Non-steroidal anti-inflammatory drugs: general aspects and role in the treatment of cancer

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Abstract

Non-steroidal anti-inflammatory drugs are commonly used for their well known anti-inflammatory, antipyretic and analgesic activities. They can cause multiple side effects, although rare in single doses, increase with multiple doses specially in the elderly. They interact with drugs binding strongly to plasma proteins. NSAIDs are, such as paracetamol, first-line agents for the treatment of mild to moderate cancer pain but can be used in other stages of the disease.

Keywords: non-steroidal anti-inflammatory drugs, cancer pain, bone metastasis.

Introduction

Non-steroidal anti-inflammatory drugs are a heterogenous group of compounds, often without any chemical connection but with common pharmacological properties.

All have anti-inflammatory, analgesic and antipyretic action in therapeutic doses.

They have been used to treat diseases of the connective tissue, rheumatic and anti-immune, in fever, inflammation, dysmenorrhoea, renal colic and many other kinds of pain, namely in chronic pain associated with cancer.

Mechanism of action

Their pharmacological actions are primarily inhibiting cyclooxygenase, an enzyme catalyzing the conversion of arachidonic acid in G_2 prostaglandin which is the substrate to forming prostacyclin, prostaglandin and thromboxane (*Fig. 1*). The way how cyclooxygenase activity is inhibited changes according to the compounds. Some, as ketoprofen and diclofenac also block lipoxygenase, inhibiting the formation of the B_4 leukotriene, a pain mediator, making them effective analgesics and anti-inflammatories[1,2] blocking lipoxygenase, inhibiting as well the formation of leukotriene C_4, D_4 and E_4 (Figure 1), that together make up the slow action anaphylactic substance. Conversely, indomethacin is a strong anti-inflammatory and a weak painkiller. This and other NSAIDs as acetylsalicylic acid, ibuprofen and tolmetin, cyclooxygenase potent inhibitors, deviate the cascade through lipoxygenase what can, at least partially, contribute to its bad analgesic effect depending on the dose. This way, NSAIDs blocking 2 routes have a theoretical advantage in terms of analgesic efficacy and safety (reducing the formation of anaphylactic slow action substance) over those blocking only cyclooxygenase. [1]

Other individual pharmacological actions explain the variability of responses observed in the clinical practice. [3]

NSAIDs anti-inflammatory properties are evident, in particular, in inflammatory arthropathies, reducing not only the pain but also the edema. With some NSAIDs, inflammatory systemic markers, as erythrocyte sedimentation rate and acute phase proteins, are reduced in the rheumatoid arthritis and do not influence however the natural history of the disease. They have an independent analgesic activity from the anti-inflammatory effect, being effective in many kinds of light to moderate pain. The analgesic dose of most NSAIDs is half of the anti-inflammatory dose for reasons not yet totally known;[1] there is a ceiling effect for analgesia, i.e., a dose beyond which there is no reduction of pain. The antipyretic activity happens at hypothalamus level. They are effective in inflammatory fever, but do not have the capacity of reducing the normal body temperature or hyperpyrexia of any other origin.

Pharmacokinetics

NSAIDs are almost totally absorbed orally. [4] After meals its absorption can be delayed but it is not reduced.

