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REVIEW ARTICLE

Recommendations for the use of anti-inflammatory drugs and indications for gastrointestinal protection in emergency departments

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed frequently in emergency departments together with proton pump inhibitors to prevent gastrointestinal complications. Such complications, peptic ulcer bleeding in particular, are among the most serious and costly side effects of NSAID treatment. An association between increased risk of cardiovascular events and treatment with selective cyclooxygenase inhibitors and certain traditional NSAIDs has also been reported. This review aims to provide an update on risk factors for gastrointestinal complications, discuss the types of gastric lesions associated with each NSAID, analyze the implications of the cardiovascular risk factors involved, and propose the best preventive strategy taking into account both gastrointestinal and cardiovascular risk factors. [Emergencias 2009;21:295-300]

Key words: Nonsteroidal anti-inflammatory drugs. Emergency care. Peptic ulcer. Gastrointestinal bleeding. Proton pump inhibitors.

Introduction: historical data

In 1899, Felix Hoffman achieved the synthesis of acetylsalicylic acid (ASA) in Bayer laboratories in Germany, and thus the first non-steroidal anti-inflammatory drug, named Aspirin®[1], initially used for the treatment of fever and rheumatic disease. In 1938, Douthwite presented the first endoscopic evidence of gastric mucosa damage caused by AAS[2]. In 1971, Sir John Vane demonstrated that aspirin inhibits the synthesis of prostaglandins and for this was awarded the Nobel Prize for medicine in 1982.

The decade of the 70s was marked by the emergence of new anti-inflammatory drugs (NSAIDs), and in 1999 the FDA approved the first selective NSAIDs for the inhibition of cyclooxygenase-2 (COX2). Finally, the XXI century has seen increased risk of cardiovascular events with use of COX2[3] and some classical NSAIDs.

Pharmacological action and mechanisms of action of NSAIDs

These are basically painkillers, antipyretics, anti-inflammatory and anti-platelet agents through their action on arachidonic acid by inhibition of cyclooxygenase involved in the pathogenic mechanisms of inflammation, pain and fever. They also act on platelet aggregation and on the defence mechanisms of the kidney and gastric mucosa, causing adverse effects (Figure 1).

Recently, two isoforms of the enzyme cyclooxygenase (COX1 and COX2) have been described. COX1 is expressed in most tissues and is responsible for the synthesis of prostaglandins with protective function of gastric mucosa and regulates renal function and platelet activity. COX2 is expressed in fewer tissues under normal conditions but is induced in response to inflammatory stimuli in macrophages, monocytes and endothelial cells, which generate prostaglandins

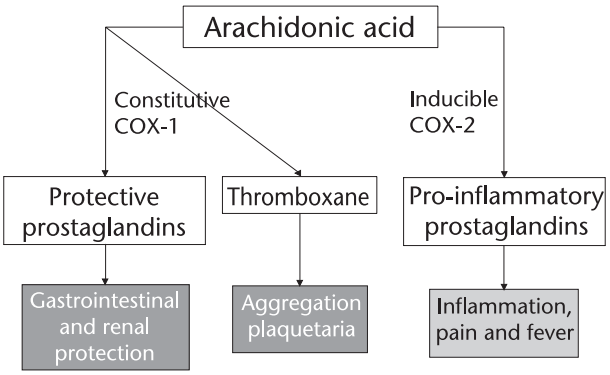

Figure 1. Arachidonic acid metabolism and pharmacological action of NSAIDs. COX: cyclooxygenase.

that mediate pain and inflammation. The inhibition of COX1 is responsible for the adverse effects of traditional NSAIDs on the gastrointestinal mucosa, while their therapeutic benefits depend on the inhibition of COX2. The main consequence of drugs that selectively inhibit COX2 is that they reduce the adverse effects produced from the inhibition of COX1.

