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Review Article

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A Review of Over-The-Counter Analgesics: Efficacy and Safety Profile

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Abstract

Chronic pain is a major health problem that affects more than 100 million adults in the US. A variety of over-the-counter (OTC) pain medications are available to patients, and they are typically broken down into two broad categories: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).

Acetaminophen is one of the most consumed OTC since its introduction due to its cost effectiveness and safety when adhered to recommended doses and uses. However, in significantly larger doses, acetaminophen can cause serious adverse effects such as: upper GI hemorrhage, acute renal failure, and acute liver failure.

NSAIDs exert their anti-inflammatory and analgesic properties via the inhibition of the enzyme cyclooxygenase (COX) isoforms. Hence, NSAIDs are classified into nonselective NSAIDs inhibiting both COX-1 and COX-2 such as ibuprofen, naproxen, diclofenac, and selective COX-2 inhibitors such as celecoxib. Despite their effectiveness, NSAIDs are associated with serious adverse events with chronic use including, gastrointestinal, cardiovascular and renal effects.

The purpose of this article is to review the efficacy and the safety profile of most popular OTC analgesics, and to provide general recommendations and preventive strategies aiming to reduce the risks and help choosing the appropriate agent.

Introduction

Acute and chronic pains are among the most frequent reasons for physician visits, and taking medications. Chronic pain is a major health problem and a leading cause of adult disability in the United States, affecting more than 100 million adults [1]. It imposes a significant financial burden and can negatively affect the quality of life, daily functioning, and productivity [1,2].

Osteoarthritis is one of the most prevalent forms of arthritis and is the primary cause of functional impairment in the elderly [3]. Osteoarthritis is characterized by the loss of articular cartilage, bone hypertrophy, crepitus, and radiographic changes [4]. The joints most commonly affected are the knee, hip, spine, and hands. Joint pain, stiffness, and swelling are the major symptoms that tend to worsen with activity. According to a recent national survey, osteoarthritis affects approximately 27 million people in the United States with an annual medical cost of 185.5 billion dollars [5].

While there are numerous therapeutic options to treat pain, many patients will first turn to over-the-counter medications (OTC) to seek relief. There are a variety of OTC pain medications that are available to patients, and they are typically broken down into two broad categories: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Because of their analgesic effect and overall safety, these agents are used to treat a large number of different disorders such as: headache, osteoarthritis, rheumatoid arthritis, gout, and dysmenorrhea etc. However, available OTC, while safe if used correctly, are not risk-free and can be associated with potentially serious side effects. Acetaminophen has been shown to cause liver damage in large doses and NSAIDs are associated with varying degrees of gastrointestinal, renal, and cardiovascular adverse events. The purpose of this article is to review the efficacy and the safety profile of popular OTC analgesics for the treatment of osteoarthritis.

Acetaminophen

Acetaminophen is one of the most widely consumed pain relievers in the world since its introduction in 1955 [6]. The mechanism of action remains unclear. However, recent studies suggest that it may involve prostaglandin inhibition in the central nervous system (CNS). Due to its low cost and ease of access, it is one of the first classes of drugs used for temporary relief of minor aches and pains due to arthritis, muscular injury, back pain, menstrual cramps, colds, headache, toothache, and for the temporary reduction of fever [3].

Dosing and Availability

Acetaminophen was universal in most households after 1960 when it became available as an OTC agent. (6) Adult OTC doses available are 325mg, 500mg, and 650mg and can be taken every 4

to 6 hours; current recommendations limit doses to 4g in a 24 hour period [6]. Acetaminophen formulations are available as immediate release agents and in 1994 became available as an extended (sustained) release formulation that allows for decreased interval dosing and a possible increase in compliance [7]. There currently exists a discrepancy between the FDA and the manufacturer on the maximum daily dosage recommend for patients. In 2011, McNeil, the manufacturer of Tylenol, modified the current label to allow for a maximum dose of 8g in 24 hours, but this was not mandated by FDA, which still recommends a limit of 4g in a 24 hour period [8,9].