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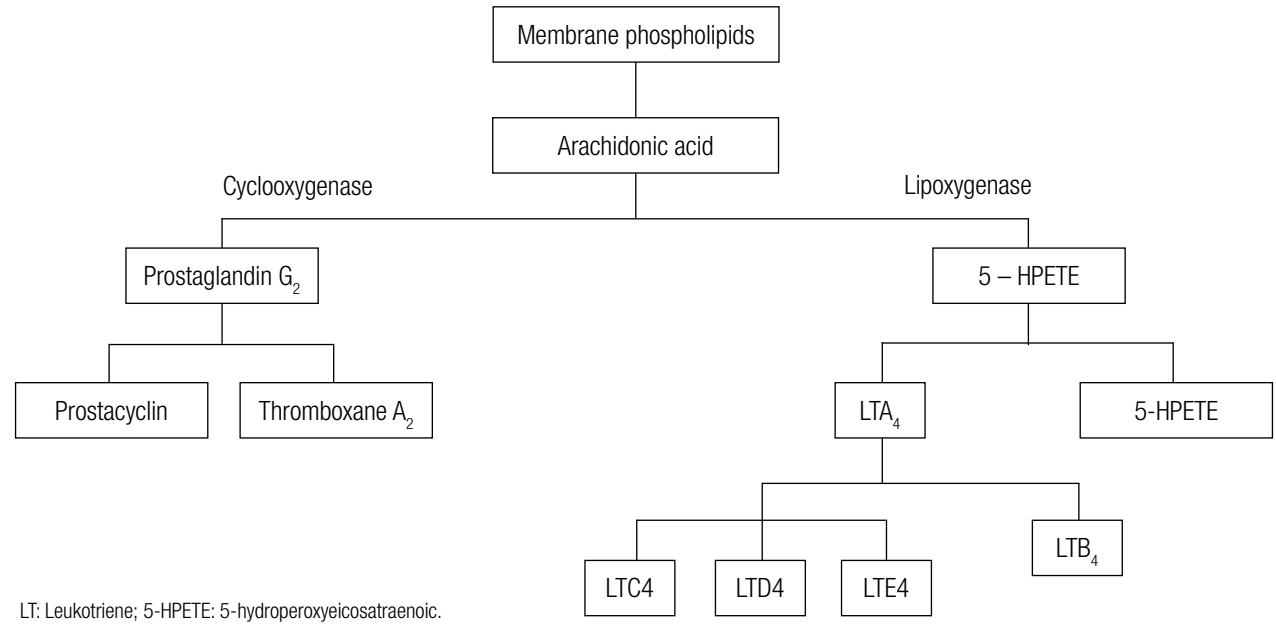

Synthesis of Prostaglandin and Leukotriene.

FIG. 1

All are extensively linked to plasma proteins, with its free fraction may be increased in hypoalbuminaemia. [3]

They can be divided in 2 groups based on the plasmatic elimination half-life: a short half life (less than six hours) – acetylsalicylic acid, diclofenac, ketoprofen, ketocorolac and indomethacin; and with a long half life (over 10 hours) – e.g. naproxen, piroxicam. Some with a short half life as sulindac and fenbufen have active metabolites which half live is higher then the mother drug. A balanced plasmatic concentration during regular administration can only be reached after around 5 half-lives, what for drugs as piroxicam means around one week. [3]

All NSAIDs are extensively metabolized in the liver through several mechanisms. Renal excretion for most is relatively insignificant in the general elimination of the unchanged drug. However, such excretion route for the unchanged drug and its pharmacologically active metabolites can be important in patients with renal dysfunction. [1]

Table 1 and 2 show the chemical classification, the beginning and duration of analgesia, and some NSAIDs doses

Adverse effects

The adverse effects can be divided: type A, predictable manifestations of normal pharmacology, depending on the dose or the compound toxicology properties, which are believed to be a consequence of the cyclooxygenase inhibition; and B type, responses which are qualitatively abnormal, unpredictable and do not relate to the dosage,[3] assuming that many of them are mediated by immunologic mechanisms, although

TABLE I

NSAID Chemical Classification

Salicylates – acetylsalicylic acid, diflunisal
Acetate – diclofenac, etodolac, indomethacin, sulindac, tolmetin
Propionate – fenbufen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, acid mefenamic
Oxicams – piroxicam, tenoxicam
Pyrazolone – azapropazone, phenylbutazone
Butazone – nabumetone

TABLE II

Dose, onset and action duration of some NSAIDs[1,15]

Agent	Analgesic action		Dose mg	Maximum daily dose
	Onset (h)	Duration (h)		
Diclofenac	1-2	6-12	50-100 every 8/12h	200
Ibuprofen	0.5	4-6	400-600 every 6 h	3200
Ketoprofen	0.5-1	4-6	25-60 every 6/8 h	300
Naproxen	0.5 – 1	Up to 7	250-275 every 6/8 h	1500
Piroxicam	1	48-72	10-20/d	20
Sulindac	1-2	Up to 12	200 every 12 h	400
Etodolac	0.5	6-12	200-400 every 6/8 h	1200
Diflunisal	1-3	8-12	500 every 12 h	1500

there is no direct proof.

