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ANALYSIS OF SIDE EFFECTS AND DISADVANTAGES OF ANTI-INFLAMMATORY DRUGS RELATED TO THEIR USE

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ABOUT ARTICLE

Key words: Cyclooxygenase enzyme, cardiovascular adverse effects, bidirectional causality, anti-arthritic, analgesic, disadvantages.

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Abstract: The long-term effects of non-steroidal anti-inflammatory medicines (NSAIDs) on the development of symptoms and joint structural degradation in knee diseases are investigated in this study. Many people with arthritic disorders use non-steroidal anti-inflammatory medications (NSAIDs) both immediately as analgesics and chronically to reduce pain and inflammation. The suppression of the cyclooxygenase (COX) enzyme is the cause of both the positive and negative effects of NSAIDs. Depending on how selective they are for COX inhibition, NSAIDs are categorized as either non-selective or COX-2-selective inhibitors (COXIBS). Nevertheless, reports about the GI adverse effects of NSAIDs, especially on the lower gastrointestinal (GI) tract, and the detrimental function of their controlled release formulations continue to surface despite their COX selectivity. The GI sparing qualities of rofecoxib, a COXIB that has been discontinued due to cardiovascular (CV) adverse effects, are also called into question by previously disclosed data kept in the sponsor's files. GI problems, renal problems, and cardiovascular events are currently the main adverse effects of NSAIDs. There is a propensity to assume that all NSAIDs have negative effects on the kidneys and cardiovascular system, a notion that is not

well-supported by data. In fact, several NSAIDs may have cardioprotective effects at lower but still therapeutic doses. These results imply that long-term NSAID use may hasten the transition to total knee replacement by significantly aggravating symptoms, while also accepting the limitations of this study due to its observational methodology and the possibility of bidirectional causality.

YALLIG‘LANISHGA QARSHI DORI VOSITALARINI QO‘LLASH BILAN BOG‘LIQ NOJO‘YA TA’SIRLAR VA KAMCHILIKLARNING TAHLILI

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MAQOLA HAQIDA

Kalit so‘zlar: siklooksigenaza fermenti, yurak-qon tomir nojo‘ya ta’sirlari, ikki yo‘nalishli sababiylik, artritga qarshi vositalar, analgetiklar, kamchiliklar.

Annotatsiya: Ushbu tadqiqotda tizza bo‘g‘imi kasalliklarida nosteroid yallig‘lanishga qarshi dorilar (NYQD, NSAID) ning uzoq muddatli qo‘llanilishi simptomlarning rivojlanishi va bo‘g‘im tuzilmasining degradatsiyasiga ta’siri o‘rganiladi. Artrit bilan og‘rigan ko‘plab bemorlar NYQDlarni og‘riqni tezda kamaytirish uchun analgetik sifatida hamda uzoq muddat davomida og‘riq va yallig‘lanishni pasaytirish maqsadida qo‘llaydilar. Siklooksigenaza (COX) fermentining bostirilishi NYQDlarning ham ijobiy, ham salbiy ta’sirlariga sabab bo‘ladi. COX ni inhibitsiya qilish selektivligiga qarab, NYQDlar neselektiv va COX-2 selektiv ingibitorlarga (koksiblar) bo‘linadi. Shunga qaramay, COX selektivligiga ega bo‘lishiga qaramasdan, NYQDlarning oshqozon-ichak tizimiga, ayniqsa pastki oshqozon-ichak traktiga salbiy ta’siri hamda ularning nazoratli chiqariladigan shakllarining zararli jihatlari haqida xabarlar hanuzgacha uchrab kelmoqda. Yurak-qon tomir (YQT) nojo‘ya ta’sirlari tufayli ishlab chiqarishdan chiqarilgan COX-2 selektiv dori — rofekoksibning oshqozon-ichak tizimini asrash xususiyatlari ham homiy hujjatlarida saqlangan avval e’lon qilingan ma’lumotlar asosida shubha ostiga olinadi. Hozirgi vaqtda NYQDlarning asosiy nojo‘ya

