Ibuprofen: An Overview

Sayali S. Dandge[1], Sangram U. Deshmukh[2], Nandkishor B. Bavage[3], Shyamlila B. Bavage[4]
[1]*B. Pharmacy, Final Year Student, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*
[2,3]*Department of Pharmaceutical Chemistry, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*
[4]*Department of Pharmacology & Toxicology, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

Abstract **- Ibuprofen was introduced in England in 1967 and in the United States in 1974 as an anti-inflammatory drug in humans. It has weak but definite anti-inflammatory properties similar to those of aspirin, milligram for milligram, but with considerably less adverse effect on the stomach. Ibuprofen is chemically related to fenoprofen and naproxen, but lack of effect for anyone in this chemical class of propionic-acid derivatives does not necessarily mean lack of effect for any other in an individual patient. The drug has analgesic properties, probably related to its anti-inflammatory effect. It inhibits prostaglandin synthesis and has no effect on the adrenopituitary axis, making it a nonsteroidal agent. Ibuprofen has been shown to be effective in rheumatoid arthritis and osteoarthritis and is probably effective in enclosing spondylitis, gout, and Bartter's syndrome.**

Index Terms **- fenoprofen, naproxen, Ibuprofen, anti-inflammatory drug.**

INTRODUCTION

Ibuprofen, a carboxylic acid, was first introduced in the UK 1969 by the Boot Pure Drug Company under the trade name Brufen. It belongs to a class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs of which there are now more than 50 on the market. Ibuprofen has a powdery white appearance and can come in the form of capsules, tablets, or powder. Today it is sold under several trade names such as Advil, Motrin and Nuprin ibuprofen, a carboxylic acid, was first introduced in the UK 1969 by the Boot Pure Drug Company under the trade name Brufen. It belongs to a class of drugs known as non-steroidal anti- inflammatory drugs or NSAIDs of which there are now more than 50 on the market. Ibuprofen has a powdery white appearance and can come in the form of capsules, tablets, or powder. Today it is sold under several trade names such as Advil, Motrin and Nuprin. It is often prescribed for "rheumatic" musculoskeletal complaints and is taken without prescription for minor aches and pains. Ibuprofen is the first-choice drug in its class since it has a low incidence of unwanted effects. It is rapidly metabolized, usually leaving the body via urination within 24 hours. Because ibuprofen has only one stereo centre, it can exist in two enantiomeric forms. The commercially available product is usually the race mate since it is difficult to separate the two enantiomers. The biologically active form is the S enantiomer and the R form is converted to this within the body thus minimizing side effects (c.f. thalidomide problem of the 1950's and 1960's). One may have assumed, therefore, that only 50% of the drug would be active but this is not the case due to biologically catalysed enantiomeric in is often prescribed for "rheumatic" musculoskeletal complaints and is taken without prescription for minor aches and pains. Ibuprofen is the first-choice drug in its class since it has a low incidence of unwanted effects. It is rapidly metabolized, usually leaving the body via urination within 24 hours. Because ibuprofen has only one stereo center, it can exist in two enantiomeric forms. The commercially available product is usually the racemate since it is difficult to separate the two enantiomers. The biologically active form is the S enantiomer and the R form is converted to this within the body thus minimizing side effects (c.f. thalidomide problem of the 1950's and 1960's). One may have assumed, therefore, that only 50% of the drug would be active but this is not the case due to biologically catalysed enantiomeric interconversion.

CHIRALITY OF IBUPROFEN

By definition, a chiral material is one which lacks reflectional symmetry, i.e. it has a nonsuperimposable mirror image structure and is referred to as being "handed". The most common type of chiral compounds are enantiomers. These materials are typically characterized by an asymmetric, tetrahedral carbon atom located at the center of the molecule. These molecules can be as stable, observable stereoisomers if their energy barrier of conversion exceeds 80 KJ/mole. In addition, compounds that are enantiomers have nearly identical physical and chemical properties in an achiral (symmetrical) environment. The specific distinguishing physical property of enantiomers is the rotation of plane polarized light. If the rotation is to the right (clockwise) the substance is dextrorotatory ((+) or (d)); if the rotation is to the left (counter clockwise) it is levorotatory ((-) or (l)). When these enantiomers are present in equimolar amounts within a mixture, the resultant mixture is termed racemic.

