Biomedicine & Pharmacotherapy 150 (2022) 112958

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Non-steroidal anti-inflammatory drugs (NSAIDs), pain and aging: Adjusting prescription to patient features

Hugo Ribeiro [a,*], Inês Rodrigues [b], Leonardo Napoleão [c], Luís Lira [b], Denise Marques [d], Manuel Veríssimo [e], José Paulo Andrade [f], Marília Dourado [g]

[a] Palliative Care Unit of Health Centers Cluster Gaia, PhD Palliative Care Student in Faculty of Medicine of University of Porto, Invited Assistant of Faculty of Medicine of University of Coimbra, Portugal
[b] Family Health Unit Barão do Corvo of Health Centers Cluster Gaia, Portugal
[c] Family Health Unit Canelas of Health Centers Cluster Espinho/Gaia, Portugal
[d] Bial medical department, Portugal
[e] Coimbra University Hospital and Faculty of Medicine of University of Coimbra, Portugal
[f] Department of Biomedicine – Unit of Anatomy, Faculty of Medicine of University of Porto, Portugal
[g] Faculty of Medicine of University of Coimbra, Portugal

ARTICLE INFO

Keywords:
Anti-inflammatory drugs
Pharmacokinetics
Pain
Aging
Narrative review

ABSTRACT

A narrative review of papers published from January 2011 to December 2021, after a literature search in selected databases using the terms "pharmacokinetics", "ibuprofen", "diclofenac", "acemetacin", "naproxen", "etodolac" and "etoricoxib" was performed. From 828 articles identified, only eight met the inclusion criteria. Selective COX-2 inhibitors are associated with higher cardiovascular risk, while non-selective COX inhibitors are associated with higher gastrointestinal risk. NSAIDs with lower renal excretion with phase 2 metabolism are less likely to induce adverse effects and drug-drug interactions. Patients with frequent NSAID use needs, such as elderly patients and patients with cardiovascular disease or impaired renal function, will benefit from lower renal excretion (e.g. acemethacin, diclofenac, and etodolac) (level of evidence 3). Polymedicated patients, elderly patients, and patients with chronic alcohol abuse will be at a lower risk for adverse effects with NSAIDs that undergo phase 2 liver biotransformation, namely, acemethacin and diclofenac (level of evidence 3). Young patients, patients dealing with acute pain, or with active and/or chronic symptomatic gastritis, selective COX-2 inhibitors (celecoxib or etoricoxib) may be a better option (level of evidence 2). Knowing the individual characteristics of the patients, combined with knowledge on basic pharmacology, offers greater safety and better adherence to therapy.

Perspective: Although there are several NSAIDs options to treat pain, physicians usually take special care to its prescription regarding cardiovascular and gastrointestinal side effects, despite the age of the patient. In this paper, based on the best evidence, the authors present a review of the safest NSAIDs to use in the elderly.

1. Introduction

According to the World Health Organization (WHO), aging is "a process of organic, functional and social decline, not a consequence of illness or accident, and which inevitably occurs over time" (WHO, 2015). It is known that, with aging, individuals present specificities and different health requirements distinguishable from those presented by younger individuals. Thus, the elderly, meaning those aged 65 years or over, are a growing group within the population that needs different medical approaches and therapeutic interventions (WHO, 2015). Since this is a highly heterogeneous group, it is not possible to decide the choice of a drug and its dose based only on age as a guide but instead on the individual characteristics of each patient.

The physical and functional characteristics of the elderly mean that diseases in aging are mostly disabling, chronic and degenerative, and almost always accompanied by pain or contributing to the genesis of pain ("[11]; Directorate-General for Health, 2013; Veríssimo et al., 2014). In fact, about 50% of the elderly in Portugal live in the community, and 83% of institutionalized have moderate or severe chronic pain (Azevedo et al., 2013). For this reason, adequate knowledge on

* Correspondence to: R. Bartolomeu Dias 316, 4430-043 Vila Nova de Gaia, Portugal.
E-mail address: haribeiro@arsnorte.min-saude.pt (H. Ribeiro).

https://doi.org/10.1016/j.biopha.2022.112958
Received 1 March 2022; Received in revised form 8 April 2022; Accepted 11 April 2022
Available online 19 April 2022

pain management, ranging from neurophysiology to pharmacology and therapy, is essential for suitable and optimized treatment of pain in geriatric patients [3].

Like any other disease, chronic pain needs treatment that is suited to its pathophysiological features and intensity, among other factors. The WHO recommends the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of mild, moderate and severe pain (WHO, 2009). We know that using these drugs entails risks, but we also recognize that the NSAIDs currently available to us are quite different, with distinct pharmacokinetic characteristics (Brune & Patrignani, 2015; DrugBank, 2021; INFARMED, 2021; Ribeiro et al., 2017).

