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A Comprehensive Review of Non-Steroidal Anti-inflammatory Drugs

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed pain medications. It is a highly effective drug class for pain and inflammation. The analgesic and anti-inflammatory properties act by inhibiting two recognized isoenzymes of prostaglandin G/H synthase also known as cycloxygenase (COX), which are COX 1 and COX 2. NSAIDs are known for multiple adverse effects including gastrointestinal bleeding, cardiovascular side effects and induced nephrotoxicity etc. Therefore, we reviewed the pharmacodynamics and pharmacokinetics, use, adverse effects and drug interaction of NSAIDs.

Keywords: Pain, Anti-inflammatory, Cyclooxygenase enzymes, Ibuprofen, Piroxicam.

INTRODUCTION

NSAIDs are one of the most commonly prescribed classes of medication for pain and inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used to treat chronic pain. In addition to their anti-inflammatory effect, NSAIDs have antipyretic and analgesic properties. Although they relieve symptoms, such relief comes at the expense of important adverse effects, most notably upper gastrointestinal toxicity [1-2]. Clinically, they are useful in relieving pain in many conditions, ranging from menstrual and postoperative pain to arthritic pain. These drugs are well-known anti-inflammatory agents, and they exert their effects through the inhibition of prostaglandin synthesis by blocking the enzyme cyclooxygenase (COX). The NSAIDs represent the single most crowded group of pharmacologic agents sharing the same therapeutic activities and mechanism of action, perhaps reflecting the unmet therapeutic need in the area of pain and musculoskeletal diseases as well as the substantial interindividual variability in response to these agents [3-4].

These medications inhibit Cyclooxygenases (COXs) enzymes, which are ratedetermining enzymes for prostaglandins and other prostanoids synthesis, such as thromboxanes. Compared with Nonselective NSAIDs that inhibit both COX-1 and COX-2, COX-2 inhibitors (as known as coxibs) inhibit only COX-2 enzymes. COX-2 plays more of a role in prostaglandin mediated pain and inflammation, while COX-1 plays some housekeeping role in the protection of gastric mucosa and in platelet hemostasis. While the gastro intestinal safety profiles of COX-2 inhibitors have improved, the cardio-nephrotoxic adverse effects are still significant [5]

PHARMACOLOGY OF NSAIDS

The major therapeutic actions of NSAIDs are primarily enacted by their ability to block certain prostaglandins (PGs) synthesis through the cyclooxygenase enzymes (COX-1 and COX-2) inhibition. COX-1 produces prostaglandins and thromboxane A2 which control mucosal barrier in GI-tract, renal homeostasis, platelet aggregation and other physiological functions. COX-2 produces PGs that related to inflammation, pain and fever. COX-1 is expressed in normal cells, while COX-2 is induced in inflammatory cells. COX-2 inhibition most likely represents the desired effect of NSAIDs' antiinflammatory, antipyretic and analgesic response; while COX-1 inhibition plays a major role in the undesired side effects such as GI and renal toxicities [6-8].

Most NSAIDs are well absorbed in the gastrointestinal tract and have high bioavailability. Some drugs such as diclofenac undergo hepatic first-pass metabolism which resulted in the reduction in bioavailability. While some drugs such as sulindac and parecoxib are prodrugs and need hepatic metabolism to become their active metabolites (sulindac sulfide and valdecoxib, respectively). NSAIDs are highly bound to plasma proteins. NSAIDs are usually metabolized in the liver and excreted in the urine. Common NSAIDs drug have a variable half-life; they can be anywhere from 0.25-0.3 hours such as aspirin or 45-50 hours such as piroxicam. All these pharmacokinetics parameters can change with aging since the elderly have low body water compared with adults. Protein binding may be reduced and volumes of distribution may be altered [9-10].

SELECTION OF RIGHT NSAIDs

The importance of selection of right chooses of NSAIDs when all have equivalent therapeutically profile for their safety, tolerability and efficacy in various diseased conditions. They also cause most frequently lethal drug toxicity such as gastrointestinal hemorrhage. Importantly, nonprescription use that is often ignored is considered to be seven folds higher than the prescription use [11-13].

Choosing an NSAID for its analgesic and antipyretic effect in indications like fever, common cold, dental pain, minor soft tissue injuries, musculo-skeletal pain and non-specific body aches is not difficult as in most circumstances the drug is to be used for a short duration only. Choice of NSAID for chronic and disabling inflammatory joint diseases like rheumatoid arthritis and osteoarthritis is governed by age, diagnosis, degree of severity, relative gastrointestinal safety, tolerability, and relative efficacy in the given clinical situation. It is a common misconception that all NSAIDs are equally therapeutically efficacious and any one of them could be used for the given indication. However, the use of multiple NSAIDs should be strongly discouraged as an agent with comparatively less GI side effects like ibuprofen and diclofenac should be preferred in place of indomethacin, piroxicam, or naproxen, which are more gastro toxic.