Efficacy

Acetaminophen is an effective agent and is often the first line treatment for patients with osteoarthritis [3]. Numerous studies have shown its superior efficacy compared to placebo for the treatment of chronic pain associated with moderate to severe osteoarthritis. Altman et al. and Prior et al. demonstrated that 3900mg (1300mg every 8 hours) was the most efficacious dose with minimal side effects [3,4]. Both studies were randomized, double-blind, placebo-controlled trials that enrolled 483 and 542 patients respectively. Each study randomized patients to either acetaminophen or placebo. The primary endpoints for both studies were the Western Ontario and McMaster Universities Arthritis Index (WOMAC) physical function subscale score, patient's global assessment of response to therapy, and WOMAC pain subscale scores[3,4]. The WOMAC is a standardized questionnaire used by researchers to assess the severity of patient's pain, stiffness or physical functioning [10].

Adverse Effects

Acetaminophen has an extremely good safety profile if a maximum 4g daily dosage is not exceeded [11]. In significantly larger doses OTC (generally greater than 10g or 200mg/kg in a day for adults) acetaminophen can cause serious adverse effects such as: upper GI hemorrhage, acute renal failure, and acute liver failure [12]. Acetaminophen at doses greater than 2g daily has been shown to have only a small increased relative risk of 1.3 of upper GI injury [13]. More data and prospective studies are needed to more definitively elucidate the relative risk of upper GI complications with acetaminophen. The etiology and mechanism are unclear. However, a possible mechanism may be via inhibition of a COX is form [14]. The mechanism of acetaminophen-induced acute tubular necrosis (ATN) is unclear but theories suggest it may be secondary to toxic metabolites accumulating when liver or kidney glutathione stores are depleted [15]. Acetaminophen has been associated with acute kidney injury (AKI) with 2% of overdoses (with 4-hour post-ingestion concentrations of greater than 150mg/L or 200mg/L) [16]. However, most studies indicate that acetaminophen is safer than other OTC analgesics, such as NSAIDs when considering upper GI hemorrhage and renal failure risks [17]. According to a recent study, acetaminophen had the lowest relative risk for GI, renal, and liver failure with 35 deaths per one million patients when compared against ibuprofen (64 deaths per one million people) and naproxen (118 deaths per one million people) [12,17].

Metabolism and Toxicity

Acetaminophen is metabolized (greater than 90%) by the liver, and after conjugation with sulfate and glucuronide, the metabolites are excreted in the urine [16,18]. The remaining acetaminophen is metabolized by cytochrome P450 (CYP2E1, CYP1A2, CYP3A4) which produces the highly toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). Under normal circumstances, the small amount of NAPQI produced is quickly converted to nontoxic metabolites via glutathione. Hepatic injury and possibly renal injury can occur when the hepatic glucuronidation and sulfation pathway is saturated, and toxic metabolites accumulate via the P450 pathway (see attached figure below). Any state that causes a depletion of intrinsic glutathione stores or production of more NAPQI is a risk factor for hepatotoxicity. Risk factors that predispose patients to hepatotoxicity are acute or chronic overdoses, advanced age, chronic alcohol use, malnutrition, p450 polymorphisms, and potential drug-drug interactions. Specific drugs that increase p450 enzymes are anticonvulsants (Carbamazepine, phenytoin, and phenobarbital) and antituberculosis (isoniazid and rifampin) medications. Unlike other OTC agents, acetaminophen toxicity has a specific treatment which is N-acetylcysteine, and it should be administered without delay if a significant overdose has occurred [18].

Hepatotoxicity can range from mild AST and ALT elevations to fulminant hepatic failure. In a retrospective study, over 1,530 acetaminophen-treated patients were evaluated from nine different osteoarthritis studies to assess the frequency and magnitude of AST and ALT elevations. Two studies were excluded due to lack of ALT data. The remaining 1,197 patients were further decreased to 1,039 patients with the added requirement of AST and ALT baseline values and ALT values at each additional visit after starting therapy. Patients consisted of mostly white females who were an average age of 60.8 with a mean BMI of 81.8. Out of the 1039 patients analyzed, only 181 (17.4%) had an ALT greater than the upper limit of reference range (ULRR). One hundred and thirty-nine of these patients underwent repeat ALT testing, of which 128 (92.1%) exhibited resolution of ALT levels. Of the original 181 patients that had an ALT greater than ULRR, 44 patients had an ALT 1.5 times greater than ULRR however, only 31 patients had repeat ALT after elevations and 29 (93.5%) showed resolution or decreasing values. Interestingly, 10 out of the 44 had ALT levels three times greater than ULRR and only 8 had repeat ATL after elevation and all 8 (100%) demonstrated decreasing ALT or resolution of elevation [19]. Thus this study demonstrates the superior safety profile of acetaminophen and highlights that the side effects are mild and transient.