Therefore, the main objective of this work is to systematize available information that would contribute to a better understanding of the pharmacokinetic and pharmacodynamic features of NSAIDs for pain management in the elderly, thus contributing to a more informed, patient-adapted choice and, consequently, reducing the incidence of adverse effects and increase the efficiency of care. The lack of information on the subject in a totally patient-centered approach that would help in daily clinical practice justified our proposition to carry out the present narrative review.

2. Methods

A literature search was carried out in Pubmed/MEDLINE, the Database of Abstracts of Reviews of Effects, Cochrane, National Guideline Clearinghouse and National Health Service Evidence (NICE) databases. For the selection of articles and other documents, equations the term Medical Subject Headings (MeSH) "pharmacokinetics" sequentially and together with the name of some of the main NSAIDs worldwide, "ibuprofen", "diclofenac", "acemetacin", "naproxen", "etodolac" and "etoricoxib" were used. Abstracts of the drug characteristics of the NSAIDs targeted in the study were also used, through a search on the website of the Portuguese National Authority for Medicines and Health Products (INFARMED), as well as their pharmacokinetic and pharmacodynamic characteristics registered in DrugBank® and Pharmgkb®.

2.1. Inclusion criteria

Articles published in English and Portuguese, from January 2011 to December 2021.

2.2. Exclusion criteria

Publications that did not address the pharmacokinetic and pharmacodynamic characteristics of NSAIDs.

Articles and documents in languages other than Portuguese or English.

2.3. Quality assessment

To assess the quality and interest of the articles, the title and abstract of the article were initially read, and those not related to the topic were excluded. Afterward, the remaining articles were read in full, verifying which ones met the established inclusion criteria and contributing relevant information to this review.

To assign evidence levels and establish recommendation strengths, the Strength of Recommendation Taxonomy (SORT) of the American Academy of Family Physicians was used (Ebell et al., 2004).

3. Results

827 articles were identified (57 in Pubmed, 742 in Cochrane and 28 in NICE), of which 800 articles were eliminated after reading the title and abstract. Of the 28 articles selected for full reading, 20 did not meet the inclusion criteria. This process resulted in 8 articles (Bacchi, 2012a; Baker & Perazella, 2020; Bally et al., 2017; Bruno A, 2014; Li, 2020; Nissen et al., 2016; Stanos, 2016; Tai & McAlindon, 2018) that met the inclusion criteria and were included to carry out this review. Guidelines and textbooks were also included (American Geriatrics Society, 2019; Cardoso, 2014; Directorate-General for Health, 2013; Directorate-General for Health, 2013; Katzung, 2004; O'Mahoney, 2015; Ritto, 2017; Veríssimo et al., 2014; World Health Organization, 2007, 2009), which addressed issues related to both the topic and objectives of the review. Fig. 1 represents the identification process of the articles used.

Globally, the cost of NSAID prescription reached 98.026 million US dollars in 2020 and is projected to rise to 125.552 million dollars by 2028 ([8].

According to a literature review carried out by Bruno et al. (2014), the analgesic benefit and anti-inflammatory properties of NSAIDs depend on COX-2 activity (Bruno A, 2014). Furthermore, a meta-analysis performed by Li et al. (2020) revealed that oral NSAIDs do not yield significant differences in terms of analgesic potency (Li et al., 2020).

50% of patients taking NSAIDs chronically develop mucosal damage of the small intestine, and 2–4% of these individuals develop GI ulcers and bleeding [16,18].

Therefore, the main issue related to the use of NSAIDs should focus on their safety profile [2,17], particularly in the elderly (Bowie, 2007; Directorate-General for Health, 2013; Li, 2020; Petrovic, 2012; Ribeiro et al., 2017), which, in turn, is related to the pharmacokinetic, pharmacodynamic and pharmacogenomic profile of each NSAID (Bowie, 2007; Petrovic, 2012; Veríssimo et al., 2014). Considering that each NSAID can exhibit a different safety profile, according to van der Petrovic (2012), it is the patient's individual characteristics that needs to be considered, since these are key to therapeutic adaptation and adequacy (Petrovic, 2012).

3.1. Features of the elderly patient that interfere with the pharmacokinetics and pharmacodynamics of NSAIDs

Aging causes important changes in the body that interfere with drug pharmacokinetics [4,9] and pharmacodynamics (Azevedo, 2012; Katzung, 2004; Petrovic, 2012; Ribeiro et al., 2017; Veríssimo et al., 2014). Table 1 shows the most frequent changes related to absorption, distribution, metabolism, and excretion of most drugs.