These preparations are optically inactive, because the net rotation of plane-polarized light is counterbalanced by equal concentrations of each enantiomer. Diastereoisomers are nonmirrored image stereoisomers that have more than one asymmetric center. Unlike enantiomers, diastereoisomers may be individually isolated because they have different as physical and chemical properties, such solubility and melting point (Sheldon, 1993). Enantiomers may be transformed into diastereoisomers by either covalent or noncovalent coupling of the enantiomers of a racemic mixture to another chiral molecule having at least one asymmetric center. This methodology defines a separation route by which two previously inseparable material may be isolated by conventional techniques. The interest in chirality and its consequences is not a new phenomenon. However, during the past decade it has raised increasing expectations for scientific and economic reasons, with the pharmaceutical industry being the main contributor and driving force.

MODES OF ACTION

As mentioned previously, ibuprofen is involved in controlling pain, acute inflammation and fever. It does so by acting on various pathways and cellular signalling systems involved in inflammation – much of this milieu of interactions is not entirely clear at this time. The main pharmacodynamic actions involved in achieving this effect, centre on the reduction in prostaglandin production. Prostaglandins are inflammatory mediators that contribute to pain and inflammation, and are derived from arachidonic acid in a process mediated by the cyclooxygenase enzymes, COX-1 and COX-2. Thus, ibuprofen can be seen to inhibit this COXmediated production of prostaglandins. Different NSAIDs inhibit COX-1 and COX-2 with varying degrees of selectivity. Prostaglandin E2 (PGE2) is the main mediator of pyresis and is produced in the hypothalamus. COX-2 is the inducible enzyme active in amplifying the production of PGE2 during inflammation. S-(+)-ibuprofen (the active enantiomer) targets COX- 2 and inhibits this synthetic process in the peripheral and central nervous system, thereby reducing PGE2 levels and providing the primary source of pain relief. The plasma profile of S- ibuprofen demonstrates parallel consistency with analgesic effects and prostaglandin inhibition. In a double-blind placebo-controlled crossover randomized controlled clinical trial (RCT), Suri and co-workers demonstrated, with the use of somatosensory evoked potentials (SEP) and subjective pain relief data, that the peak analgesic effects of ibuprofen occur around 2.5 h after administration. With regard to plasma levels, peak values occur at 1.3 and 2.2 h for R-ibuprofen and S-ibuprofen, respectively, supporting the claim that the S enantiomer is in fact the

Predominant driver of the analgesic effect. Ibuprofen and the other NSAIDs also inhibit COX-1, a constitutive enzyme that produces many prostaglandins mainly with 'housekeeping' functions. In fact, some prostaglandins are important protectants in the gastrointestinal tract and also play a role in regulating renal perfusion. The concomitant inhibition of COX-1 by S-ibuprofen is thought to underlie some of the adverse effects associated with ibuprofen, such as gastric ulcers, gastrointestinal bleeding and renal dysfunction] Understandably then, it is hypothesized that the ratio of COX-1 versus COX-2 inhibition by a given NSAID bears relation to the toxicity of the drug. That is, if a drug favours COX-1 inhibition, it may be suspected to exhibit higher toxicity. This concept underlay the development of COX-2 selective inhibitors, known as coxibs (e.g. celecoxib,

rofecoxib), in the late 1990s, which appeared to successfully reduce gastrointestinal and renal adverse events. However, a number of coxibs were subsequently withdrawn due to the occurrence of cardiovascular adverse events. Ibuprofen has one of the lowest gastrointestinal and renal toxicity profiles of all the traditional NSAIDs, but this cannot be predicted by looking solely at its COX-1/COX-2 selectivity (not necessarily correlated to toxicity). A factor likely contributing to its relatively low incidence of adverse effects is the short plasma elimination of ibuprofen. This may provide some explanation for the low risk of upper gastrointestinal toxicity compared with other NSAIDs with longer half-lives. Another line of reasoning stems from the idea of the inactive R enantiomer competing with active S-ibuprofen for the active binding site on COX-1. It is possible that the R-ibuprofen isomer may diminish the expected inhibitory effects of S-ibuprofen on COX-1 in the stomach. This prevents S-ibuprofen from inhibiting gastric prostaglandin (protectant) production to the extent that would be expected, thereby reducing the risk of ulcers. There are a number of COX-independent clinical effects attributed to the actions of ibuprofen, some of which may have a bearing on the overall analgesic results.
These COX-independent effects are non-enantioselective (i.e. induced by both R-ibuprofen and S-ibuprofen). Such effects may include inhibition of neutrophil attraction and activation, which contributes in part to the antipyretic effect of ibuprofen. Additionally, NSAIDs in general may infiltrate cell membranes and disrupt the activity of G proteins, thereby interfering with cellular signalling processes.