Current status: clinical, economic and social impact

NSAIDs are among the most widely used pharmacological treatment groups in medicine. They are taken by 20% of people over 65 years and prescribed to 20% of patients requiring hospitalization. These drugs are easily accessible since no prescription is required, which indicates a high percentage of self-medication. So, despite being safe when administered at the appropriate dose and in selected patients, they are associated with a high number of adverse effects and potentially serious complications.

NSAID consumption has doubled in less than 15 years[4], and both ibuprofen and the most commonly used drugs in preventing gastrointestinal toxicity due to NSAIDs (omeprazole, lansoprazole and pantoprazole) are among the ten most prescribed agents within the National Health System in terms of packets[5]. In 2007, 8.3% and 10% of the total cost of drugs prescribed by the Sabadell Hospital emergency department were for NSAIDs and antisecretion drugs (97.5% were proton pump inhibitors).

Adverse effects of NSAIDs are common and, among these, digestive complications stand out because of their frequency and severity, specifically those related to gastroduodenal mucosa damage. However, NSAID damage is not limited to the upper gastrointestinal tract; between 15-50% of the complications due to NSAIDs occur in the small intestine or colon[6]. Digestive complications are the cause of 50,000 annual admissions, 1,000-2,500 deaths per year in Spain[7] and 16,500 deaths per year in USA[9]. These figures are comparable to the number of deaths caused by AIDS and considerably greater than the number of deaths due to conditions such as multiple myeloma, asthma, cervical cancer or Hodgkin's disease, which is why it has been called the "silent epidemic". In 1998, the estimated cost attributable to the consumption of NSAIDs and their complications was 80-200 million euros in Spain[8].

Upper gastrointestinal tract symptoms associated with NSAIDs may significantly affect the quality of life and reduce work productivity and daily activities, as shown in the study by Wahlqvist et al.[10] who suggested that digestive tract symptoms associated with NSAIDs result in a decline of 13% in work productivity and 26% in daily activities.

Similarly, there are relevant studies showing that prophylaxis for NSAID gastropathy is administered incorrectly in our setting. Thus, Lanas et al8 found that prescription of gastroprotective treatment was inappropriate in 80% of cases, and King et al.[11] confirmed that gastroprotective therapy was administered to only 12% of patients receiving NSAIDs with one risk factor for digestive complications and to 32% with two or more risk factors.

Finally, there is significant dissociation between the clinical manifestations referred by the patient and the presence of gastroduodenal lesions. Thus, only 30% of patients taking NSAIDs present dyspeptic symptoms, and of these only 30% have an ulcer. Similarly, only one in two patients with gastrointestinal bleeding associated with NSAIDs had previously referred dyspeptic symptoms, so clinical manifestations are no guide to patient selection for gastroprotective therapy[12,13]. It is therefore imperative to identify the predictive factors for development of an ulcer or gastrointestinal bleeding.

Choice of NSAID

Before prescribing NSAIDs, four questions must be addressed:- What kind of NSAID? What dose? Is it necessary to associate two NSAIDs? Is gastrointestinal protection indicated?

Regarding the first question, assuming similar efficacy between NSAIDs, the basic criterion is to minimize side effects, mainly gastrointestinal and cardiovascular. For the second question, use the lowest effective dose possible and for the shortest time possible to control symptoms according to the therapeutic objective established. For the third, prescription should be based on the safety profiles of each of the active ingredients. Not all NSAIDs have the same safety profile from the digestive tract or cardiovascular point of view. And for the fourth question, from the digestive tract point of view, there is a group of NSAIDs with lower risk of presenting digestive complications[14-16], including aceclofenac, diclofenac and ibuprofen, and another group of drugs with a higher risk, including ketorolac, piroxicam, meloxicam and indomethacin (Table 1).