In a more recent prospective, double-blind, randomized, multicenter trial, acetaminophen was demonstrated to be generally well tolerated for osteoarthritis of the knee or hip for periods of up to 12 months. Temple et al. randomized 2 groups with over 290 patients receiving acetaminophen 4g daily and 291 patients receiving naproxen 750 mg daily. This study demonstrated no hepatic failure or dysfunction, no AST or ALT greater than 2x ULRR, or creatinine greater than 1.5 ULRR in either group [11].

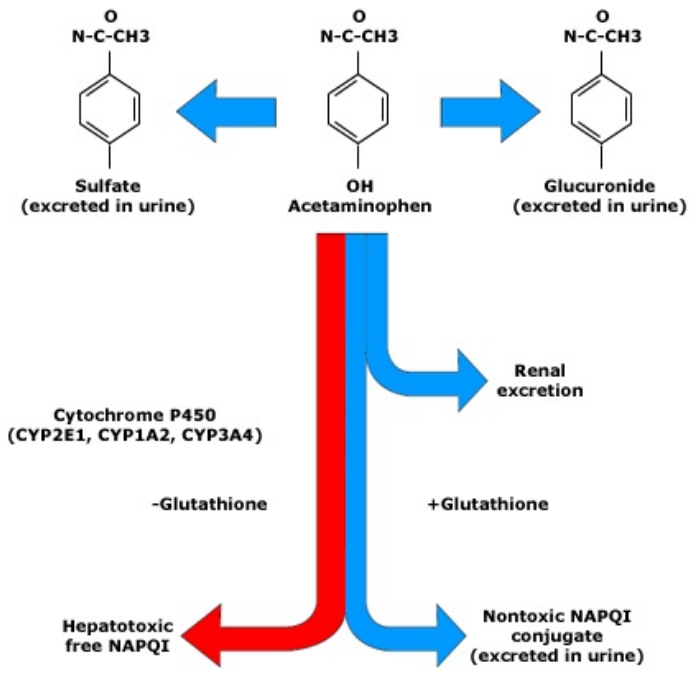

Figure 1: Metabolism of acetaminophen.

This figure displays acetaminophen metabolism by the major pathway of glucuronidation and sulfation. Metabolism is secondarily achieved by the minor pathway of cytochrome p450 that can produce the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) in the presence of glutathione depletion or exhaustion [20].

Nsaids

Mechanism of Action

NSAIDs have both anti-inflammatory and analgesic properties with the main mode of action being inhibition of the enzyme cyclooxygenase (COX) [21]. COX mediates the conversion of arachidonic acid to prostaglandin (PG) G2 and then to PGH2 which will eventually be transformed via tissue-specific isomerases into various prostanoids (PGD2, PGE2, PGF2α, PGI2, and thromboxane A2) that interact with different receptors leading to various effects. COX has two isoforms (COX-1 and COX-2), serving different functions [22-24].

In general, COX-1 is constitutively expressed in many tissues and is involved in gastroprotection and thromboxane (TX) formation by platelets. In contrast, COX-2 is induced in response to inflammatory stimuli and has been associated with inflammation and pain [22,25]. Hence, NSAIDs are classified into traditional nonselective NSAIDs inhibiting both COX-1 and COX-2 such as ibuprofen, indomethacin, naproxen, diclofenac, and the selective COX-2 inhibitors known as "coxibs" as demonstrated by celecoxib. Due to these differences in inhibition, there are different therapeutic effects and potential side effects.

NSAIDs can be chemically classified into different groups:

- Acetic acids: indomethacin, diclofenac;
- Propionic acids (profens): ibuprofen, ketoprofen, naproxen;
- Anthranilic acids (fenamates): mefenamic acid;
- Enoloic acids (oxicams): lornoxicam, piroxicam, meloxicam;
- Coxibs: celecoxib, valdecoxib, etoricoxib [26].

Availability and Dosage

Some of the COX nonspecific NSAIDs are currently available as OTC (i.e. ibuprofen and naproxen), whereas coxibs and most of the nonselective agents, can be obtained by prescription only. Various brand names and formulations of OTC NSAIDs are available on the market. Different formulations (i.e. salts) of the drugs and solubilized forms may enhance efficacy since changes in preparation can affect the absorption, and hence the onset and duration of analgesia [26,27]. Higher doses have a faster onset, higher peak effect and longer duration. In addition, the longer the half-life, the slower the onset [27]. For adults, OTC Ibuprofen is available in 200 and 400 mg preparations taken every 4-6 hours with a maximum daily dose of 1,200 mg per 24 hours. The approved OTC naproxen sodium dose is 220 mg every 8-12 hours with the total dosage not to exceed 660 mg/day [27].