Drug absorption is not significantly affected by aging per se, but essentially through the adding-up of multiple factors that interact with each other as we age, namely: changes in nutritional habits, consumption of over-the-counter drugs (e.g., antacids; laxatives; and others), reduced gastric and intestinal motility, reduced gastric emptying and increased pH, reduced splanchnic blood flow, less enzyme secretion and mucosal atrophy (Katzung, 2004; Veríssimo et al., 2014).

When analyzing drug distribution, since the elderly show a decrease in body water when compared to the young adult population, caution is warranted with the use of water-soluble drugs, as they will easily reach critical toxicity concentrations (Katzung, 2004; Petrovic, 2012; Veríssimo et al., 2014). In other words, the maximum tolerated doses will be lower in geriatric age [4]. In contrast, fat-soluble drugs have a prolonged time of action due to the body's increase in adipose tissue with aging, especially abdominal fat [4]. Care must be taken in the titration of fat-soluble drugs, in the recommended/administered doses and the timing between doses, which should be extended to assure better safety (Katzung, 2004; Petrovic, 2012; Veríssimo et al., 2014). It is also necessary to consider the decrease in serum albumin, a known feature of aging, and the increase in α1-acid glycoprotein (Veríssimo et al., 2014). These aspects affect both the pharmacokinetics of cationic/acidic drugs (e.g. NSAIDs), with greater binding to albumin and the reduction of their volume of distribution, like that of anionic/basic drugs (e.g., opioids), which tend to increase their volume of distribution (Katzung, 2004; Petrovic, 2012; Veríssimo et al., 2014).

Regarding metabolism, aging causes a decrease in hepatic blood flow (Katzung, 2004; Petrovic, 2012) and a decrease in enzyme activity

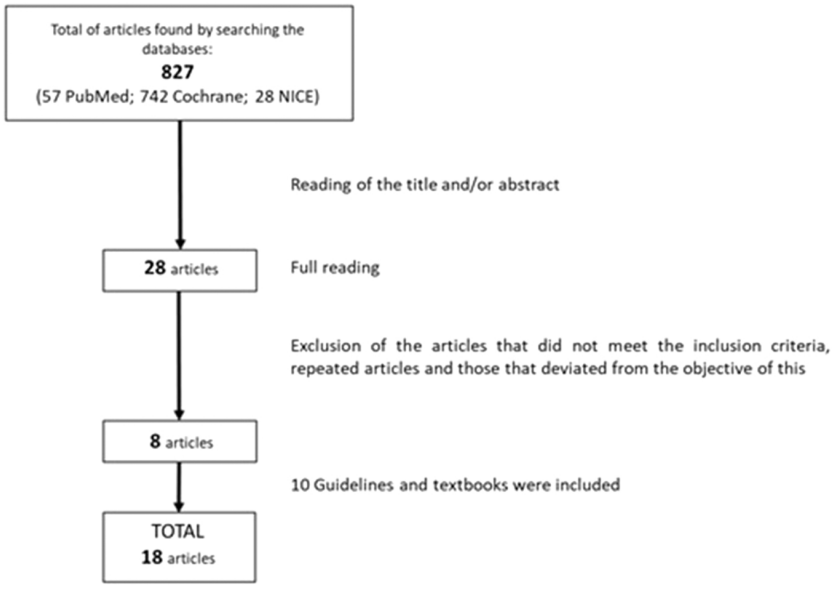

Fig. 1. Graphic representation of the identification process of articles to be included in the review through bibliographical research.

Table 1
Most frequent body changes in aging, which can interfere with pharmacokinetics, Adapted from Katzung, 2004.

Variable	Young adults (20–30 years)	Elderly (60–80 years)
Body Water (% of body weight)	61	53
Lean Mass (% of body weight)	19	12
Adipose Tissue (% of body weight)	26–33 (women) 18–20 (men)	38–45 (woman) 36–38 (men)
Serum albumin (g)	4.7	3.8
Renal function (%)	100	50–60
Liver function (CYP450 activity/phase 1 biotransformation)	100	50–70

involved in oxidation, reduction, and hydrolysis (phase 1 of biotransformation, which includes cytochrome P450 activity) [9]. The activity of enzymes involved in glucuronidation, acetylation, and sulfation (phase 2 of hepatic biotransformation) remains practically unchanged (Petrovic, 2012; Veríssimo et al., 2014). Thus, drugs that undergo phase 1 hepatic metabolism will have an extended duration of action, higher toxicity potential, in addition to presenting greater potential for drug and food interactions [9].

Renal elimination is the most frequently altered pharmacokinetic feature with age (Katzung, 2004). After age 40, the glomerular filtration rate decreases by about 0.75 ml/min/year (Veríssimo et al., 2014), so at age 70, a reduction in renal function of about 50% is expected [4].