ta’sirlari oshqozon-ichak muammolari, buyrak faoliyati buzilishlari va yurak-qon tomir hodisalari hisoblanadi. Barcha NYQDlar buyraklar va yurak-qon tomir tizimiga salbiy ta’sir ko‘rsatadi degan qarash mavjud, biroq bu fikr yetarli darajada ilmiy ma’lumotlar bilan tasdiqlanmagan. Aksincha, ayrim NYQDlar pastroq, ammo terapevtik jihatdan samarali dozalarda kardioprotektiv ta’sir ko‘rsatishi mumkin. Ushbu natijalar NYQDlarni uzoq muddat qo‘llash simptomlarni sezilarli darajada kuchaytirish orqali tizza bo‘g‘imini to‘liq almashtirish jarayonini tezlashtirishi mumkinligini ko‘rsatadi, shu bilan birga tadqiqotning kuzatuvchi metodologiyasi va ikki yo‘nalishli sabab-oqibat ehtimoli bilan bog‘liq cheklovlari ham e’tiborga olinadi.

АНАЛИЗ ПОБОЧНЫХ ЭФФЕКТОВ И НЕДОСТАТКОВ ПРОТИВОВОСПАЛИТЕЛЬНЫХ ПРЕПАРАТОВ, СВЯЗАННЫХ С ИХ ПРИМЕНЕНИЕМ

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О СТАТЬЕ

Ключевые слова: фермент циклооксигеназы, сердечно-сосудистые побочные эффекты, двунаправленная причинность, противоартритные средства, анальгетики, недостатки.

Аннотация: В данном исследовании изучаются долгосрочные эффекты нестероидных противовоспалительных препаратов (НПВП) на развитие симптомов и структурную деградацию суставов при заболеваниях коленного сустава. Многие пациенты с артритическими заболеваниями применяют НПВП как для немедленного обезболивания, так и для длительного снижения боли и воспаления. Подавление фермента циклооксигеназы (ЦОГ) является причиной как положительных, так и отрицательных эффектов НПВП. В зависимости от селективности ингибирования ЦОГ, НПВП классифицируются на неселективные и селективные ингибиторы ЦОГ-2 (коксибы). Тем не менее, несмотря на их ЦОГ-селективность, продолжают появляться

сообщения о желудочно-кишечных (ЖКТ) побочных эффектах НПВП, особенно в отношении нижних отделов желудочно-кишечного тракта, а также о неблагоприятном воздействии их форм с контролируемым высвобождением. Ранее обнародованные данные, хранившиеся в архивах спонсора, также ставят под сомнение ЖКТ-безопасность рофекоксиба — коксиба, снятого с производства из-за сердечно-сосудистых (СС) побочных эффектов. В настоящее время основными побочными эффектами НПВП являются желудочно-кишечные осложнения, нарушения функции почек и сердечно-сосудистые события. Существует тенденция считать, что все НПВП оказывают негативное влияние на почки и сердечно-сосудистую систему, однако это предположение недостаточно подтверждено данными. Более того, некоторые НПВП при более низких, но терапевтически эффективных дозах могут обладать кардиопротективными свойствами. Полученные результаты свидетельствуют о том, что длительное применение НПВП может ускорять переход к тотальному эндопротезированию коленного сустава за счет значительного усугубления симптомов, при этом учитываются ограничения данного исследования, связанные с его наблюдательным характером и возможностью двунаправленной причинно-следственной связи.