In situations, e.g., osteoarthritis where inflammation of joints is minimal, analgesics like paracetamol should be preferred over anti-inflammatory drugs like ibuprofen [14-18].

Some physicians consider combination of NSAIDs in the treatment of inflammatory joint diseases. There is little evidence to support this practice because therapeutic benefits do not add but side effects do. Moreover there is no evidence that fixed dose combinations of NSAIDs are superior to individual drugs in the long-term management of arthritis. Choice of NSAIDs in children is generally restricted to paracetamol, aspirin, naproxan, and now nimesulide. Although nimesulide has been shown to be superior to the existing drugs in childhood febrile illnesses like upper respiratory infections, but it is more costly than the conventional NSAIDs. Aspirin is not recommended as a routine analgesic and antipyretic drug in childhood viral illness because of fear of Reyes syndrome [19-20]. NSAIDs have large inter-patient variations, reasons that are not entirely clear. Even when drugs are from the same chemical family or are structurally similar, they can be substituted. One patient may respond to one agent of one class but may not respond to another agent of the same class. Determination of the therapeutically effective dose for a particular patient is difficult and is often based on 'hit and trial' method. Treatment should be started on low dose and response should be awaited. If response is adequate, treatment is continued for one week as most side effects of NSAIDs appear in the first week. In the case of no response, change of NSAIDs should be considered. Persistent dyspepsia is one of the most frequent side effects of NSAIDs and with few exceptions it can be an indicator of onset of future gastrointestinal (GI) toxicity. Topical NSAIDs represent an attractive alternative to systemically administered drugs. Studies have shown that topically applied NSAIDs directly get to the synovial fluid, menisci and articular cartilages and generally, 70-80% of the plasma concentration reaches the articular tissues [14, 21-22].

THERAPEUTIC VALUES OF NASIDs

Analgesic and antipyretic action

The analgesic action is mainly due to peripheral pain receptors and prevention of PG mediated sensitization of nerve endings. A central subcortical action, raising threshold to pain perception also contributes. No sedation, tolerance, and dependence are produced. Commonly NASIDs resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss (sweating, cutaneous vasodilation), but does not decrease heat production [23].

Acid-base/ electrolyte balance

NASIDs initially respiratory stimulation predominates and tends to wash out CO_2 despite increased production and the result is respiratory alkalosis, which is compensated by increased renal excretion of HCO_3- (with accompanying Na^+, K^+ and water) [24].

Metabolic effects

The cellular metabolism is increased, particularly at the skeletal muscles, due to the uncoupling of oxidative phosphorylation resulting from the increase in heat production. There is increased utilization of glucose and blood sugar may decrease particularly in diabetics and liver glycogen is depleted. However, hyperglycemia is often seen at toxic doses: this is due to central sympathetic stimulation and release of adrenaline and GCS [24].

Cardiovascular system effect

Very high doses of Aspirin have been shown to increase cardiac output to meet increased peripheral oxygen demand and can cause direct vasodilatation [25].

ADVERSE EFFECTS OF NASIDs

Effect on Kidneys

Compared with GI and cardiovascular risks, Renal side effects of NSAIDs are considered uncommon. However, advanced age puts patients at higher risk of developing nephrotoxicity from NSAIDs. NSAIDs cause inhibition of prostaglandin and thromboxane synthesis leading to renal vasoconstriction and consequently reduced renal perfusion and aberrant renal function. Clinical manifestations of NSAID induced nephrotoxicity includes electrolyte imbalance such as hyperkalemia, reduce glomerular filtration rate, nephrotic syndrome related to drug induced minimal

change disease, chronic kidney disease, acute interstitial nephritis, sodium retention, edema, and renal papillary necrosis. In a patient with normal renal function, inhibition of prostaglandin synthesis does not pose a large problem; however, in a patient with renal dysfunction, these prostaglandins play a greater role and can be the source of problems when reduced via NSAIDs. Complications that can occur include acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome/ interstitial nephritis [26-27].

Effect on Cardiovascular

NSAIDs increase the risk of myocardial infarction and stroke they are not recommended for those who have had a previous heart attack as they increase the risk of death and recurrent MI. Since rofecoxib and valdecoxib, were withdrawn from market in 2004 and 2005 respectively, due to adverse cardiovascular events such as edema, myocardial infarction, thrombotic events, stroke and hypertension, concerns regarding all COX-2 inhibitors potential for cardiovascular adverse effects have been raised [28-30].