Regarding pharmacodynamics, around 20–40% of the elderly will experience adverse drug reactions annually (Bowie, 2007; Veríssimo et al., 2014). The main factors contributing to this high side-effect incidence in the elderly are polymedication, including self-medication, and a greater number of comorbidities, with a change in drug availability/effect due to disease. This change translates into a greater systemic effect, an increased sensitivity to the drug's effect, and altered pharmacokinetics (Bowie, 2007; Katzung, 2004; Veríssimo et al., 2014).

Considering those adverse reactions, drug interactions and side effects are frequent and relevant in the elderly. Therefore, it is important to have instruments that make it possible to avoid them due to their ability to predict the onset. The Beers and START-STOPP criteria (O'Mahoney, 2015) are tools available to help identify potentially inappropriate drug use in the elderly, specifically in the presence of certain health conditions, diseases, or other drugs, thus avoiding consequences that could be disastrous for the elderly (Veríssimo et al., 2014).

To increase adherence to therapy and avoid adverse drug effects, it is essential to respect some prescription rules, namely (Ribeiro et al., 2017):

1. Start with reduced doses and titrate to the lowest effective dose;
2. Wait for three age-adjusted half-lives before increasing the dose;
3. If the therapeutic response does not appear, measure the plasma levels or switch to another drug.

Choosing a specific pharmacological group and, within it, a particular drug should be done by answering a few points in which the reasons for efficacy, the safety data, the convenience of the drug, and its cost should stand out (Ribeiro et al., 2017).

3.2. Mechanism of action and safety profile of different NSAIDs

NSAIDs inhibit cyclooxygenases-1 and − 2 enzymes (COX-1 and COX-2) [13], both responsible for arachidonic acid metabolism that results in the production of prostaglandins and thromboxane (Fig. 2) (Bacchi, 2012).

However, NSAIDs have different affinities with the COX enzyme, conditioning different potential for adverse effects (Baker & Perazella, 2020; Batlouni, 2010; Stanos, 2016).

As shown in Figs. 3 and 4, the preferential inhibition of COX-1 entails greater risks of adverse gastrointestinal (GI) effects due to the constitutive presence of this enzyme in the gastroduodenal muscle. On the other hand, the preferential inhibition of COX-2 holds greater risks of adverse cardiovascular effects (CV), essentially due to the higher concentration of this enzyme in the vascular endothelium of the kidney, which leads to the inhibition of prostaglandin production, essentially at a tubular or glomerular level, compromising the GFR and contributing to greater sodium retention, edema, thus contributing to heart and kidney failure [1,5,15]. Fig. 5 depicts the main effects of NSAIDs on the kidney (Baker & Perazella, 2020).

Table 2 identifies the main adverse effects of NSAIDs by NSAID

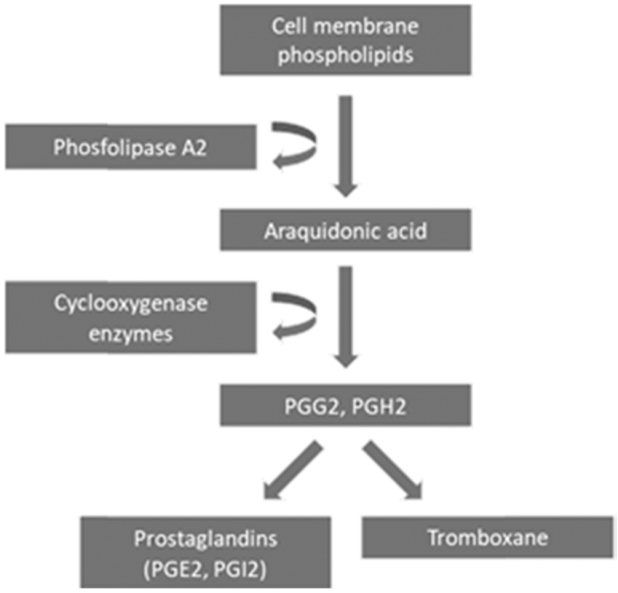

Fig. 2. Bacchi et al., 2012). Abbreviation: PGG, Prostaglandin G2; PGH2, Prostaglandin H2; PGE2, Prostaglandin E2; PGI2, Prostaglandin I2.
Breakdown of arachidonic acid into prostaglandins and thromboxane (adapted from S.

"subclass" (Bacchi, 2012; Wongrakpanich, 2018).

The separation of NSAIDs into "subclasses" as shown in Table 2 is not consensual (INFARMED, 2021; Katzung, 2004; [10]). However, this separation helps us understand the consequences that may result from the differences in the mechanism of action of various NSAIDs, however slight.

Regarding pharmacokinetics, NSAIDs have different profiles, as shown in Table 3.

All NSAIDs directly and indirectly impact the gastrointestinal (GI) mucosa (Tai & McAlindon, 2018). It is believed that NSAID prodrugs (acemethacin) may have a less direct impact, although further studies are needed to support existing evidence (DrugBank, 2021; [6,12,14]).