Introduction. Many conditions for which non-steroidal anti-inflammatory medications (NSAIDs) are prescribed because of their ability to relieve pain. They do, however, come with serious dangers, accounting for 30% of hospital admissions due to severe medication responses. Serious gastrointestinal issues, an increased risk of cardiovascular disease, and renal failure are some of these dangers. More precisely, studies show that 13–15% of NSAID users have upper gastrointestinal side effects6, and NSAID use alone may be the cause of 25% of peptic ulcer occurrences. Additionally, a 25% higher risk of cardiovascular events is linked to NSAIDs. NSAIDs, or nonsteroidal anti-inflammatory drugs, are among the most widely used medications in the world. Their broad analgesic, anti-inflammatory, and antipyretic properties make them beneficial for a wide range of indications. NSAIDs help lessen the burden of acute and chronic opioid usage, but they are sometimes underutilized. However, balancing varying benefit and risk

in the context of individual patients presents a considerable difficulty to clinical decision-making when it comes to the appropriate prescription of NSAIDs [1-5]. The cardiovascular, renal, and gastrointestinal systems are among the well-known adverse effects of NSAIDs. Therefore, patient variables and the relative toxicity profile of the NSAID must be taken into consideration when choosing a safe and acceptable NSAID. As a result, international guidelines advise only short-term use of NSAIDs and oppose their use in some people, especially those with comorbidities or cardiovascular disease. Long-term NSAID use is nonetheless common despite the aforementioned recommendations. According to a recent study, during the course of three years of surveillance, patients with hip and knee diseases were prescribed NSAIDs for an average of almost 16 months. Furthermore, long-term NSAID use is becoming more common. In the United States of America (USA), 29 million persons (12.1%) reported using NSAIDs for longer than three months in 2010. This is a 41% increase since 2005. A large percentage of these users are individuals with more diseases; in the USA, around 65% of patients with more diseases and persistent low back pain are prescribed NSAIDs for the treatment of chronic pain. Generally speaking, the likelihood of an NSAID causing dyspepsia increases with its ability to reduce inflammation [6-11]. They may occasionally be prescribed by your doctor together with medication to reduce the risk of ulcers. One drug even combines the two ingredients. Although some NSAIDs are thought to be less prone to irritate the digestive (gastrointestinal) tract and more specific in treating inflammation, this issue has not yet been completely resolved. The drugs vary in strength and side effects. As with other drugs, the likelihood of adverse effects increases with therapeutic effectiveness. This analgesic has anti-inflammatory properties. When someone has a fever, the majority of NSAIDs also lower their body temperature [12,13,14].

The main purpose of the presented manuscript is to provide a brief analysis of the importance of anti-inflammatory drugs in medical practice, as well as side effects and disadvantages associated with their use, based on the results of reputable scientific research.

Epidemiology of the side effects of non-steroidal anti-inflammatory medications. In many nations, nonaspirin, nonsteroidal anti-inflammatory medicines (NSAIDs) are among the most often used medications. Most NSAIDs are used more frequently as people age, mostly to treat the symptoms of osteoarthritis and other long-term musculoskeletal disorders. According to population-based studies, 10–20% of older adults (> or = 65 years old) had a current or recent NSAID prescription on any given day. In Alberta, Canada, 27% of senior citizens received NSAID prescriptions during a six-month period. Additionally, 40% of senior citizens in Tennessee (USA) were prescribed NSAIDs at least once a year, and 6% were prescribed NSAIDs for more than 75% of the year [4-10]. NSAIDs have a wide range of adverse effects. Upper gastrointestinal tract

dyspepsia, peptic ulcers, bleeding, and perforation—which can be fatal in certain cases—are the most clinically significant adverse effects (figure1).