Effect on Gastrointestinal tract

It is known that GI bleeding and ulceration from NSAIDs use increase in severity and frequency with increasing age. NSAIDs use increases the risk of GI bleeding in the elderly four folds. The mechanism underlying NSAIDs induced GI adverse effects lies in the fact that these medications inhibit prostaglandin synthesis, causing weakening of the protective GI mucosal barrier, and predisposing one to bleeding. NASIDs irritate gastric mucosa and cause epigastralgia, nausea, and vomiting. In higher doses it also stimulates CTZ. The mechanism involves endothelial effects, epithelial effects, direct toxicity ion trapping, ulcer and erosion [31-32]

Effect on Hepatic

Hepatic adverse effects are less common; NSAID-associated risk of hepatotoxicity (raised amino transferase levels) is not very common, and liver-related hospitalization is very rare. Among the various NSAIDs, Diclofenac has a higher rate of hepatotoxic effects [33].

Urinary incontinence

In animal models, NSAIDs improved bladder function and decrease micturition frequency. In humans, Saito et al. investigated the effectiveness of loxoprofen sodium in the management of nocturia in benign prostatic hyperplasia and overactive bladder in elderly patients. They found significant improvement in term of frequency and volume of nocturia. This finding highlights the treatment benefits of NSAIDs in overactive bladder [34-35].

Drug Interaction

NSAIDs reduce renal blood flw and thereby decrease the efficacy of diuretics, and inhibit the elimination of lithium and methotrexate. NSAIDs cause hypocoagulability, which may be serious when combined with other drugs that also decrease blood clotting, such as warfarin. NSAIDs may aggravate hypertension and thereby antagonize the effect of antihypertensive drugs such as the ACEinhibitors. NSAIDs may also interfere and reduce effiiency some antidepressants. Most wisely used NSAIDs are known to enhance endocannabinoid signaling by blocking the anandamide-degrading membrane enzyme fatty acid amide hydrolase (FAAD) [32, 36-38].

Common NASIDs

Aspirin

Aspirin in high dose reduces renal tubular excretion of urate(both substances are transported by the same mechanism). As analgesic (300 to 600mg during 6 to 8h) for head-ache, backache, pulled muscle, toothache, neuralgias as antipyretic in fever of any origin in the same doses as for analglesia. However, paracetamol and metamizole are safer, and generally preferred. Acute rheumatic fever Aspirin is the first drug of choice. Other drugs substitute Aspirin only when it fails or in severe cases. Antirheumatic doses are 75 to 100mg/kg/24h (resp. 4–6g daily) in the first weeks. Rheumatoid arthritis Aspirin a dose of 3 to 5g/24h after meal is effective in most cases.

Ibuprofen

This is a derivative of phenylpropionic acid. In doses of 2.4g daily it is is equivalent to 4g of Aspirin in anti-inflmmatory effect. Oral ibuprofen is often prescribed in lower doses (<2.4g/d), at which it has analgesic but not antiinflmmatory effiacy. It is available in low dose forms under several trade names (e. g. Nurofen®–fim-tabl 400mg). A topical cream preparation is absorbed into fascia and muscle. A liquid gel preparation of ibuprofen provides prompt relief in postsurgical dental pain. In comparison with indometacin, ibuprofen decreases urine output less and also causes less fluid retention. It is effective in closing ductus arteriosus in preterm infants, with much the same efficacy as indomethacin.

Flurbiprofen

Flurbiprofen is a propionic acid derivative with a possibly more complex mechanism of action than other NSAIDs. Its (S) (-) enantiomer inhibits COX non selectively, but it has been shown in rat tissue to also affect TNF-α and NO synthesis Hepatic metabolism is extensive. It does demonstrate enterohepatic circulation. The efficacy of flrbiprofen at dosages of 200-400mg/d is comparable to that of Aspirin and other NSAIDs for patients with rheumatoid arthritis, ankylosing spondylitis, gout, and osteoarthritis. Flurbiprofen i.v. is

effective for perioperative analgesia in minor ear, neck, and nose surgery and in lozenge form for sore throat Its adverse effect profile is similar to other NSAIDs

Ketoprofen
Ketoprofen is a propionic acid derivative that inhibits both COX (nonselectively) and lipoxygenase. Concurrent administration of probenecid elevates ketoprofen levels and prolongs its plasma half-life. The effectiveness of ketoprofen at dosages of 100–300mg/d is equivalent to that of other NSAIDs in the treatment of rheumatoid arthritis, osteoarthritis, gout, dysmenorrhea, and other painful conditions. In spite of its dual effect on prostaglandins and leukotrienes, ketoprofen is not superior to other NSAIDs. Its major adverse effects are on the GIT and the CNS.

