% of the patients. Although in general children complain less than adults, especially about gastropathy secondary to NSAID use, this does not mean that they are free from endoscopic lesions, as has been demonstrated.[22]

The major debate and the greatest uncertainties perhaps reside in sporadic or short-term (a few days) use of NSAIDs. What are the true risks? There are no studies in the literature that prove the safety of these medications under these treatment regimes. This does not rule out the possibility of erosive damage and even bleeding from gastro-duodenal mucosa after three or four doses.

Gastrointestinal events

Advanced age, previous peptic ulcer, previous bleeding and concurrent use of another NSAID or corticosteroids are risk factors for gastric complications such as mucosal ulceration, reflux esophagitis, esophageal thinning and peptic ulcers.[23] Since these effects are primarily mediated by COX 1 inhibition, it is believed that selective COX 2 inhibitors are a safer alternative. Nevertheless, although some studies have reported lower frequencies of gastrointestinal complications with COX 2 inhibitors than with traditional NSAIDs, recent concerns regarding cardiovascular safety have limited the use of these medications.

Renal events

Conditions such as congestive heart failure, cirrhosis, diabetes, hypertensive nephropathy, advanced age and volume depletion constitute risk factors that can predispose patients to renal complications. Salt retention, acute reversible renal insufficiency and tubulointerstitial nephritis are some of the undesirable effects. While selective specific COX 2 inhibitors may cause less renal alterations, they are not free from inducing some of these alterations.[24]

Cutaneous events

Photosensitivity, erythema multiforme, urticaria and Steven-Johnson syndrome have all been observed with NSAIDs in general. One study with 381 adults who exhibited "pseudoallergic" reactions to NSAIDs showed that nimesulide and meloxicam were well-tolerated.[23]

Hepatic events: liver toxicity with elevated transaminases, cholestasis and necrosis may occur, especially with COX 1 inhibitors.

Hematological events

Hemolytic anemia, neutropenia, thrombocytopenia and medulla aplasia are observed rarely with NSAIDs nowadays, especially with COX 2 inhibitors.

Central nervous system events: headaches, tingling sensations and dizziness, although possible, are rarely reported by children and adolescents.

Cardiovascular events

Countless studies have been published recently on the cardiovascular toxicity of several NSAIDs, especially the selective COX 2 inhibitors.[25] It has not yet been established whether the risk is specific to one COX 2 inhibitor in particular, applicable to all COX 2 inhibitors, or characteristic of all NSAIDs.[26] Acute myocardial infarction, cerebrovascular ischemia, hypertension and exacerbation of congestive heart failure appear to be associated with the use of at least some NSAIDs.[27] The mechanism responsible for the cardiovascular toxicity of COX 2 inhibitors has not yet been fully explained. The most probable hypothesis involves an imbalance between prostacyclin and thromboxane A2. Prostacyclin is a vasodilator and inhibits platelet aggregation and vascular proliferation, while thromboxane A2 causes platelet aggregation, vasoconstriction and proliferation of smooth muscle. Platelets, which only express COX 1, are the primary products of thromboxane A2, and endothelial

cells produce prostacyclin in response to COX 2.[25,28] Those NSAIDs that inhibit both COX 1 and COX 2 maintain a certain homeostasis between prostacyclin and thromboxane A2. In contrast, selective COX 2 inhibitors predominantly suppress prostacyclin, upsetting the balance in favor of thromboxane. In a recent study with 33,309 patients who presented myocardial infarction, it was observed that any NSAID used at habitual doses can increase the risk of this complication, especially in older patients.[27] Although children and adolescents do not, in general, belong to a group at major risk of cardiovascular complications, we should be alert, particularly when dealing with patients with chronic diseases whose underlying disease already represents a risk for the development of atherosclerosis and thromboembolic phenomena.

Another major concern is the growing number of children and adolescents observed during recent years with hypertension and/or obesity as a result of inadequate diet and of inactivity.

Nonsteroidal anti-inflammatory drugs are contraindicated for children and adolescents in the following situations: dyspeptic syndromes, viral diseases, compromised renal function, cardiac disease, (especially congestive heart failure), liver failure, systemic arterial hypertension, coagulation disorders, history of allergic reaction to NSAIDs and the use of oral anticoagulants and hypoglycemic.

In a randomized double-blind study of 225 children with juvenile idiopathic arthritis, the authors evaluated the efficacy and safety of two doses of meloxicam compared with naproxen, observing at least one adverse effect in 74% of the patients who were given 0.125 mg/kg/day of meloxicam, 80% in the group who were given 0.25 mg/kg/day of meloxicam and 85% in the naproxen group.[14] Gastrointestinal disorders such as pain, diarrhea, nausea and vomiting were the most frequent complaints, (Table 3).

Drug interactions

Nonsteroidal anti-inflammatories bind strongly to plasma proteins and as a result they may displace other medications from their binding sites, which can occurs with methotrexate, phenytoin and sulfonylureas, increasing their activity and toxicity.

Summing up, in general NSAIDs should only be used when there is a precise indication, since they can cause adverse effects even when used for short periods. Selective COX 2 inhibitors are not yet licensed for use with children. Long-term randomized controlled studies are needed, especially in order to confirm safety.

Table 3 - Principal adverse effects observed in children given meloxicam or naproxen

Adverse event	Meloxicam 0.125 mg/kg (n = 73)	Meloxicam 0.25 mg/kg (n = 74)	Naproxen 10 mg/kg (n = 78)	p
Gastrointestinal	28 (38)	27 (37)	25 (32)	0.7
Infection/infestation	30 (41)	38 (51)	39 (50)	0.4
Respiratory alterations	22 (30)	19 (26)	26 (33)	0.6
Headaches	9 (12)	10 (14)	5 (6)	0.3
Cutaneous alterations	4 (6)	5 (7)	13 (17)	0.049*
Bleeding	3 (4)	2 (3)	9 (12)	0.07

* $p < 0.05$ = significant.
Ruperto et al.[14]

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