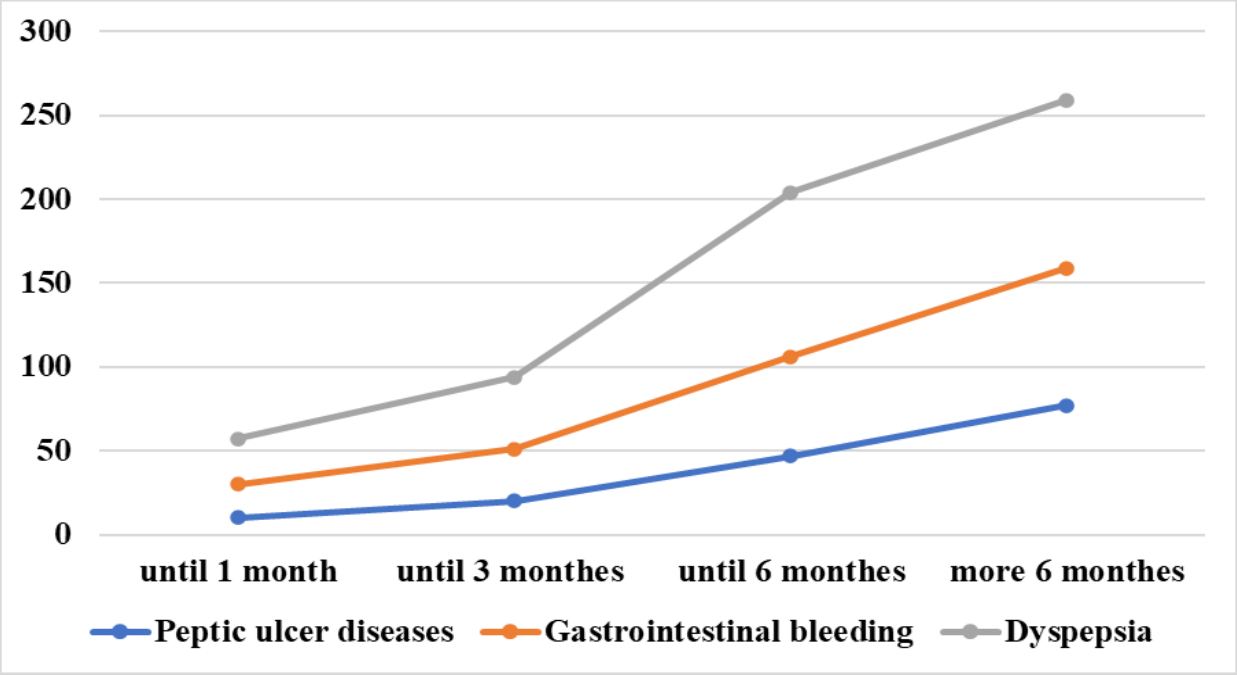

Figure 1. Side effects of non-steroidal anti-inflammatory medications.

Epigastric discomfort and indigestion are the most frequent NSAID-related gastrointestinal adverse effects. NSAID discontinuation and co-treatment with another medication are frequently caused by gastrointestinal adverse effects. In fact, regular NSAID users (20–26%) were almost twice as likely as non-NSAID users (11%) to use medications to prevent peptic ulcers or treat dyspepsia in two population-based investigations of those over 65. NSAID use is thought to be responsible for 28% of all anti-ulcer medication prescriptions in Alberta, Canada, for individuals 65 years of age or older. NSAIDs are believed to be responsible for 15–35% of all peptic ulcer complications in a number of different populations. Numerous studies have now demonstrated that NSAIDs raise the risk of peptic ulcer complications by three to five times. An estimated 41,000 hospitalizations and 3,300 deaths among the elderly are linked to NSAIDs in the United States alone each year. Older age, a history of peptic ulcer disease, gastrointestinal bleeding, dyspepsia, and/or prior NSAID intolerance, together with a number of indicators of poor health, are factors that raise the risk of significant peptic ulcer disease [7-13].