Toxic effects are most frequent at all levels in advanced age. In a single dose, they produce few side-effects, but keeping the administration for 7 to 10 days, incidence does increase. Conversely to what succeeds with analgesia, there is not a ceiling effect relating to toxicity.[5]

Gastrointestinal toxicity

Gastrointestinal toxicity is the most common NSAIDs. In 10 to 20% of patients upper gastrointestinal symptoms – nausea, vomiting, dyspepsia occur. The two major problems are diffuse gastritis and both duodenal and gastric ulcer, but the toxicity it is not limited to the upper part of the digestive system, with the small and large intestine also damaged by the chronicle use of NSAIDs.[6] After oral administration there is almost always a hidden hemorrhage, but it might occur a gastrointestinal perforation or evident hemorrhage due to an acute damage of mucosa or peptic ulcer. When taken by other routes, also causing gastrointestinal toxicity and, through rectal route, the risk seems to be higher than through oral route,[7] such facts favor the hypothesis that NSAIDs exert, at least, in part its adverse effects at gastrointestinal level, after systemic absorption. Serious complications are not, often, preceded by symptoms[6,8] and the presence of those does not predict any particular gastric pathology. [4] The acetylsalicylic acid is the one producing the highest gastrointestinal toxicity; etodolac and nabumetone are the least toxics.[1] Rarer side-effects are: esophageal ulcer, esophageal stenosis, stomatitis and pancreatitis.[9] Mefenamic acid, flufenamic acid and indomethacin can also cause diarrhoea.[9]

There are several risk factors for the side effects at gastrointestinal level: advanced age, especially in females, NSAIDs dose, ulcer history or gastrointestinal complications associated to NSAIDs, a previous need of using anti-acids or H_2 blockers, and the use of corticosteroids. [8] Alcohol, caffeine and tobacco as well as the presence of simultaneous diseases have also been considered risk factors, but data has not been conclusive.[6] Most gastrointestinal lesions occur in the first weeks of treatment. [8] The risk of serious side effects seems to be reduced at the end of four weeks of administration; apparently, there is another adaptation, developing a partial resistance to mucosa damage, in special in the gastric body and fundus.[6] The incidence of gastric and duodenal ulcer can be reduced with misoprostol in the dose of 200 µg 4 times per day; diarrhoea, its main side effect is self-limited and can be controlled if administered after meals.[8] H_2 antagonists also reduced the incidence of duodenal ulcer, but not of gastric ulcer.[1] No other drug has proven to be effective in reducing the incidence of gastrointestinal damage produced by NSAIDs.[6]

It is difficult to outline a strategy for the prophylactic use of mucosa protectors, by absence of data, but it is reasonable to you to use them in patients with a history of peptic disease and gastrointestinal hemorrhage. It is not clear for how long such protectors should be used as adaptation may happen as already mentioned.

Nephrotoxicity

In some hospitals, NSAIDs are the most common cause of acute kidney failure, needing to be assisted by a nephrologist.[10]

Prostaglandins contributed more to keeping the renal haemodynamic in adverse circumstances then in normal ones. [11] The risk of kidney failure is therefore higher in certain circumstances, as advanced age, cardiac failure, liver cirrhosis with ascites, nephrotic syndrome, renal artery stenosis, hypovolaemia, hypotension, kidney disease (specially lupus nephritis), gout, insulin-dependent diabetes and when there is simultaneously exposure to radiologic contrast

products, aminoglycosides and other nephrotoxic drugs, diuretics (specially triamterene) and angiotensin conversion enzyme inhibitors (particularly captopril).[2,10,12]

Indomethacin and naproxen, in particular, having a high renal clearance of their metabolite must be avoided in kidney failure. Sulindac, diflunisal, nabumetone and etodolac can be tried in such patients, monitoring the kidney function.[10]

There are three types of acute kidney dysfunction associated to NSAIDs use, acute kidney failure, hyperkalaemia, acute interstitial nephritis, with or without intense proteinuria (sometimes nephrotic). The most common form is reversible kidney failure, depending on prostaglandin, featured by onset oliguria followed by a non-oliguric course,[9] weight gain, quickly ascending creatine level and sometimes hyperkalaemia; the fractioned excretion of sodium is usually low but can be high in the most serious cases, indicating an acute tubular necrosis.[10] Acute kidney failure is usually reversible withdrawing the drug, even when it is necessary to use dialysis but in some cases, it results from a terminal kidney failure requiring chronic replacement therapy.[12]

NSAIDs prolonged use may cause chronic kidney failure – analgesic nephropathy – featured by interstitial nephritis and papillary necrosis[11] more frequently associated to phenacetin, but also other NSAIDs; salicylates when used isolate are not associated to papillary necrosis. [12] This in general is not reversible with the suspension of the responsible analgesic drug.

Kidney prostaglandins also regulate the water balance. Its inhibition causes water and sodium retention. Water retention can be disproportionate in relation to sodium, causing hyponatraemia in some patients; with thiazides such effect is additional. [11] Sodium and water retention causes a reduction on the response to the diuretics drugs.