Regarding distribution, fat-soluble NSAIDs, such as ibuprofen, acemethacin, and naproxen, have longer half-lives in patients with more adipose tissue, such as the obese and elderly. Regarding water-soluble NSAIDs (diclofenac, etodolac, and etoricoxib), patients with less body water may have a greater potential for toxicity (DrugBank, 2021; [4]).

Looking at metabolism, the only NSAID, among those studied here, that presents phase 2 metabolism is acemethacin (DrugBank, 2021).

Regarding elimination, the drugs with less renal excretion are, in ascending order of percentage of drug excreted by the urinary system: 1-acemethacin; 2- diclofenac; 3- etodolac; 4- etoricoxib; 5- ibuprofen; 6-naproxen (DrugBank, 2021).

A randomized controlled clinical trial involving 24081 patients demonstrated that naproxen and ibuprofen do not have a better cardiovascular safety profile than COX-2 selective NSAIDs, suggesting that non-selective NSAIDs do not have a better cardiovascular safety profile compared to COX-selective 2 NSAIDs. (Nissen et al., 2016). In this study, naproxen exhibited no cardioprotective effect, with a 25% higher mortality rate due to CV disease in the group taking naproxen. Ibuprofen had the highest rate of CV events, with the highest relative risk of major CV events. It was also observed that the risk for GI events was significantly lower with celecoxib compared to naproxen, even with a proton pump inhibitor (PPI). The risk of renal events associated with ibuprofen was significantly higher (64%); than that observed with celecoxib. Globally, naproxen and ibuprofen showed a higher risk for CV, GI, and renal

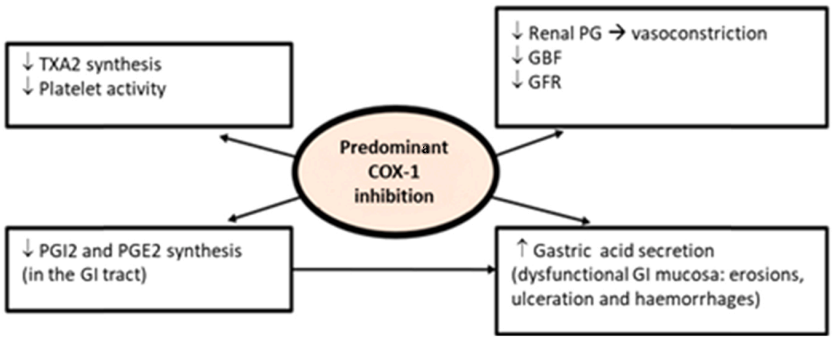

Fig. 3. Abbreviation: TXA2, Thromboxane A2; PG, Prostaglandin; PGI2, Prostaglandin I2; PGE2, Prostaglandin E2; GBF, Glomerular blood flow; GI, gastrointestinal.
Consequences of the predominant inhibition of COX-1 (adapted from Batlouni, 2010).

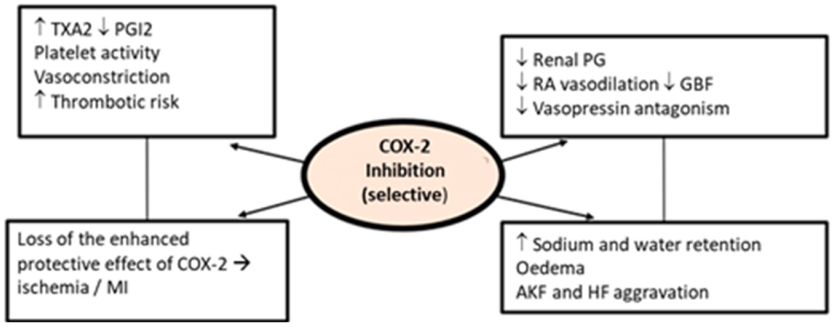

Fig. 4. Abbreviation: TXA2, Thromboxane A2; PG, Prostaglandin; PGI2, Prostaglandin I2; RA, Renal arteriole; GBF, glomerular blood flood; MI, myocardial infarction; AKF, Acute kidney failure; HF, Heart failure.
Consequences of the predominant inhibition of COX-2 (adapted from Batlouni, 2010).