Analgesic Efficacy of Nsaids

The use of NSAIDs in acute or chronic pain conditions have been demonstrated to be effective compared to placebo in a variety of studies [28,29]. The Oxford League Table is a comparison of the effects of different analgesics in acute pain, constructed by the Oxford Pain Group from a number of systematic reviews of randomized and double-blinded studies in patients with moderate to severe pain following different procedures [30]. The efficacy of various analgesics is presented using the number of patients who need to receive the drug to achieve at least 50% pain relief compared with placebo over a 4 to 6 hour treatment period [31] (Figure 2).

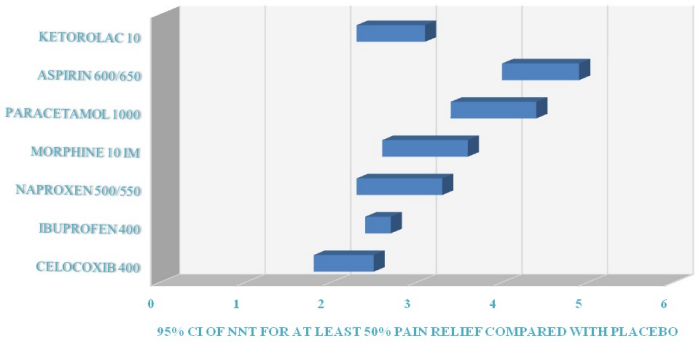

Figure 2: 2007 Oxford League table showing 95% confidence intervals (CI) for the number needed to treat (NNT) for at least 50% pain relief [30].

In certain circumstances, as a group, NSAIDs can be more efficacious than intramuscular morphine for acute pain however; individual NSAIDs differ in their analgesic efficacy [27,29,30]. There is some controversy regarding the individual comparison of different NSAIDs used in chronic pain conditions, and there is no consensus about which NSAID has superior efficacy [27].

Adverse Effects of Nsaids

Despite their effectiveness, NSAIDs are associated with serious

adverse events with chronic use including, gastrointestinal bleeding as well as cardiovascular and renal effects. Many factors may contribute to the occurrence of adverse effects such as dose, duration of use, selectivity for COX isoforms and drug–drug interactions between the NSAID and concomitant medications. Therefore, consideration of these factors is important when assessing the safety profile of NSAIDs and the risk of potential adverse events [27].

OTC NSAIDs are typically used in lower doses and shorter durations than prescription NSAIDs thus, users of these products are not routinely monitored for adverse effects by health care providers, which in some ways may put them at increased risk. Large-scale randomized controlled trials and meta-analyses have shown that the side effect profiles of OTC ibuprofen (≤1200 mg/day) and naproxen (≤660 mg/day) are no different than that of acetaminophen for short-term use [32,33].

Risk factors for different adverse events in general include: [25].

- Age ≥65 years
- Serious comorbid medical conditions
- Use of high NSAID doses
- Long duration of treatment

Gastrointestinal Risk of Nsaids

As a class, NSAIDs are often associated with gastrointestinal (GI) injuries that range from minor erosions to more serious ulcers, which can result in complications including hemorrhage, perforation, and obstruction [34]. Different mechanisms for NSAID-induced GI lesions have been suggested. PGE2 and PGI2 help protect the GI tract by stimulating epithelial proliferation, increasing mucosal blood flow by vasodilation, and promoting the secretion of mucus and bicarbonate. Therefore, by inhibiting these prostanoids, NSAIDs affect the upper GI tract by decreasing its mucosal blood flow and make it more susceptible to injury. Some NSAIDs, being weak acids, produce direct epithelial damage by contact with the GI mucosa [35]. In addition, blocking TXA2 production through COX-1 inhibition will increase any active GI bleeding [36].

The risk for gastrointestinal side effects increases in the following conditions: [25].