As a result, in 2007 the Spanish Agency of Medicines and Healthcare Products issued an informative bulletin[17] on the risk/benefit ratio concerning the use of the NSAIDs ketorolac, piroxicam and ketoprofen. Systemic ketorolac is now considered a drug for hospital use and should be restricted to authorized indications (short-term treatment of postoperative pain, moderate or severe pain caused by renal colic), with a maximum treatment duration not exceeding two days of parenteral treatment or seven days of oral treatment. Piroxicam, due to its association with serious adverse gastrointestinal reactions, is now classified by the Committee for Human Medicinal Products as being suitable for hospital use only.

From a cardiovascular perspective, different recently published studies[3,18-22] have examined the risk of severe cardiovascular problems associated with NSAIDs. Coxibs present increased atherothrombotic risk, mainly acute myocardial infarction, stroke and peripheral arterial vascular problems compared with untreated patients, and is higher for patients with a history of cardiovascular disease[22]. In addition, the administration of diclofenac 150 mg/24 hours and ibuprofen 2400 mg/24 hours has been associated with increased risk of atherothrombotic events comparable to some coxibs[20]. Current data on the use of naproxen at a dose of 1,000 mg/24 hours suggest a reduced risk of atherothrombotic events when compared with COX-2 (coxibs), but no protective effect can be deduced, since it presents increased gastrointestinal risk compared to diclofenac and ibuprofen. Finally, for the remaining NSAIDs on the market in Spain, data are very limited or nonexistent. Therefore, the available data suggest that cardiovascular risk (especially of acute myocardial infarction) of NSAIDs may be a class effect and not only the coxibs, especially when used at high doses and for prolonged periods[23].

Table 1. Risk of gastrointestinal complications according to NSAID[16]

NSAID	RR (CI95%)
Aceclofenac	2.6 (1.5-4.6)
Diclofenac	3.1 (2.3-4.2)
Ibuprofen	4.1 (3.1-5.3)
Naproxen	7.3 (4.7-11.4)
Ketoprofen	8.6 (2.5-29.2)
Indomethacin	9 (3.9-20.7)
Meloxicam	9.8 (4.0-23.8)
Piroxicam	12.6 (7.8-20.3)
Ketorolac	14.4 (5.2-39.9)

RR: relative risk, CI confidence interval; NSAID: non-steroidal anti-inflammatory drug.

Indications for gastrointestinal protection

The use of NSAIDs increases the risk of gastrointestinal complications at any dose or duration of treatment, but increases with dose and duration. The risk also increases with age and gastroprotective treatment is justified for patients from 60 years of age, and especially after age 75 years.

Other risk factors for gastrointestinal complications are the association of more than one NSAID - a combination that does not increase analgesic efficacy and should therefore be avoided - or the combination of NSAIDs with anticoagulants, antiplatelets, corticosteroids or antidepressant selective serotonin reuptake inhibitors.

Finally, a history of ulcer and especially of ulcer complications and the severity of the patient's underlying disease are significant risk factors.

Gastroprotective therapy is recommended in all patients receiving NSAIDs and present at least one of the risk factors shown in Table 2[6,16]. Figure 2 is a schematic representation of the strategy for gastrointestinal protection for patients who require NSAIDs.

Prophylactic treatment of NSAID-induced gastropathy

The prophylactic treatment of choice in our setting, whose effectiveness has been demonstrated in clinical trials and epidemiological studies[16,25-27], is a proton pump inhibitor (PPI) at standard doses (omeprazole 20 mg/24 h, 30 mg/24 h lansoprazole, pantoprazole 40 mg/24 h, rabeprazole 20 mg/24 h or esomeprazole 40 mg/24 h)[24]. Efficacy at lower doses has not been established and

Table 2. Risk factors for gastrointestinal complications due to NSAIDs[6,16]

Risk Factors	Increased Risk
Previous history of ulcer	5.2-6.7
Previous history of complication	12.6-18.9
Age >60 years	1.5-3
>75 years	3-6
Severity of underlying disease	1.3-1.8
2 NSAIDs or NSAID + antiaggregant	12.7-14.5
NSAIDs + anticoagulant	6.3-25.7
NSAID + corticosteroid	4-12.7
NSAIDs + SSRIs	15

NSAID: non-steroidal anti-inflammatory drug. SSRIs: selective serotonin reuptake inhibitors (antidepressants).

should therefore be avoided. Gastroprotective therapy should be initiated at the same time as NSAID initiation and maintained until 7-14 days after the end of NSAID treatment[6].