Use and comparision of the side effects of non-steroidal anti-inflammatory drugs. NSAIDs prevent cyclooxygenase (COX) enzymes from metabolizing arachidonic acid into prostaglandin H2, which is the starting point for prostaglandins and thromboxanes. While thromboxanes are mainly involved in platelet function and hemostasis, prostaglandins are signaling molecules that regulate pain, inflammation, fever, and vasodilation, among other effects. When there is an inflammatory component, such as in rheumatic and musculoskeletal disorders or in the

postoperative environment, NSAIDs are useful in relieving mild to moderate pain. When prostaglandins are not the primary mediators of pain, as in neuropathic pain, their effectiveness is probably restricted [5-10]. COX selectivity Two different COX isoforms, COX-1 and COX-2, were identified in the 1990s.3 COX-1 was identified as a constitutive enzyme crucial for generating prostaglandins with physiological functions, such as protecting the gastrointestinal tract's mucosa and preserving normal renal function, while COX-2 was identified as an inducible enzyme expressed in the context of inflammation, which causes pain, fever, and swelling [11-14].

Table 1: Nonsteroidal anti-inflammatory medication (NSAID) comparison

NSAID	Aspirin	Celecoxib	Diclofenac	Etoricoxib	Ibuprofen	Meloxicam
COX selectivity	nonselective	COX-2 selective	COX-2 preferential	COX-2 selective	nonselective	COX-2 selective
Route of administration	oral	oral	oral, topical, rectal	oral	oral, topical	Oral and intravenous, intramuscular
Dose frequency	When taken as an anti-inflammatory, every four to six hours.	1 to 2 times daily	2 to 3 times daily	once daily	every 4 to 6 hours	once daily

While COX-2 selective NSAIDs, like celecoxib and meloxicam, were created to target COX-2 and preserve gastric mucosal integrity mediated by COX-1, nonselective NSAIDs, including ibuprofen, indometacin, and naproxen, inhibit both COX-1 and COX-2. In actuality, many of the theoretical safety benefits of COX-2 selective NSAIDs over COX-1 (table 1) are negligible, and both have comparable factors to take into account while using them in clinical settings [15,16,17].

Common misconceptions and practice points. Cytochrome P450 (CYP) 2C9 metabolizes the majority of NSAIDs, including celecoxib, ibuprofen, meloxicam, and piroxicam. Higher NSAID concentrations and enhanced toxicity may result from impaired CYP2C9 (either from poor metabolizer polymorphisms or co-administration with inhibitors). While not all NSAID users need to be co-prescribed proton pump inhibitor (PPI) therapy, patients with traditional upper gastrointestinal risk factors (such as older age, a history of peptic ulcer disease, concurrent systemic glucocorticoid therapy, and longer intended NSAID duration) should be given consideration. Although PPI co-administration reduces the incidence of NSAID-related upper gastrointestinal problems, it does not shield the lower gastrointestinal tract's mucosa from damage like ulceration or perforation. When beginning an NSAID, patients with pre-existing lower gastrointestinal pathology—such as mucosal ulcers, increased gut permeability, inflammatory disorders, and malabsorption—need to be closely monitored. The necessity of taking NSAIDs with food is still debatable [7-12]. Only animal models have been used to study the impact on gastrointestinal damage; given with meal enhanced small bowel damage, while fasting produced more stomach unfavorable effects. When NSAIDs are given with only water instead of food, the

time to maximum plasma concentrations is attained more quickly. Faster onset may enhance overall pain management and lower the total amount of NSAIDs needed for acute pain. When using NSAIDs for an extended period of time and reaching a steady state, this might not be as important. It is still debatable whether NSAIDs can hinder bone repair. Lower dosages and shorter-term use seem to have less harm, however this is still conceivable. NSAIDs are often more appropriate than opioids and play a significant role in the management of pain for many people. Even though NSAIDs are generally similar, choosing the best medication for a particular situation may be aided by the pharmacokinetic characteristics and adverse effect profile of each NSAID [13-20].