Pulmonary toxicity

Bronchospasm might occur in a percentage reaching 20% of adult asthmatics with the administration of acetylsalicylic acid or any other NSAID, oral route, existing even a syndrome characterized by nasal polyposis and hypersensitivity to acetylsalicylic acid. Therefore caution must be exercised when administering to asthmatic patients and never in patients with a history of such kind of reaction. Ketoprofen and diclofenac can cause less toxicity at this level.[9]

Several NSAIDs were associated to hypersensitive pneumonitis, manifested by fever, non-productive cough, wheezing and crepitations; on thorax X-Ray there are usually bilateral infiltrations. [11]

Hepatic toxicity

All NSAIDs have the potential to increase the level of liver enzymes. The toxic effects can be hepatocellular (transaminases increased), cholestatic (increase on alkaline phosphatases and bilirubins) or mixed.[1] The risk is higher when there is hepatic disease, alcoholism or congestive cardiac insufficiency. [1] With diclofenac it was registered hepatotoxicity in several patients and some deaths were directly attributed to it. [13] In most patients, signs and symptoms were solved in 4 to 6 weeks after withdrawing the drug. Some of these patients re-start other NSAIDs (naproxen, piroxicam) without any problem. [1]

Acetylsalicylic acid has been associated to Reye's syndrome.

It is prudent to reduce NSAID dose, with the possible exception of etodolac, in 25 to 50% of patients with a history of hepatic disease. All patients must be monitored for hepatic disease before beginning NSAID use and again within six weeks.[1]

Toxicity of the central nervous system

Minor adverse reaction of the central nervous system may occur, as headaches, tinnitus, dizziness, probably with all AINE, but more frequently with indomethacin. Tinnitus is the most common sign of nervous system toxicity introduced by acetylsalicylic acid,[1] along with hypoacusia; usually early symptoms of toxicity are reversible with the reduction or the withdrawal of the drug.[14]

They can also cause light mood swings, cognitive and perception changes.[4]

Rare cases of serious depression were described with indomethacin.[9]

Almost all cases of aseptic meningitis associated to NSAID involved ibuprofen. Such reaction has been reproduced in some cases only with one pill.

It is featured by headache, chills, mental confusion and nuke stiffness; in the CSF there is a rise in leukocytes and proteins but without evidence of infection.[11]

Haematologic toxicity

In patients with serious coagulopathies NSAIDs must

be avoided. In patients taking anticoagulant drugs, ibuprofen administration, starting with doses not higher than 200 mg 3 times a day, can provide enough pain relief without precipitating a gastrointestinal hemorrhage.[3] NSAID change platelet aggregation, inhibiting reversibly thromboxane A, whilst acetylsalicylic acid inhibits it irreversibly.[1]

More rare side effects are: thrombocytopenia caused by diclofenac, ibuprofen, piroxicam and indomethacin, [3] hemolytic anaemia associated to mefenamic acid, diclofenac, ibuprofen and naproxen, agranulocytosis and aplastic anaemia with phenylbutazone

Cutaneous toxicity

Hives is the skin reaction more common to acetylsalicylic acid, but can also occur with other NSAIDs.[11] Morbilliform rashes may also emerge with several of them, especially with fenbufen.[3] There are described cases of angioedema with ibuprofen, azapropazone and piroxicam.[3]

Several photosensitivity reactions have been reported, with the emergence of vesicles and blisters in the areas exposed to the sun, associated to piroxicam and more rarely to other NSAIDs.[9] Those two drugs are also the most frequently associated to multiform erythema and its variant, Stevens – Johnson syndrome, the most serious dermatologic complications, with the percentage of fatal cases from 6 to 25%.[9]

Anaphylaxis

Most NSAIDs can cause anaphylaxis

Interactions (*Table 3*)

NSAIDs are strongly linked to serum proteins (mainly albumin), displacing other drugs. Therefore interactions are frequent which drugs also linked to proteins.

Fenoprofen, ibuprofen, naproxen and etodolac do not interfere with hypocoagulating therapy, but increase the risk of hemorrhage as they inhibit the platelet function. Phenylbutazone, oxybutazone, acetylsalicylic acid and indomethacin must be particularly avoided in patients in hypocoagulation.[1]

All NSAIDs reduce aminoglycosides clearance, and might potentiate mutual nephrotoxicity, reason why the aminoglycoside serum concentration must be monitored and the dose adjusted.