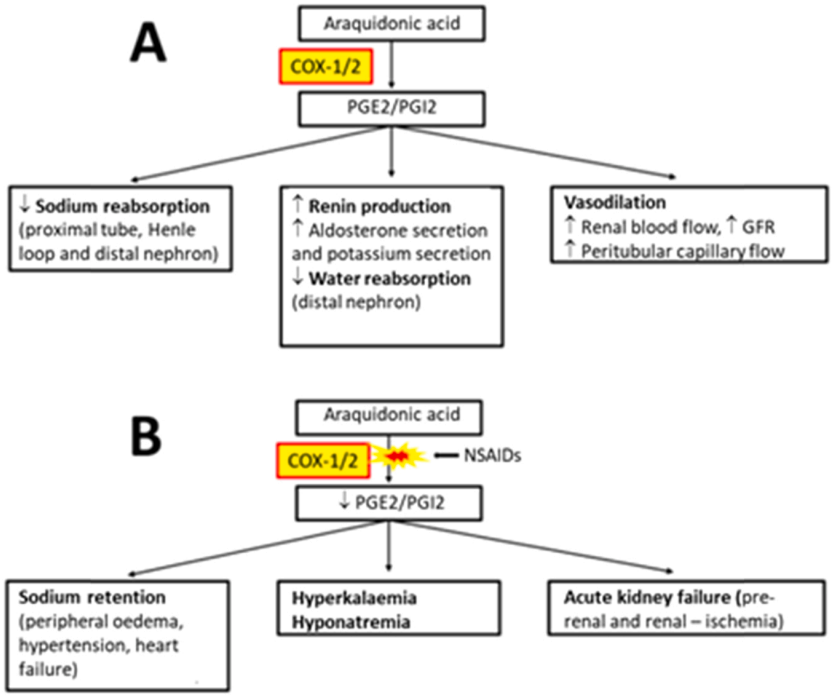

Fig. 5. 2020). Abbreviation: PGE2, Prostaglandin E2; PGI2, Prostaglandin I2; GFR, Glomerular Filtration Rate.
Prostaglandins and the kidney – A: physiological effect of PGE2 and PGI2; B: Effect of NSAIDs (adapted from Baker M, Perazella MA.

Table 2
Main adverse effects of NSAIDs by drug class, Adapted from S. Bacchi., et al., 2012 and Wongrakpanich S., et al., 2018.

Drug class	Drug	Clinical use	Adverse effects
Selective COX-1 inhibitors	Acetylsalicylic acid	antiplatelet	Gastrointestinal problems; bleeding; pulmonary, hematological and cutaneous problems (+++); cardiovascular problems (—)
Non-selective COX inhibitors	Piroxicam, indometacin, diclofenac, ibuprofen	inflammation	Gastrointestinal problems; bleeding; pulmonary, hematological and cutaneous problems (++); cardiovascular problems (–)
Selective COX-2 inhibitors	Meloxicam, etodolac, naproxen, nimesulide	inflammation	Gastrointestinal problems; bleeding; pulmonary, hematological and cutaneous problems (-); cardiovascular problems (+)
Highly selective COX-2 inhibitors	Celecoxib, etoricoxib	inflammation	Gastrointestinal problems; bleeding; pulmonary, hematological and cutaneous problems (—); cardiovascular problems (+++)

events than celecoxib.

Baly, et al. (2017) demonstrated, in a meta-analysis of individual data from Canadian and European databases, with a sample of 446,763 patients, that there was a general increase of 20–50% in acute myocardial infarction (AMI) in individuals taking NSAIDs (diclofenac, ibuprofen, naproxen, celecocib, rofecoxib). In this study, the greatest probability of increased risk was found with ibuprofen and naproxen (75%). Short-term use (8–30 days), as well as the use of higher doses of NSAIDs, showed the greatest increase in risk (doses: diclofenac > 100 mg; ibuprofen > 1200 mg; naproxen > 750 mg), (Bally et al., 2017). These results are in line with what would be expected due both to the mechanism of action and the pharmacokinetic profile of the analyzed drugs (Bruno A, 2014; DrugBank, 2021; INFARMED, 2021; Katzung, 2004).

4. Discussion

Although COX-2 selective NSAIDs are often considered to have a greater potential for CV adverse effects and some guidelines assume that naproxen is the NSAID with the best CV safety profile, current evidence demonstrates that naproxen has a worse safety profile than COX-2 selective NSAIDs (level of evidence 1) (Bally et al., 2017; DrugBank, 2021; Li, 2020; Nissen et al., 2016; [7]).

According to the pharmacokinetic profiles, we can assume that doses should be administered more sparingly in time for fat-soluble NSAIDs (ibuprofen, acemetacin, and naproxen) both elderly and obese patients,

Table 3
Pharmacokinetic characteristics of NSAIDs, (Drugbank; Pharmgkb, INFARMED 2021).

