REVIEW ON DRUG UTILIZATION & EVALUATION OF NSAIDS IN PHARMA INDUSTRY

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ABSTRACT

Overview of non-steroidal anti-inflammatory medications (NSAIDS), whose prescribing trends have changed significantly worldwide. They are regarded as being quite efficient in managing a variety of illness situations, such as gastrointestinal bleeding, CVS cardiovascular, inflammation, and pain. These negative effects are typically exacerbated when NSAIDS are taken along with other medications that have similar negative effects and toxicity. These NSAIDS that inhibit cyclo-oxygenase (cox-1 and cox-2) enzymes are a family of drugs that exhibits higher therapeutic efficacy, stability, and safety. NSAIDs are typically divided into groups based on their chemical structure and selectivity: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen, acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam) anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and selective COX-2 inhibitors (celecoxib, etoricoxib). NSAIDs have analgesic, antipyretic and anti-inflammatory activity. Antipyretic activity is exerted by inhibiting the rise of levels of PG in the brain, which acts as pyrogens, acting directly on the thermo-regulatory center in the hypothalamus, to increase body temperature. Their analgesic and anti inflammatory effect is due to inhibition of PG synthesis in the inflammed tissues and therefore is on a peripheral level. PG cause little pain themselves but potentiate the pain caused by other mediators with bradykinin and histamine.

KEYWORDS Non-steroidal anti-inflammatory drugs, thromboxane, prostaglandins, gastro-intestinal disorders, comorbidity, and proton pump inhibitors.

INTRODUCTION

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) are prescribed drugs that are widely used to treat skeletal disease conditions by decreasing oxidative stress, analgesic, and antipyretic discomfort. These are linked to the suppression of COX-1 and COX-2 enzymes.While NSAIDs' COX-1 (cyclo-oxygenase-1) isoform is inhibited and linked to negative side effects, COX-2 is inhibited and linked to positive pharmacological actions, such as analgesic and anti-inflammatory properties [1]. The development of NSAIDs that inhibit COX-2 in order to lessen the risk of gastrointestinal damage was made possible by the fact that the therapeutic

action of these medicines is highly mediated by COX-2 inhibition [2]. NSAIDS have been reported in a variety of populations, and so this medication study was acquired through self-medication, prescription stating the dosage, timing, duration, and instructions for reporting side effects [3].Oral routes are favoured as they are more effective in the later stages of recovery, whereas parenteral routes (IV/IM) are still thought to be appropriate for patients in an emergency [4]. Digoxin and methotrexate are two commonly prescribed medications for elderly patients who have rheumatoid arthritis and symptomatic heart failure. However, because of their low therapeutic index, their plasma concentration levels may rise, posing a risk of toxicity.NSAID use of any kind makes things more difficult. All NSAIDs except aspirin can increase CVS diseases such as edema, stroke, myocardial infarction (MI), and congestive heart failure. Drug use of NSAIDs causes renal toxicity, gastrointestinal, (GIT) hepatotoxicity and its Continuous bleeding, and ulcers [5].

METHODS

FORMULATIONS OF NSAIDS.

Topical non steroidal anti-inflammatory drug formulations.

It may be beneficial to use NSAIDs in topical applications to reduce the probability that a patient would have side effects from systemic medication. Medications that are administered topically might have either local or systemic effects. In order to have the desired therapeutic effect, drugs that are applied topically (e.gTopical patches, creams, gels, ointments, solutions, etc.) are meant to penetrate local tissue.Buprenorphine or fentanyl transdermal delivery, for example, aims to produce systemic concentrations that are comparable to those of drugs taken orally. It is recommended to use diclofenac sodium topical solution 1.5% w/w (PENNSAID) used to treat the symptoms and signs of osteoarthritis of the knee.

The diclofenac 1.3% topical patch (Flector Patch) is recommended for the topically applied management of acute pain resulting from small contusions, sprains, and strains. The patch is made up of an adhesive substance with 1.3% diclofenac that is layered over a non-woven polyester felt backing and coated with a polypropylene film release liner (which is removed prior to application)[6].Indomethacin/Prochlorperazine/Caffeine formulations were efficacious and generally well tolerated in the treatment of episodic tension-type headache (TTH) and migraine in adult patients taking part in randomised, multicenter, active-comparator controlled studies[7].