H2 receptor antagonists (H2RA) are not indicated since at least one double dose is needed to prevent gastric and duodenal ulcers. In addition, effectiveness at preventing complications associated with the long-term use of NSAIDs is unknown. So, their use is not recommended[24].

Misoprostol at doses of 600-800 mcg/24h is as effective as PPI treatment, but its effectiveness is lower if the dose used is 400 mcg/24 h[25,28,29]. However, its high rate of side effects (up to 20% of patients may develop abdominal pain or diarrhea at the higher dose of 800 mcg/24-h) and difficult dosage (3-4 times/24 h) do not favour recommending misoprostol[24].

COX2 selective inhibitors (coxibs) present the anti-inflammatory effects of classical NSAIDs classic and a marked reduction in both upper and lower gastrointestinal complications[16,18,30]. In the case of lower gastrointestinal complications, coxibs are the only group that has demonstrated reduction of complications, so for long-term treatment these are the drugs of choice[30].

Particular situations

1. Low-dose ASA and other antiplatelet

The behaviour of patients on low-dose ASA is similar to that of patients taking NSAIDs, although the risk of bleeding is remarkably lower[16]. In general, ASA is recommended at doses as low as possible (80-100 mg/24 hours) as the risk of gastrointestinal complications is directly proportional to increasing dose[31]. The indications for gastrointestinal protection are the same as for NSAIDs.

Particular features should be emphasized (Table 3): the non-ASA antiplatelets, such as clopidogrel, are also associated with significantly increased risk of gastrointestinal complications with a similar risk to ASA[16,32]. Iin patients who have had

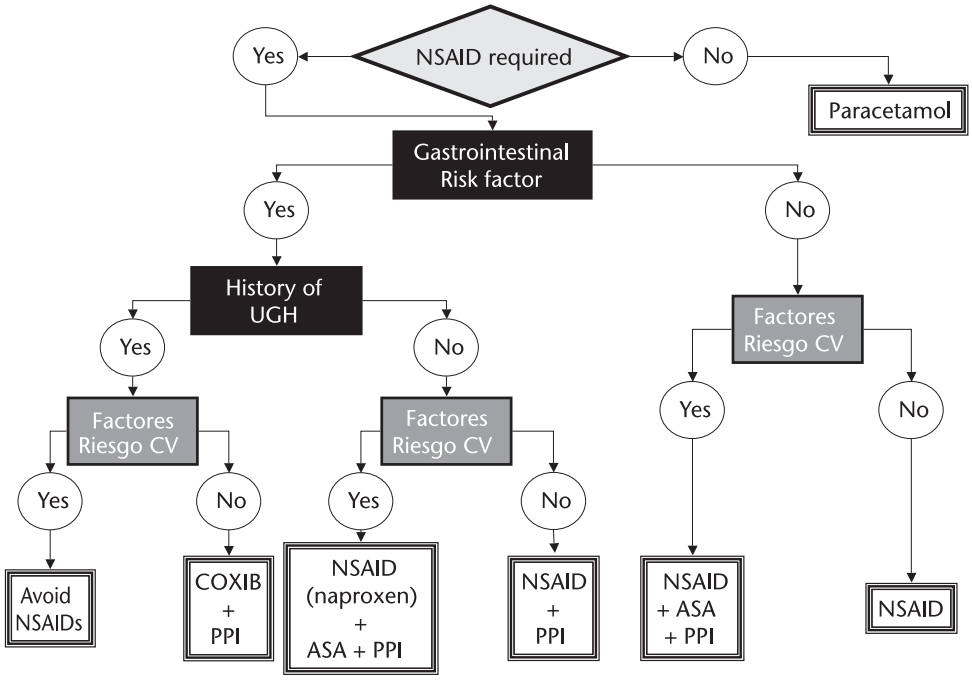

Figure 2. Strategy for gastrointestinal protection in patients taking NSAIDs. NSAID: nonsteroidal anti-inflammatory drugs; ASA: acetyl salicylic acid; PPI: Proton pump inhibitor; CV: Cardiovascular. UGB: Upper gastrointestinal bleeding.

