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Review

Appropriate prescription, adherence and safety of non-steroidal anti-inflammatory drugs☆

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most numerous category of drugs sharing the same mechanism of action and therapeutic activities (anti-inflammatory, analgesic and anti-pyretic). Despite having similar efficacy for pain relieve, the different available NSAIDs show variability in its safety profile. The risk of gastrointestinal and cardiovascular complications varies depending on the dose of NSAID and also the presence of different risk factors. It is necessary, therefore, an individualised case assessment before establishing the indication of the best NSAID for each patient, taking account of the best gastroprotection strategy. Improved prescription and enhanced treatment adherence are central objectives to reduce NSAID-related complications. A recent consensus of the Spanish Association of Gastroenterology and the Spanish societies of Cardiology and Rheumatology intends to promote the rational use of NSAIDs according to new recent studies. This review provides additional aspects to facilitate the optimal decision-making process in the routine use of these drugs in clinical practice.

Prescripción apropiada, adherencia y seguridad de los antiinflamatorios no esteroideos

Palabras clave:
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Adherencia

RESUMEN

Los antiinflamatorios no esteroideos (AINE) configuran la familia más numerosa de fármacos que comparten los mismos mecanismos de acción y actividades terapéuticas (antiinflamatoria, analgésica y antipirética). A pesar de tener una eficacia similar para controlar el dolor, los diferentes AINE disponibles presentan variabilidad en su perfil de seguridad. El riesgo de complicaciones gastrointestinales y cardiovasculares varía en función del AINE y de la dosis que utilicemos, además de la presencia de factores de riesgo. Es necesaria una evaluación individualizada de cada caso antes de sentar tanto la indicación del AINE «ideal» como la estrategia de prevención gastrointestinal si fuera necesaria. Una correcta prescripción y una adecuada adherencia al tratamiento gastroprotector son los objetivos que hay que plantearse para conseguir reducir las complicaciones secundarias al tratamiento con AINE. Recientemente se han publicado unas recomendaciones de prescripción adecuada fruto de la colaboración de la Asociación Española de Gastroenterología y las sociedades españolas de Reumatología y Cardiología que tiene por objeto impulsar un uso racional de los AINE en función de los últimos estudios publicados. Esta revisión completa aspectos adicionales necesarios para facilitar la toma de decisiones óptima en el uso habitual de estos fármacos en la práctica clínica diaria.

Introduction

Pain is one of the main factors contributing to the global burden of disease, measured by years lived with disability. Patients in pain, especially musculoskeletal pain, represent a significant percentage of the population and demand treatment; the most

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commonly used medication for this scenario are nonsteroidal anti-inflammatory drugs (NSAIDs), of the analgesic variety.[1] Traditional NSAIDs are associated with a significantly increased risk of gastrointestinal (GI) events, which varies depending on the NSAID and dose, and the existence of risk factors.[2] Within NSAIDs, COX-2 inhibitors, also known as coxibs, have a better GI safety profile, but as a result of their marketing it became known that these, and subsequently other non-selective NSAIDs, increased cardiovascular (CV) risk, which led to different regulatory agencies stating that NSAIDs in general may pose a significant risk to health.[3]

Thus, despite the undoubted beneficial effects of NSAIDs to control pain and inflammation in musculoskeletal diseases, the presence of adverse GI events and CV risk mean that the 'ideal' choice of NSAID is a sometimes complicated decision in routine clinical practice. Recently a consensus document was published by 3 Spanish scientific societies on the appropriate prescription based on the secondary effects of different NSAIDs.[4] This article also discussed other issues that decisively affect the end safety of patients being prescribed NSAIDs, while also referring to the appropriateness of the prescription and adherence to treatment by patients.

Nonsteroidal anti-inflammatory drugs and gastrointestinal damage

The main indication of NSAIDs is the reduction of pain. Clinical practice guidelines recommend their prescription after assessing other non-pharmacological or paracetamol options.[5] The response to NSAIDs varies from patient to patient, but no NSAID (including coxibs) has proven to be more effective than another.[6] Today it is widely accepted that NSAIDs (traditional and coxibs) can damage the entire GI tract, although there are clear differences between traditional NSAIDs and coxibs in this regard. The spectrum of lesions is variable, ranging from ulcers or erosions to severe complications such as bleeding and perforation. Many of these lesions are asymptomatic. However, more than 40% of NSAID takers have reported symptoms in the upper GI tract during treatment, the most frequent being gastroesophageal reflux and dyspeptic symptoms.[7] Approximately 1–4% of patients will have symptomatic GI ulcers or complications from treatment with NSAIDs. Observational studies have shown that the average relative risk (RR) of developing a peptic ulcer complication is 4–5 times higher in patients treated with NSAIDs compared to those who are not.[8] There is less evidence available of damage to the lower GI tract caused by NSAIDs than for the upper GI tract. It has recently been shown that hospital admissions for lower GI complications are increasing, while upper GI tract complications are decreasing.[9]