THERAPEUTIC APPLICATION

Treated with over-the-counter medications. It is widely used as an analgesic, an anti-inflammatory and an antipyretic agent. Racemic ibuprofen and S(+) enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis and soft tissue disorder. A number of other actions of NSAIDs can also be attributed to the inhibition of prostaglandins or thromboxane synthesis, including alteration in platelet function, prolongation of gestation and labor, gastrointestinal mucosal damage, fluid and electrolyte imbalance, premature closure of ducts arteriosus and bronchial asthma.
The main therapeutic applications of ibuprofen are as follows:

PATENT DUCTUS ARTEROSUS (PDA)

This is a frequent complication in premature infants. So far, intravenous indomethacin is the standard mode of medical therapy. However, because of adverse effects of indomethacin, other
PG inhibitors such as ibuprofen have been studied for the closure of ducts arteriosus, and results indicated that ibuprofen is as effective as indomethacin.

RHEUMATOID AND OSTEO-ARTHRITIS (RA AND OA)

Ibuprofen is widely used in the management of numerous inflammatory, musculoskeletal and rheumatic disorders, because they are highly effective having minimal toxicities. Ibuprofen 2400 mg per day resulted in rapid improvement and complete resolution of gouty arthritis within 72 hours. In doses of approximately 2400 mg daily, it is equivalent to 4g of aspirin in terms of anti- inflammatory effects. Higher doses, 1200 to 1600 mg per day have been compared with a number of NSAIDs and it has been found to be as effective and well tolerated. Osteoarthritis is very common and treatment involves NSAIDs, particularly ibuprofen. For control of joint symptoms, diclofenac, ibuprofen, tolmetin and naproxen are equally effective. Roughly 1% of rheumatoid arthritis (RA) patients receiving NSAIDs are prone to develop major GI bleeds. With ibuprofen, gastric toxicity has been observed in 10 - 32% of patients.

INTERACTIONS OF IBUPROFEN

Sometimes, one medication can interfere with the effects of another. Specialists refer to this as drug interaction.
Drugs that may interact with ibuprofen include Trusted Source:

- Lithium
- Warfarin
- Oral hypoglycemics
- High dose methotrexate

- Medication for lowering blood pressure
- Angiotensin-converting enzyme inhibitors
- Beta-blockers
- Diuretics

CHEMISTRY OF IBUPROFEN

Ibuprofen is practically insoluble in water, but very soluble in most organic solvents like ethanol (66.18 g/100 mL at 40 °C for 90% EtOH), methanol, acetone and dichloromethane. The original synthesis of ibuprofen by the Boots Group started with the compound 2-methylpropylbenzene. The synthesis took six steps. A modern, greener technique for the synthesis involves only three steps. (R)-Ibuprofen Structural Formula V1.svg (S)-Ibuprofen Ibuprofen, like other 2-arylpropionate derivatives such as ketoprofen, flurbiprofen and naproxen, contains a stereo center in the α-position of the propionate moiety.

The product sold in pharmacies is a racemic mixture of the S and R-isomers. The S (dextrorotatory) isomer is the more biologically active; this isomer has been isolated and used medically (see dexibuprofen for details). the isomerase enzyme, alpha-methylacyl-CoA racemase, converts (R)-ibuprofen into the (S)-enantiomer.

SIDE EFFECTS

Heartburn and a rash. Compared to other NSAIDs, it may have other side effects such as gastrointestinal bleeding. It increases the risk of heart failure, kidney failure, and liver failure. At low doses, it does not appear to increase the risk of heart attack; however, at higher doses it may. Ibuprofen can also worsen asthma. While it is unclear if it is safe in early pregnancy, it appears to be harmful in later pregnancy and therefore is not recommended. Like other NSAIDs, it works by inhibiting the production of prostaglandins by decreasing the activity of the enzyme cyclooxygenase (COX). Ibuprofen is a weaker anti-inflammatory agent than other NSAIDs.