Discussion. The purpose of this study is to give doctors a general understanding of the advantages and disadvantages of using nonsteroidal anti-inflammatory medicines (NSAIDs) to treat patients with mild-to-moderate osteoarthritis (OA). The existing recommendations for the use of NSAIDs in the treatment of patients with OA have been revised in response to new evidence regarding the inflammatory component of OA and the cardiovascular (CV) risk associated with cyclooxygenase (COX)-2-specific inhibitors. According to clinical research, acetaminophen, the conventional first-line treatment, has no discernible anti-inflammatory action in the joints, but naproxen and ibuprofen are much more effective at reducing OA pain. The growing frequency and severity of side effects associated with the various classes of anti-inflammatory, anti-arthritic and analgesic medications have been a major source of worry in the media and in the ordinary and specialized medical press over this decade. Our goal should be to: (i) determine the true cause of these side effects from epidemiological and clinical perspectives; and (ii) determine the true incidence and contributing factors through in-depth biochemical, cellular, and physio-pathological investigations in experimental models and isolated cell systems in laboratory animals and, when applicable, in humans [3,4,5,7]. Even if political demands and effects are ubiquitous and even persuasive, it is crucial to distinguish them from the scientific challenges that are the focus of this meeting. NSAIDs are among the oldest and most effective medications in modern medicine. By preventing prostaglandin synthesis, they effectively reduce pain, fever, and inflammation. Aspirin, on the other hand, effectively prevents cardiovascular disease due to its irreversible inhibition of blood platelet function. NSAIDs can cause gastrointestinal ulcers, serious cardiovascular events, hypertension, acute renal failure, and worsening of preexisting heart failure. These side effects can be avoided by limiting NSAID dosage and duration. Misoprostol, COX-2 selective NSAIDs, and/or concurrent proton-pump inhibitors may be used to treat patients who are at risk for gastroduodenal ulcers. Naproxen and a proton-pump inhibitor or misoprostol may be used to treat cardiovascular event risk, but NSAID use should be completely avoided. Clinical trials have shown the potential benefit of COX-2-specific inhibitors in lowering gastrointestinal (GI) damage

[8,11,12]. Lower NSAID dosages for shorter periods of time or concurrent use of a proton-pump inhibitor can minimize GI problems. A black box warning about CV risks is included with every prescription NSAID; these risks differ depending on the NSAID. Naproxen was linked to a neutral CV risk in comparison to a placebo, however ibuprofen and diclofenac are linked to an elevated CV risk. Aspirin's antiplatelet actions are lessened by ibuprofen but not by naproxen. When selecting an NSAID, it's critical to comprehend the advantages and disadvantages. Using the terms "ibuprofen," "naproxen," "COX-2-specific NSAIDs," "nonspecific NSAIDs," "low-dose aspirin," and "nonprescription dosage," a thorough search of the medical literature published since 1990 was carried out. MEDLINE, EMBASE, and SCISEARCH were among the databases that were searched. This article gives primary care doctors the knowledge they need to help them manage patients with mild-to-moderate OA pain [14,15,16].

Conclusions. For many illnesses, nonsteroidal anti-inflammatory medications (NSAIDs) are helpful, often outperforming alternative treatments like opioids. They have a significant impact on acute musculoskeletal injuries, osteoarthritis, headache disorders, dysmenorrhea, and tooth discomfort. They are the first-line treatment for axial spondyloarthritis and can alter the course of the condition. Despite having distinct pharmacodynamic effects, the majority of NSAIDs are equally effective for the majority of diseases. For acute or chronic diseases, the pharmacokinetic profile of various NSAIDs may offer varied risks and benefits that affect their choice. Cardiovascular, renal, and gastrointestinal concerns are among the well-known side effects of NSAIDs.

All NSAIDs carry some increased risk, even though these dangers differ. Lower gastrointestinal problems are not lessened by proton pump inhibitors, whereas upper gastrointestinal problems are. Pregnancy and hypersensitivity responses are two more crucial safety measures. The advantages and disadvantages of the NSAIDs now on the market must be carefully considered while managing individuals with mild-to-moderate OA. Pain severity, inflammation, and GI and cardiovascular risk factors should all be taken into consideration when choosing medication. Acetaminophen may not be as beneficial as NSAIDs in patients with pain and inflammatory symptoms, according to recent evidence.

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