- Patients with a history of previous peptic ulcer disease or upper GI bleeding
- Patients taking corticosteroids and/or selective serotonin reuptake inhibitors
- Patients taking antiplatelet therapy (e.g., aspirin, clopidogrel) and other anti-coagulants
- Concomitant Helicobacter pylori infection
- Cigarette smoking
- Alcohol consumption

COX-1 is involved in gastric cytoprotection and COX-2 selective agents tend to show less GI toxicity, (34) however, NSAIDs in general inhibit both COX-1 and COX-2 to varying degrees [34,37-39]. This selectivity can be determined in vitro (using human whole blood assays and assessing the potency to inhibit COX-1 and COX-2 by 50%, i.e., IC50) and ex vivo (i.e., after drug administration, depending on the dose [25,40-42]. Ibuprofen and naproxen are more selective for COX-1, while diclofenac and celecoxib are more potent at inhibiting COX-2 [25].

A 2012 meta-analysis of a number of observational studies demonstrated a low risk of upper GI complications (relative risk [RR] <2) for celecoxib and ibuprofen, and, intermediate to high risk (RR 2–5) for diclofenac, ketoprofen and naproxen, with the highest risk (RR >5) being shown for ketorolac and piroxicam [38]. A number of meta-analyses of large-scale published randomized clinical trials concluded that the "coxibs" carry a significantly lower risk of GI complications compared to nonselective NSAIDs [43,44]. In the Celecoxib Long-Term Arthritis Safety Study (CLASS), patients treated with celecoxib at doses higher than those indicated clinically, had a significantly lower incidence of upper GI complications compared to those treated with nonselective NSAIDs at standard dosages (Incident rates were 0.44 vs. 1.27%; $p = 0.04$) provided they were not taking aspirin [41,45]. The concomitant use of proton pump inhibitors (PPIs), such as omeprazole, is an advisable prevention strategy, especially in patients with risk factors shown by different epidemiological studies due to the fact that PPIs suppress gastric acid secretion [46,47].

Cardiovascular Risks of Nsaids

It was not until COX-2 inhibitors were introduced into clinical practice that the risk of NSAIDs-associated cardiovascular (CV) adverse events was truly appreciated [48]. COX-2 selective, and most non-selective NSAIDs, have been associated with a small but absolute risk of CV complications such as: hypertension, myocardial infarction, heart failure, stroke and death, even in patients with no known CV disease [49-51]. This risk appears to be mainly associated with a PGI2/TXA2 imbalance which seems to occur through the inhibition of COX-2-dependent PGI2 (prostacyclin) production leaving COX-1 unopposed, causing an increase in TXA2 [27]. When the physiological roles of these agents are considered, it becomes somewhat clear why an issue may occur, PGI2 has a cardioprotective role in inhibiting platelet aggregation and promoting vasodilation, while TXA2 is proaggregatory and vasoconstrictive.

A 2013 meta-analysis of data, including over 300,000 patients from more than 600 randomized trials, demonstrated the magnitude of CV events by comparing nonselective NSAIDs, selective NSAIDs, and placebo [52]. It was found that major cardiovascular events were significantly higher with high-dose diclofenac (adjusted rate ratio [ARR] 1.41) and with the coxibs (ARR 1.37), compared to placebo. The use of high-dose ibuprofen was associated with an increase in major coronary events (ARR 2.22), whereas high-dose naproxen did not significantly increase major cardiovascular events (ARR 0.93) [52]. It has been suggested that the reason naproxen might have differentiated itself is due to its potent COX-1 inhibition and long half-life, resulting in sustained prevention of

platelet aggregation at therapeutic doses [51,53].

As with many other adverse events, the CV risk increases with increasing doses and duration of treatment. (41) Additionally, the CV risk of NSAID may also be associated with reduced sodium excretion resulting from COX-2 inhibition in the kidneys which leads to fluid retention, increased preload, and hypertension [26,29].

The U.S. Food and Drug Administration (FDA) requires a black boxed warning regarding the potentially serious adverse CV events for all COX-2 drugs and prescription non-selective NSAIDs [54]. There is insufficient evidence to support claims of actual cardiovascular risk with the use of OTC NSAIDs.

Risk factors for CV events include a history of hypertension, heart failure, unstable angina, myocardial infarction, and recent cardiac bypass surgery or stent placement.

Preventive strategies have been suggested for patients at risk in order to reduce CV risks such as:

- Careful monitoring of blood pressure and tight blood pressure control.
- Avoid using NSAIDs within 3 to 6 months of an acute cardiovascular event or procedure.