Indometacin
This is a potent nonselective COX inhibitor and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T cell and B cell proliferation. Probenecid prolongs indometacin's half-life by inhibiting both renal and biliary clearance. Indometacin is indicated for use in juvenile rheumatoid arthritis, gout and ankylosing spondylitis, postepisio-tomy pain, etc. It has been used to treat patent ductus arteriosus. An ophthalmic preparation seems to be efficacious for conjunctival inflammation and to reduce pain after traumatic corneal abrasion. Gingival inflammation is reduced after administration of indometacin oral rinse. A high incidence (up to 50%) of GI and CNS side effects is produced: GI bleeding, diarrhoea, frontal headache, mental confusion, etc.

Diclofenac
Diclofenac is a phenylacetic acid derivative. A 0.1% ophthalmic preparation is recommended for prevention of postoperative ophthalmic inflammation and can be used after intraocular lens implantation and strabismus surgery. A topical gel containing 3% diclofenac is effective for solar keratoses. Diclofenac in rectal suppository form can be considered a drug of choice for analgesia and postoperative nausea. It is also available for intramuscular and oral administration. Side effects occur in approximately 20%: GI distress and occult bleeding, gastric ulceration. A preparation combining diclofenac and misoprostol decreases upper GI ulceration but may result in diarrhea.

Piroxicam
This is an oxicam (enolate derivative), is a nonselective COX-1/ COX-2 inhibitor that at high concentrations also inhibits polymorphonuclear leukocyte migration, decreases oxygen radical production, and inhibits lymphocyte function. Its long half-life permits once-daily

dosing. Piroxicam can be used for the usual rheumatic indications. Toxicity includes GI symptoms (20% of patients), dizziness, and tinnitus, and headache, rash. .When piroxicam is used in dosages higher than 20mg/d, an increased incidence of peptic ulcer and bleeding is encountered. This risk is as much as 10 times higher with piroxicam than with other NSAIDs.

Metamizole
This is a derivative of pyrazolone. It is a potent and promptly acting analgesic, antipyretic, and spasmolytic but has poor anti-inflammatory and not uricosuric activity. Analgin can be given orally, i.m. as well as i.v. (very slowly). Pain at the i.m. injection site and rarely abscess can occur. Occasionally an i.v. injection produces fall in BP. Few cases of agranulocytosis were reported and metamizole was banned in the USA and some European country. However, it has been extensively used in Bulgaria and much other European country, as well as in India and Russia. Adverse reaction data collected over four decades shows that the risk of serious toxicity with metamizole is very low than with Aspirin or many other NSAIDs.

Paracetamol
Although equivalent to Aspirin as an effective analgesic and antipyretic agent, paracetamol differs in that it lacks anti-inflammatory properties. It does not affect uric acid levels and lacks platelet inhibiting properties. The drug is useful in mild to moderate pain: headache, myalgia, postpartum pain. Paracetamol alone is inadequate therapy for inflammatory conditions such as rheumatoid arthritis, although it may be used as an analgesic adjunct to anti-inflammatory therapy. For mild analgesia, paracetamol is the preferred drug in patients' allergic to Aspirin or when salicylates are poorly tolerated it is preferable to Aspirin in patients with hemophilia or a history of peptic ulcer and bronchospasm. It is preferred to Aspirin in children with viral infections [24, 39–41].

CONCLUSIONS

Currently available NSAIDs represent a heterogeneous group of therapeutic agents characterized by a variable benefit/risk pro- file. The development of a new class of selective COX-2 inhibitors, the coxibs, has contributed importantly to clarifying the discrete roles of COX-2 vs. COX-1 inhibition in different aspects of NSAID-related efficacy and safety. Cardiovascular toxicity has emerged as a previously unrecognized, mechanism-based effect of COX-2 inhibitors. The legal issues surrounding the withdrawal of rofe- coxib as well as the political nuances of subsequent regulatory actions have somewhat clouded the scientific debate on the deter-minants, attributable risk and risk management of NSAID-related cardiotoxicity. It is reasonable to expect that a less emotional and more evidence-based debate on these issues may allow the medi- cal/scientific and regulatory communities to reach a consensus on treatment guidelines for NSAID therapy. Moreover, it is hoped that lessons learned from the many facets of the coxib failure story may help guiding the successful development of a new class of safer NSAIDs, targeting

mediators unrelated to arachidonic acid metabolism or molecular targets downstream of COX-isozymes.

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