Pharmacokinetics	Diclofenac	Ibuprofen	Acemethacina	Naproxen	Etodolac	Celecoxib
Absorption	Gastroduodenal	Gastroduodenal	Gastroduodenal	Gastroduodenal	Gastroduodenal	Gastroduodenal
Distribution	Albumin (99%) Hydrosoluble	Albumin (99%) Liposoluble	Albumin (87,6%) Liposoluble	Albumin (99%) Liposoluble	Albumin (99%) Hydrosoluble	Albumin (99%) Hydrosoluble
Metabolism	Phase I e II	Phase I	Phase II	Phase I e II	Phase I e II	Phase I e II
Elimination	Renal 60% Fecal 40%	Renal 90% Fecal 10%	Renal 40% Fecal 60%	Renal 95% Fecal 5%	Renal 70% Fecal 30%	Renal 80% Fecal 20%

due to the expected extended duration of action of these NSAIDs. On the other hand, water-soluble NSAIDs (diclofenac, etodolac, and etoricoxib) should maintain the recommended rate of administration, although with a reduction in the dose suggested in the summary of the product's characteristics (SPC), due to the lower toxicity threshold seen in the elderly (strength of recommendation B) (Bacchi, 2012a; Bowie, 2007; DrugBank, 2021; Katzung, 2004; Petrovic, 2012; Ribeiro et al., 2017; Wongrakpanich, 2018; [4,9]).

Regarding metabolism, in polymedicated patients, elderly patients, and patients with chronic alcohol abuse, NSAIDs with the best safety profile will be those with phase 2 hepatic biotransformation, such as acemetacin and diclofenac (strength of recommendation C) (DrugBank, 2021; Fura, 2006; Guengerich, 2003; Wilkinson, 2005; Wongrakpanich, 2018; [3,9,11]).

As for the elimination process, the NSAIDs with the best safety profile will be those with lower renal excretion, such as acemethacin, etodolac, and diclofenac (strength of recommendation B) (Baker & Perazella, 2020; Batlouni, 2010; Bowie, 2007; DrugBank, 2021; Nissen et al., 2016; Petrovic, 2012; Wongrakpanich, 2018).

In conclusion, we can say that greater knowledge concerning a drug's pharmacological features is essential for a physician to uphold safer therapeutic choices. It also means knowing and taking into account the patient's individual features, including anthropomorphic data (biotype, weight, fat mass/mass lean); liver and kidney function; personal history; usual medication; physical, nutritional, mental, cognitive, and functional assessment, all as complete as possible.

Pharmacokinetic data should support therapeutic decision-making, namely because they help make decisions based on safety, in addition to efficacy.

In the case of NSAIDs, if no NSAID stands out for having greater efficacy, safety profiles must be carefully considered before making a therapeutic decision, always considering the type of pain eliciting treatment and individual patient features. Overall, when comparing NSAIDs, differences in pharmacokinetics and pharmacodynamics are obvious. In the absence of prospective randomized studies, drug choice can be guided by these parameters, bearing in mind risks imposed by drug-drug interactions, advanced age, organ impairment, dosage, formulation, protein binding, therapeutic half-life, and other clinically relevant pharmacological features. Current data allows NSAID prescriptions to be tailored according to specific patient needs, improving not only therapeutic outcomes but, above all, minimizing the iatrogenic risk.

More studies are needed in this area, namely controlled and randomized clinical trials that allow us to assign higher levels of evidence and strengths of recommendation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Hugo Ribeiro, Conceptualization; Data curation; Formal analysis, Investigation; Methodology; Project administration, original draft; Writing – review & editing. **Inês Rodrigues:** Investigation; Methodology; Project administration. **Leonardo Napoleão:** Investigation; Methodology; Project administration. **Luís Lira:** Investigation; Methodology; Project administration. **Denise Marques:** Supervision; Validation; Visualization. **Manuel Veríssimo:** Supervision; Validation; Visualization. **José Paulo Andrade:** Writing – original draft; Writing – review & editing. **Marília Dourado:** original draft; Writing – review & editing.

Conflict of interest statement

Denise Marques is employee of Bial. Other authors have no conflicts of interest to declare.

Data availability

No data was used for the research described in the article.

References

[1] A. Arfè, L. Scotti, C. Varas-Lorenzo, F. Nicotra, A. Zambon, B. Kollhorst, T. Schink, E. Garbe, R. Herings, H. Straatman, R. Schade, M. Villa, S. Lucchi, V. Valkhoff, S. Romio, F. Thiessard, M. Schuemie, A. Pariente, M. Sturkenboom, G. Corrao, Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study, BMJ (2016) i4857, https://doi.org/10.1136/bmj.i4857.

[2] L.J. Crofford, Use of NSAIDs in treating patients with arthritis, Arthritis Res. Ther. 15 (S3) (2013) S2, https://doi.org/10.1186/ar4174.

[3] N.M. Davies, N.M. Skjodt, Choosing the right nonsteroidal anti-inflammatory drug for the right patient, Clin. Pharmacokinet. 38 (5) (2000) 377–392, https://doi.org/10.2165/00003088-200038050-00001.