Renal Risk of Nsaids

NSAIDs assert their action at the kidney by reducing prostaglandin synthesis through inhibiting COX-1, which is involved in renal hemodynamics and glomerular filtration, and COX-2, which mediates salt and water excretion [26,55]. Renal toxicity is an uncommon adverse event for all NSAIDs. Their use has been associated with sodium retention leading to peripheral edema and increased blood pressure, weight gain, hyperkalemia, and acute renal failure [26]. Patients on NSAIDs have been shown to develop hyporeninemic hypoaldosteronism that can lead to type IV renal tubular acidosis [26].

Acute renal failure is a serious adverse event that is attributed to the vasoconstrictive effects of NSAIDs that can lead to a reduction of papillary blood flow and ultimately papillary necrosis. Fortunately, this reaction is uncommon and in most cases, brief and reversible [26]. The risk is increased in patients with preexisting congestive heart failure, severe hepatic or renal dysfunction, diabetes, hypertension and dehydration [32]. Ibuprofen in general has been shown to have a lower risk of renal toxicity and OTC doses have not been associated with an increased risk for acute renal failure [32].

Drug-Drug Interactions

Adverse effects of NSAIDs may be attributed in many cases to drug-drug interactions. NSAIDs can interfere with antihypertensive medications such as: β-blockers, angiotensin-converting enzyme inhibitors, and thiazides; blunting their effects due to inhibition of renal prostaglandins and increased fluid retention, leading to de-stabilization of blood pressure control [56, 57]. This interaction appears to be less frequent with calcium channel blockers and loop diuretics [32, 58].

Concurrent use of NSAIDs and anticoagulants has been shown to carry an increased risk of bleeding. NSAIDs can displace warfarin from plasma proteins, increasing its free concentration in plasma thus, the reason patients taking NSAIDs (particularly naproxen) together with warfarin may be at a higher risk of bleeding complications [59]. Co-administration of NSAID with aspirin can reduce its cardioprotective benefits and increase GI risk [60,61]. Some nonselective NSAIDs, with more COX-1 effect, may interfere with aspirin's irreversible inhibition of platelet COX-1, therefore, increasing the risk for thrombotic events [51]. In contrast, aspirin's antiplatelet effect might increase the likelihood of GI bleeding and even decrease the gastroprotective benefit of COX-2 inhibitors. (62) The FDA recommends that aspirin and NSAIDs should be administered at different times [63,64].

Finally, concomitant use of NSAIDs in patients taking selective serotonin reuptake inhibitors (SSRIs) can substantially increase the risk of GI bleeding as SSRIs inhibit platelet adhesion and function and increase gastric acid secretion [65,66].

Nsaids and Malignancy

NSAIDs may have a protective role against several malignancies including colorectal, breast, and prostate cancer. This effect could occur via the inhibition of COX-2, decreasing inflammation. Another suggested mechanism is inducing the apoptosis of cancer cells and inhibiting cell proliferation [67-69]. In contrast, regular use of NSAIDs has been associated with an increased risk of renal cell carcinoma (RCC). (70) A large prospective study involving over 100,000 participants during 16 to 20 years of follow-up demonstrated an increase in RCC risk with an increased duration of NSAIDs use (RR 1.5) [70]. This risk was not increased with either aspirin or acetaminophen use, and it was independent of other risk factors such as smoking, hypertension, and obesity [71,72].

General Recommendations for the Use of Nsaids

NSAIDs are widely used in the management of multiple disorders due to their well-demonstrated efficacy in reducing pain and inflammation. In complicated patients, choosing the best anti-inflammatory analgesic therapy can be difficult. Besides offering effective pain control, an accurate assessment of cardiovascular and gastrointestinal risks should be considered before initiation of repetitive NSAIDs use. In addition, reviewing co-morbid conditions and concomitant drug use can help provide optimal therapy while minimizing the risk profile.

General rules to minimize the adverse effects:

- High-risk patients should be routinely monitored by health care providers.
- Use the lowest effective NSAID dose for the shortest period of time [73].
- Immediate-release, short half-life NSAID formulations are preferred, with repeated administration as necessary [37].

Summary Statement

In summary, it appears that acetaminophen is a desirable first-line agent, particularly for mild pain. It is an effective and safe analgesic at the recommended therapeutic doses. Suggested second-line drug therapy could be ibuprofen, at the lowest effective dose, supplemented with gastroprotective agents for those at increased GI risk. Should different NSAID be required, naproxen would appear to be a reasonable second choice.

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