gastrointestinal bleeding, the most useful combination is ASA plus a PPI, better than the use of clopidogrel for prevention of secondary recurrent bleeding[33], and the concomitant use of ASA annuls the gastroprotective effect of the coxibs on the gastric mucosa[16,34].

2. NSAIDs and a history of gastrointestinal bleeding

In patients with previous complications due to NSAIDs, especially gastrointestinal bleeding, but should maintain the treatment, the use of NSAIDs with a PPI, or the use of a coxib, provides insufficient protection[35,36], so a combination of two methods of gastrointestinal protection is recommended: usually a PPI and a coxib succeeds in preventing re-bleeding[37].

3. NSAIDs and Helicobacter pylori

Helicobacter pylori infection and concomitant NSAID use are two independent factors for significantly increased risk of peptic ulcer and gastrointestinal bleeding. Both factors could act synergistically, so peptic ulcer disease is rare in patients who do not consume NSAIDs and do not present infection by *Helicobacter pylori*[38].

Eradication has a modest protective effect in patients starting on NSAIDs for the first time. However, its effect is minimal in patients already receiving continuous treatment with NSAIDs. Specifically, the prophylactic effect of *Helicobacter pylori* eradication seems very limited in patients already receiving gastroprotective treatment[39]. Current recommendations are consistent with the current state of knowledge and recommend eradication in patients with a history of ulcer, active or complicated ulcer, but not generally recommended for all patients initiating or already taking NSAIDs[6]. However, in the light of most recent information, it is reasonable to extend the indication for eradication in all patients about to initiate NSAID treatment, especially if they meet the criteria for gastrointestinal protection[39].

Table 3. Risk of gastrointestinal complications associated with the use of NSAIDs, aspirin, clopidogrel and coxibs[16]

Drug	Increased Risk
NSAIDs	5.3
COXIB	1.0
ASA 100 mg	2.7
ASA 300 mg	6.1
Clopidogrel	3.1
NSAIDs + ASA	12.7
COXIB + ASA	14.5

NSAID: nonsteroidal anti-inflammatory, ASA: acetylsalicylic acid; COXIB: Cyclooxygenase[2].

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Recomendaciones en la prescripción de antiinflamatorios e indicaciones de gastroprotección en urgencias

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En los servicios de urgencias, la prescripción de antiinflamatorios no esteroideos (AINEs) y de fármacos antisecretores para la profilaxis de las complicaciones digestivas es elevada. El tratamiento con AINEs se asocia a múltiples efectos adversos, entre los que destacan por su gravedad y su elevado coste las complicaciones digestivas, especialmente la hemorragia por úlcera péptica, así como un aumento del riesgo de episodios cardiovasculares asociado al tratamiento con inhibidores selectivos de la ciclooxigenasa (COXIBS), así como con algunos AINEs clásicos. El objetivo de esta revisión es actualizar tanto los factores de riesgo de las complicaciones gastrointestinales como el perfil gastrolesivo de los diferentes AINEs, analizar las implicaciones que tienen los factores de riesgo cardiovascular y proponer la mejor estrategia de prevención en función de los factores de riesgo digestivos y cardiovasculares. [Emergencias 2009;21:295-300]

Palabras clave: Antiinflamatorios no esteroideos. Urgencias. Úlcera péptica. Hemorragia digestiva. Inhibidores de la bomba protones.