Estimation of paracetamol and naproxen tablet formulation.

The average weight of 20 tablets was estimated after they were weighed. To make a fine powder, the tablets were crushed with precision A measured amount of tablet powder containing 25 mg was sonicated for 15 minutes with 15 ml of methanol before the volume was increased to 25.0 ml. The solution was filtered, and 1.0 ml of the clear filtrate was then diluted with diluent to yield 10.0 ml. The resulting solution (2.0 ml) was then diluted to 10.0 ml with diluent to achieve the desired final concentrations of 20 g/ml for paracetamol and 12 g/ml for naproxen based on the labelled claim. Similar methods were used to prepare five copies of the sample solutions[8].

Combination of Ibuprofen and diclofenac sodium.

Non-steroidal anti-inflammatory (NSAID) analgesics like ibuprofen and diclofenac are both often used. The objective of this review is to contrast the relative efficacy of the two medications while also taking cost and safety concerns into account. Ibuprofen and diclofenac are both efficient analgesics for postoperative pain, according to the results, and they both have a low rate of side effects. According to this investigation, ibuprofen and diclofenac are equally effective when taken as a single dose. The difference between the two medications' relative efficacy can be boiled down to dose; although 400 mg of ibuprofen is only one sixth of the recommended daily dose, 50 mg of diclofenac is one third of that amount. Ibuprofen appears to function similarly to diclofenac 50 mg at 600 mg[9].

Preparation of core aspirin tablets.

The direct compression method was used to create the enteric coating pill. Aspirin, microcrystalline cellulose, and maize starch were sieved after being weighed until size 40The shifting materials mentioned above were blended using planetary mixture for 10 minutes. The components that had been moved were lubricated for five minutes in an octagonal blender with colloidal silicon dioxide, talc, and stearic acid. These combined substances were prepared for compression[10].

Formulation of mefenamic acid.

Mefenamic acid 200 mg controlled release matrix tablets were created utilising 100 mg of the medication and appropriate concentrations of the polymer and excipients. Magnesium stearate was employed as a lubricant and starch was used as filler.

Preparation

All excipients were added, with the exception of lubricant, after the drug and polymer were taken from the mortar and ground to a fine powder. After three passes through a 20-mesh filter with this mixture, lubricant was added, and the process was repeated through the same sieve. Utilising a single punch tableting machine, the produced powder was compressed into tablets with an average hardness of 7 kg/cm2 [11].

MECHANISM OF ACTION OF NSAIDS.

Inhibition of COX-1 and COX-2.

Analgesic, antipyretic, and anti-inflammatory drugs (NSAIDS) work by three major mechanisms: In 1976, cyclo-oxygenase (COX), also known as prostaglandin endoperoxide synthase, was isolated as a homogenous, enzymatically active substance. The endoplasmic reticulum of prostanoid-forming cells contained the highest concentrations of this membrane-bound glycoprotein, which had a molecular mass of 71 kiloDaltons (kDa). When arachidonic acid was cycled by the glycoprotein and the 15-hydroperoxy group was added to create prostaglandin G2, it was demonstrated that the glycoprotein exhibited COX activity. Prostaglandin G2 has known hydroperoxy groups.

Functions of COX-1 and COX-2

COX-1, an isoform of COX, has definite physiological purposes. activation of it For example, when released with gastric mucosa, the formation of prostacyclin is cytoprotective. It has been six years since the discovery of the COX-2 inducible isoform, which is triggered by pro-inflammatory[12].

CLASSIFICATION OF NSAIDS ACCORDING TO CHEMICAL STRUCTURE [13].

CHEMICAL GROUP	DRUGS
Propionic acid derivatives	**I**buprofen [Naproxen,Fenoprofen].
Enolic acid derivatives	Pyrazolones[phenylbutazone
Selective COX-2 inhibitors	Celecoxib[withdrawn from market].
Para- aminophenol	Acetaminophen[paracetamol].
Acetic acid derivatives	Diclofenac [Etodolac,ketorolac].
Salicylic acid derivatives	Aspirin [acetylsalicylic acid].
Fenamic acid derivatives	Mefenamic acid[meclofenamic acid].