The risk of GI complications is not the same for all patients, but depends–aside from the dose and type of NSAID–on a series of risk factors that must be taken into account when deciding on treatment. Age, >60 years-old, is an independent risk factor for the occurrence of GI complications. Risk increases progressively with age. The presence of a history of gastroduodenal peptic ulcer has proven to be the most important risk factor for developing GI complications in patients taking NSAIDs.[2] The *combination of 2 or more NSAIDs* increases the risk of bleeding associated for each NSAID individually. This increased risk is also observed with the involvement of a classic NSAID or coxib with acetylsalicylic acid (ASA) at low doses, a combination very often used in clinical practice. Based on these risk factors, patients requiring NSAIDs have been categorised into 3 groups[4]:

1. *High risk*: a complicated personal history of peptic ulcers; use of anticoagulants or combination of >2 accepted risk factors.
2. *Medium risk*: patients without a history of complicated ulcer and no anticoagulation with some other isolated risk factor.
3. *Low risk*: patients without risk factors. No consumption of ASA.

Nonsteroidal anti-inflammatory drugs and cardiovascular damage

The patient who requires NSAIDs also requires a CV risk assessment. CV risk is currently measured by following the *Systematic Coronary Risk Evaluation*[10] model, based on studies with European populations. It is well established that the administration of NSAIDs increases the risk of developing acute coronary syndrome or other CV risk episodes of an atherothrombotic nature. This has been certified by data published since coxibs entered the market, current clinical practice guidelines, consensus documents and regulatory agencies.[4,11,12]

The most recent large meta-analysis study indicates that coxibs and NSAIDs have an increased cardiovascular risk compared to placebo, with no significant differences between them in general. From all the traditional NSAIDs, the one that posed a greater risk of CV risk was diclofenac, presenting a similar risk to that of coxibs. Naproxen at doses of 500 mg/12 h was not associated with an increased CV risk, unlike ibuprofen and diclofenac.[13] More recently the Spanish Medicines Agency (AEMPS) has warned that available data indicate the need to emphasise that ibuprofen at high doses (2400 mg/day) and dexibuprofen (1200 mg/day) (medications that are widely used in Spain and available without prescription) present a CV risk similar to coxibs at standard doses, such that, except at doses at or below 1200 mg/day or 600 mg/day, respectively, and used for only short periods of time, these molecules should be taken with the same precautions than coxibs.[14]

Prescribing recommendations based on gastrointestinal and cardiovascular risk

The main objective of managing patients treated with NSAIDs is preventing the development of complications. For this, a GI and CV risk profile must be made for each case before prescribing the 'ideal' NSAID, in addition to a gastroprotection strategy if necessary. This full profile would be what guides the type, dose and schedule for NSAIDs administered in each case (Fig. 1).

We know that the GI safety profile of coxibs is superior to that of traditional NSAIDs.[15] A recent meta-analysis study showed that compared with traditional NSAIDs, celecoxib is associated with a significantly lower risk of all clinically significant GI events throughout the entire GI tract.[16] Naproxen has the lowest CV risk, while other medications like diclofenac and etoricoxib pose the greatest risk at present. This was confirmed by a recent meta-analysis study[13] which showed that CV risks from diclofenac and ibuprofen at high doses are comparable to coxibs, while doses of 500 mg/12 h of naproxen are associated with lower CV risks. In any case, if coxibs (especially celecoxib at doses of 200 mg/day) has the safest GI profile, naproxen has the safest CV risk profile. Celecoxib and diclofenac do not interfere with antiplatelet activity of ASA at low-dosis[17] or clopidogrel. This would make celecoxib at low-doses the most suitable NSAID for patients receiving ASA; however, the EMA (European Medicines Agency) maintains contraindication of its use in patients taking ASA for secondary prevention. There are conflicting data regarding the interference of the antiplatelet effect of ASA in the presence of naproxen; in any case, this interaction appears to be lower than that observed with ibuprofen.

Current recommendations are reflected in a consensus document prepared by three Spanish scientific societies.[4] Based on these recommendations, any NSAID is acceptable in patients with low CV and GI risk. Patients at high GI risk should avoid treatment with NSAIDs; if it is necessary, *Helicobacter pylori* should be eradicated in patients with history of ulcers and infected ulcers and prescribed celecoxib + proton-pump inhibitor (PPI) if CV risk is low. In patients with high CV risk the best treatment option is naproxen