NSAIDs in general, and indomethacin in particular, can interfere with the hypertension pharmacologic control and heart failure in patients taking β-blockers, angiotensin conversion enzyme and diuretics.[1]

TABLE III

NSAIDs more common interactions

Aminoglycoside
Anticoagulant
Antihypertensive – ACEi, β-blockers, diuretics
Digoxin
Lithium
Methotrexate
Metoclopramide
Phenytoin

The potential reduction of the renal function can reduce the clearance and consequently, increase serum concentration and the risk of toxicity from drugs as digoxin, reason why in such case, they must be avoided or if that is not possible to frequently measure the concentration of digoxin and/or creatinine.[4]

They inhibit lithium renal excretion, increasing its serum concentration and toxicity risk.[4]

Methotrexate clearance is also inhibited by NSAID, through an unknown mechanism.[4]

Metoclopramide increases the speed and absorption extension of NSAIDs.[4]

NSAID displace phenytoin of serum proteins. This way, even for the same level of active free drug, it is necessary to reach a lower total concentration, reason why serum levels must be construed carefully.[4]

Treatment of oncologic pain

NSAIDs are, together with paracetamol, first-line agents in the treatment of light to moderate cancer pain, being the first degree of the analgesic ladder of the World Health Organization;[17] they can also be used in other stages. In regular treatment, they are used alone or in combination with opioids with which they have at least an additive action. NSAIDs have as it was mentioned before a ceiling effect and above a certain dose there is no analgesia increase. [1] They do not cause addiction and apparently there is no tolerance developed to its effect.[16]

NSAIDs have been considered particularly useful in the treatment of pain associated to bone metastases. After discovering the role of prostaglandin in bone destruction induced by tumors, some even thought

there was a specific action on the evolution of this kind of metastasis. However some studies performed posteriorly to evaluate such action did not show any benefit in terms of recurrence or in the development of bone metastases.[18, 19] In reality, such results are not surprising as the investigation revealed the involvement of many other mediators in bone metastization, besides prostaglandin.[20] The absence of effect on the evolution of bone metastasis would not eliminate however a particular efficacy in the pain associated to it. Therefore, some authors consider that NSAIDs have a very important role treating bone pain;[21,23] however others show less certainty about such importance. [18] As a matter of fact, the authors who reviewed the already published studies could not conclude that NSAIDs are particularly effective in bone pain.[5,18]

NSAIDs can be taken by oral, rectal, intramuscular, topical route and even in continuous, endovenous or subcutaneous perfusion. Oral route is the most convenient in most situations, being therefore the most used. The intramuscular route is not appropriated for repeated use so it must be reserved for special cases, as in acute pain of kidney colic. Naproxen, diclofenac and ketorolac have been used with good results, in continuous subcutaneous perfusion,[18] in the treatment of oncological pain, and this form of administration may become an alternative useful route to the oral one, when this cannot be used for some reason (e.g., vomits or dysphagia), as it happens frequently in advanced cancer.

In rheumatoid arthritis, it has been verified a wide variability in the individual response to the different NSAIDs. Such observation has been extrapolated for the pain associated with cancer, therefore if a patient does not tolerate or doesn't get any benefit from a NSAIDs, it is often recommended to try another one from a different chemical class.[23] Although there are not clinical trials legitimizing such practice, it is sensible to keep it.

Studies performed are not able to indicate which NSAIDs is particularly effective in the treatment of oncological pain. However, some generic recommendations can be made, bearing in mind that cancer patients are often elderly or debilitated, factors which increase the toxicity risk of a NSAID as mentioned before. It is better to use drugs is with a short half life and starting with the lower recommended doses increasing them every 2 to 3 days according to the clinical answer. It is better to avoid the most recent NSAIDs until its safety, in special that Type B side--effects are established in other specialties.[3]

NSAIDs presenting toxic side effects type B, with a certain frequency, as fenamate, (diarrhoea), fenbufen (eruptions) and pyrazole (blood dyscrasia).[3]

According to such principles therapy with a NSAIDs, such as ketoprofen, can be started and then change to diclofenac (belonging to a different chemical group) in intolerant or refractory patients or vice-versa. Such drugs are only indicated as an example and the options may be different, considering factors like the personal experience and the patient's previous experience.

It can be concluded that NSAIDs are useful drugs to treat cancer pain. However in spite of being used for many years for such purpose, there are still aspects lacking conclusive studies as knowing whether have a particular effect in bone pain. ■

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