PHARMACODYNAMICS AND PHARMACOKINETICS OF NSAIDS.

An important necessity for determining the clinical effects of selective and nonselective inhibition of COX-isozymes in humans is the pharmacodynamic of cyclooxygenase inhibitors in humans catalysis of cyclooxygenase (COX)-1 and COX-2 in health and illness. Additionally, we discuss the pharmacodynamic and pharmacokinetic properties of the most common conventional nonsteroidal anti-inflammatory medications (tNSAIDs) and coxibs (selective COX-2 inhibitors), which are crucial to both their efficacy and toxicity. Important information from our pharmacological investigations has made it clear that nonselective COX inhibitors should be regarded as the tNSAIDs with a balanced inhibitory impact on both COX-isozymes (exemplified by ibuprofen and naproxen). Contrarily, coxibs (such as celecoxib, valdecoxib, rofecoxib, etoricoxib, and lumiracoxib) and tNSAIDs [such as meloxicam, nimesulide, and diclofenac, which are between 18 and 29 times more powerful towards COX-2 dependent prostacyclin PGI2][14].

Disease with chronic Inflammatory components.

It describes about some diseases with Inflammatory cell infiltration has been shows for acute respiratory distress syndrome,sarcoidosis, atherosclerosis and many other diseases.

Table 1: List of various inflammatory diseases with inflammatory disease infiltrate

INFLAMMATORY DISEASE	INFLAMMATORY CELL INFILTRATE
Atherosclerosis	T cells, monocytes.
Bronchial asthma	Eosinophils,T cell, monocytes, basophil

Osteoarthritis	Monocytes, neutrophil.
Psoriasis	T cell, neutrophil.
Sarcoidosis	T cell, neutrophil.
Glomerulonephritis	Monocyte, neutrophil.
Acute respiratory distress	Neutrophil.
Inflammatory bowel distress	Monocyte, neutrophil, T cell
Rheumatoid arthritis	Monocyte, neutrophil.
Glomerulonephritis	Monocyte, neutrophil

EFFECTS OF NSAIDS.

Respiratory action.

At anti-inflammatory levels, both peripheral (increased CO2 generation) and central (increased sensitivity of the respiratory centre to CO2) actions enhance respiration. In salicylate poisoning, hyperventilation is common. An increase in salicylate levels that is too great results in mortality and respiratory failure (2).

Cardiovascular Risk of Non-Steroidal Anti-Inflammatory drugs.

It is also commonly acknowledged that there is a chance of blood pressure increase and the emergence of congestive heart failure. A higher rate of acute myocardial infarction rofecoxib clinical trials brought attention to the possible cardiotoxicity of selective cyclooxygenase-2 inhibitors, and similar concerns have been raised about the cardiovascular safety non-selective NSAIDs. Numerous retrospective and prospective clinical studies and meta-analyses have recently been conducted to examine the safety of NSAIDs in relation to cardiovascular events. The findings show that cardiotoxicity is a class impact, but the risk's severity varies greatly among different NSAIDs[15].

Gastro-intestinal tract effect.

An increased risk of dysplasia and cancer is related to gastric intestinal metaplasia, a precancerous change in the stomach's mucosa with intestinal epithelium. According to the Correa theory, inflammation, followed by intramucosal cancer and invasion, is the transition from normal gastric epithelium to invasive cancer that leads to the development of gastric cancer. The emergence of gastric intestinal metaplasia interaction has been linked to a number of risk factors, including as Helicobacter pylori infection and related genomics, host genetic variables, environmental milieu, rheumatologic diseases, nutrition, and intestinal microbiota. In nations with high incidence, screening recommendations have been set internationally. Due to lower, albeit rising, incidence, no equivalent guidelines have been

produced in the United States. The American Society for Gastrointestinal Endoscopy suggests treating each patient individually[16].

Analgesic and antipyretic effects.