[4] D. Fialová, B. Laffon, V. Marinković, L. Tasić, P. Doro, G. Sóos, J. Mota, S. Dogan, J. Brkić, J.P. Teixeira, V. Valdiglesias, S. Costa, Medication use in older patients and age-blind approach: narrative literature review (insufficient evidence on the efficacy and safety of drugs in older age, frequent use of PIMs and polypharmacy, and underuse of highly beneficial nonpharmacological strategies), Eur. J. Clin. Pharmacol. 75 (4) (2019) 451–466, https://doi.org/10.1007/s00228-018-2603-5.

[5] B.R. Gunter, K.A. Butler, R.L. Wallace, S.M. Smith, S. Harirforoosh, Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis, J. Clin. Pharm. Ther. 42 (1) (2017) 27–38, https://doi.org/10.1111/jcpt.12484.

[6] P. Halen, P. Murumkar, R. Giridhar, M. Yadav, Prodrug designing of NSAIDs, Mini-Rev. Med. Chem. 9 (1) (2009) 124–139, https://doi.org/10.2174/138955709787001695.

[7] T.M. MacDonald, C.J. Hawkey, I. Ford, J.J.V. McMurray, J.M. Scheiman, J. Hallas, E. Findlay, D.E. Grobbee, F.D.R. Hobbs, S.H. Ralston, D.M. Reid, M.R. Walters, J. Webster, F. Ruschitzka, L.D. Ritchie, S. Perez-Gutthann, E. Connolly, N. Greenlaw, A. Wilson, I.S. Mackenzie, Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT), Eur. Heart J. (2016) ehw387, https://doi.org/10.1093/eurheartj/ehw387.

[8] Market research data. Report published online by AMR on Jun 2021. ⟨https://www.alliedmarketresearch.com/anti-inflammatory-therapeutics-market⟩. Last accessed on Dec.2021. (n.d.).

[9] P.H. Novaes, D.T. da Cruz, A.L.G. Lucchetti, I.C.G. Leite, G. Lucchetti, The "iatrogenic triad": polypharmacy, drug–drug interactions, and potentially inappropriate medications in older adults, Int. J. Clin. Pharm. 39 (4) (2017) 818–825, https://doi.org/10.1007/s11096-017-0470-2.

[10] J.-P. Pelletier, J. Martel-Pelletier, F. Rannou, C. Cooper, Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: evidence from real-life setting trials and surveys, Semin. Arthritis Rheum. 45 (4) (2016) S22–S27, https://doi.org/10.1016/j.semarthrit.2015.11.009.

[11] Pharmacological Management of Persistent Pain in Older Persons, J. Am. Geriatr. Soc. 57 (8) (2009) 1331–1346, https://doi.org/10.1111/j.1532-5415.2009.02376.x.

[12] A. Qandil, Prodrugs of nonsteroidal anti-inflammatory drugs (NSAIDs), more than meets the eye: a critical review, Int. J. Mol. Sci. 13 (12) (2012) 17244–17274, https://doi.org/10.3390/ijms131217244.

[13] P. Rao, E.E. Knaus, Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond, J. Pharm. Pharm. Sci. 11 (2) (2008) 81, https://doi.org/10.18433/J3T886.

[14] S. Sehajpal, D.N. Prasad, R.K. Singh, Prodrugs of non-steroidal anti-inflammatory drugs (NSAIDs): a long march towards synthesis of safer NSAIDs, Mini-Rev. Med. Chem. 18 (14) (2018) 1199–1219, https://doi.org/10.2174/1389557518666180330112416.

[15] K.B. Sondergaard, P. Weeke, M. Wissenberg, A.-M. Schjerning Olsen, E.L. Fosbol, F. K. Lippert, C. Torp-Pedersen, G.H. Gislason, F. Folke, Non-steroidal anti-inflammatory drug use is associated with increased risk of out-of-hospital cardiac arrest: a nationwide case–time–control study, Eur. Heart J. - Cardiovasc. Pharmacother. (2016) pvw041, https://doi.org/10.1093/ehjcvp/pvw041.

[16] S.K. Suthar, M. Sharma, Recent developments in chimeric NSAIDs as safer anti-inflammatory agents, Med. Res. Rev. 35 (2) (2015) 341–407, https://doi.org/10.1002/med.21331.

[17] J.L. Wallace, P. del Soldato, The therapeutic potential of NO-NSAIDs, Fundam. Clin. Pharmacol. 17 (1) (2003) 11–20, https://doi.org/10.1046/j.1472-8206.2003.00125.x.

[18] B.J.R. Whittle, Gastrointestinal effects of nonsteroidal anti-inflammatory drugs, Fundam. Clin. Pharmacol. 17 (3) (2003) 301–313, https://doi.org/10.1046/j.1472-8206.2003.00135.x.