MEDICAL USES

Ibuprofen is used primarily to treat fever (including post-vaccination fever), mild to moderate pain (including pain relief after surgery), painful menstruation, osteoarthritis, dental pain, headaches, and pain from kidney stones. About 60% of people respond to any NSAID; those who do not respond well to a particular one may respond to another.

It is used for inflammatory diseases such as juvenile idiopathic arthritis and rheumatoid arthritis. It is also used for pericarditis and patent ducts arteriosush.

DOSE

For minor aches, mild to moderate pain, menstrual cramps, and fever, the usual adult dose is 200 or 400 mg every 4 to 6 hours. Arthritis is treated with 300 to 800 mg 3 or 4 times daily. When under the care of a physician, the maximum dose of ibuprofen is 3.2 g daily.

Otherwise, the maximum over-the-counter (OTC) dose is 1.2 g daily, depending upon the age, weight, and any current medical conditions of the patient.

Individuals should not use ibuprofen for more than 10 days for the treatment of pain or more than 3 days for the treatment of a fever unless directed by a physician.

Children 6 months to 12 years of age usually are given 5-10 mg/kg of ibuprofen every 6-8 hours for the treatment of fever and pain. The maximum dose is 40 mg/kg daily.

Juvenile arthritis is treated with 20 to 40 mg/kg/day in 3-4 divided doses. Ibuprofen should be taken with meals to prevent stomach upset.

Recent advances

NASAL AIRWAY INFLAMMATION CAUSED BY RHINOVIRUS

In ammation initiated by viral infection is a dynamic process, a complex series of reactions for the purpose of protecting and restoring natural function. The reactions in the nose will be discussed based on the four classic signs of in ammation:

1. Vasodilatation (redness)
2. Edema (swelling)
3. Cellular in ltration
4. Pain (sensory nerve stimulation and hyper-responsiveness).

1)Nasal vasodilatation

Vasodilatation causes hyperemia and increased blood flow and volume due to distension of submucosal venous sinuses (Mygind, 1986). Increased blood flow in the nasal mucosa by itself does not lead to plasma

exudation. The nasal mucosa is normally red, so objective changes during viral infection are difficult to detect. Nasal obstruction is thought to be a marker for vasodilatation. Nasal obstruction is present during the first week of a viral cold (Hendley et al., 1969) and can be evaluated by acoustic rhinometry (Hytoenen et al., 1996) or self-assessment (Groenborg et al., 1983b).

2)Nasal and sinus mucosal edema

Increased microvascular permeability leads to plasma exudation which causes both mucosal edema and an increase in nasal secretions. Mucosal swelling is not evident by anterior rhinoscopy or in biopsies from the inferior turbinate in patients with colds (Winther et al., 1984a). Albumin may be used as a marker for exudation since only a minor proportion of albumin is thought to originate from nasal and lacrimal glands (Mygind, 1996). Both albumin and brinogen levels increase in nasal secretions in symptomatic patients with rhinovirus infections (Winther et al., 2002a). Inflammatory edema in the nasal mucosa seems to produce vascular leakage and exudation resulting in increased nasal secretions rather than mucosal edema/swelling.

Opacication of the paranasal sinus by computerized tomography (CT scan) is present in the majority of patients with colds (Gwaltney et al., 1994). This is Often referred to as “mucosal thickening” but is in fact more likely to be secretion (Winther et al., 2002a). Likewise, Eustachian tube dysfunction, which is present in the majority of patients with colds (Winther et al., 2002b), may be caused by increased secretions in the Eustachian tube rather than by “true mucosal swelling”.

3)Cellular in Itration

Viral infection in the nasal mucosa results in an early and transient in ltration of neutrophils (Winther et al., 1984a, c). This accumulation of neutrophils occurs in spite of the absence of a concomitant bacterial infection (Winther et al., 1984b). The number of neutrophils in nasal washes seems to correlate with symptoms (Naclerio et al., 1987). No changes in the number of lymphocytes in the lamina propria

CONCLUSION

Ibuprofen is a drug which provide analgesic effect. But at the standard doses used in different painful conditions, ibuprofen is usually superior. This means that Ibuprofen provides more patients with a degree of pain relief that patients feel worthwhile.

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