While concurrent inhibition of cyclooxygenase-1 (COX-1) substantially but not entirely accounts for unfavourable side effects in the GI tract, it is assumed that cyclooxygenase-2 (COX-2) mediates, in large part, the antipyretic, analgesic, and anti-inflammatory properties of tNSAIDs. A subclass of NSAIDs is selective COX-2 inhibitors, such as celecoxib, etoricoxib, and lumiracoxib, which is also covered. We discuss aspirin, which acetylates COX irreversibly, as well as several structural subclasses of tNSAIDs, such as propionic acid derivatives (ibuprofen, naproxen), acetic acid derivatives (indomethacin), and enolic acids (piroxicam), which all compete with the arachidonic acid (AA) substrate at the active site of COX-1 and COX-2 in a reversible manner At usual doses, acetaminophen (paracetamol), a mild anti-inflammatory medication, serves as an analgesic and antipyretic[17].

Anti- Inflammatory effects.

Although some COX-independent effects have been reported recently, the primary mechanism for the therapeutic effects of NSAIDs has traditionally been thought to be the reduction of PG production at sites of inflammation. Although the mechanisms underlying NSAIDs' positive effects are largely unclear, epidemiological studies show that they are neuroprotective. Microglial cells are frequently considered to be one of the main causes of neurodegeneration since they play a significant role in brain inflammation. NSAIDs' potential target in the brain is thus microglia[18].

Advantages of NSAIDs

1. NSAIDS and COXIBs provide equivalent analgesic, antipyretic, anti-Inflammatory activity
   to show its therapeutic efficacy
2. Gastrointestinal tract is associated with NSAIDs is considerable
3. These agents have evidence of tolerability reducing less serious gastrointestinal effects
   mainly dyspepsia.
4. Proton pump inhibitors provide little benefit for bleeding and ulceration of lower intestine[19].

Disadvantages of NSAIDs

1. Toxicity effects of NSAIDs relates to reproduction and physiological implications
2. Mixed culture enriched in treatment unit may leads to higher removal of NSAIDs
3. Several bacterial strains known to degrade NSAIDs this microbial ability is attributed to hydroxylation by cytochrome p-450 enzyme.
4. Moreover processes like decarboxylation, dehydration, dechlorination, subsequent oxidation, demethylation etc also constitute the degradation pathways[20].

UTILISATION OF NSAIDS.

As one of the most recent classes of xenobiotics, analgesics and nonsteroidal anti-inflammatory medications (NSAIDs) have been found in a variety of natural matrices. The most extensively utilised of these to relieve mild to moderate pain are ibuprofen and monocyclic paracetamol. Degradation of such pollutants has grown to be a serious problem as long-term negative consequences of these xenobiotics and their biological and pharmacokinetic activities, especially at environmentally relevant doses, are well established. Additionally, conventional wastewater treatment plants (WWTPs) are currently not fully equipped to remove that particular type of micropollutant. The employment of bacterial strains with enhanced breakdown capabilities in bioremediation processes appears to be a promising alternative to the chemical techniques now in use [21].

Use of NSAIDS in children.

The only NSAIDs accessible to children usually are paracetamol, aspirin, naproxen, and now nimesulide. Although nimesulide has been demonstrated to be more effective than currently available medications in treating febrile illnesses in children, such as upper respiratory infections, it is more expensive than traditional NSAIDs. Because of the risk of Reye's syndrome, aspirin is not advised for usage as a standard analgesic and antipyretic medication in paediatric viral disease. However, it is well known for its effectiveness as an anti-inflammatory drug in the treatment of rheumatic fever and paediatric arthropathies.

Use of NSAIDS in pregnancy.

NSAIDS are not advised during pregnancy, especially throughout the trimester.Aspirin is used in combination with heparin in pregnant women with antibodies. Indomethacin is also used in pregnancy to treat polyhydramnios by reducing foetal urine production. While NSAIDS as a class are not direct teratogens, they may cause premature closure of the foetal ductus and renal ADRs. Contrarily, paracetamol is considered to be safe and well-tolerated during pregnancy, but the doses must be taken in the prescribed manner to prevent any potential risk of hepatotoxicity in pregnant women (2)

CONCLUSION

NSAIDs seem to affect fusion rates in a dose- and time-dependent manner. It seems sensible to use low-dose NSAIDs for a brief period of time before spinal fusion surgery. Therefore, we conclude that use of NSAIDs worldwide is a more prominent role of action to the patients with prevention Cure and treatment to give best therapeutic approaches. Spine surgeons can consider incorporating NSAIDs into pain control regimens for spinal fusion patients with the goal of improving pain control and reducing the costs and complications associated with opioids.

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