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Review on Ketoprofen (Anti-Inflammatory Drug)

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ABSTRACT

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) widely utilized for its analgesic, anti-inflammatory, and antipyretic properties. This review article examines ketoprofen's pharmacological profile, efficacy, and therapeutic applications, particularly in the management of acute and chronic pain, including dysmenorrhea, osteoarthritis, and rheumatoid arthritis. Ketoprofen exerts its effect by inhibiting the cyclooxygenase (COX) enzymes, COX-1 and COX- 2, reducing the synthesis of prostaglandins responsible for pain and inflammation. Various formulations of ketoprofen are available, including oral tablets, topical gels, suppositories, and injectables, each tailored to specific clinical needs and patient preferences. Recent advancements in topical and extended-release formulations have improved patient adherence and minimized gastrointestinal side effects traditionally associated with NSAIDs. However, ketoprofen remains contraindicated in patients with certain cardiovascular, renal, and gastrointestinal conditions, underscoring the need for careful patient selection and dosage adjustment. This review highlights ketoprofen's clinical efficacy, safety profile, and evolving therapeutic applications, providing insight into its role within the broader scope of pain management strategies.

Keywords- Ketoprofen, Dysmenorrhea, Osteoarthritis, Cyclooxygenase**.**

I. INTRODUCTION

Non-steroidal anti-inflammatory medicines (NSAIDs) are commonly used to treat musculoskeletal illnesses such rheumatoid arthritis and osteoarthritis, as well as symptoms after trauma. Systemic NSAIDs can cause substantial side effects, particularly in the gastrointestinal, renal, and cardiovascular.[1] Ketoprofen is an NSAID with analgesic, anti- inflammatory, and antipyretic effects. K is a widely utilized NSAID because to its fast and effective activity.[2] It suppresses the manufacture of prostaglandins by reversibly inhibiting cyclooxygenases.1 This oral medication treats acute and chronic pain caused by inflammatory responses, and is commonly recommended for arthritis-related pain.[3] The oral intake of ketoprofen, like other NSAIDs, has negative side effects on the gastrointestinal tract.[4] Topical medicines offer fast and effective treatment with minimal side effects.[5] Transdermal delivery of ketoprofen is gaining popularity as an alternative to oral administration to reduce systemic effects. Ketoprofen is applied to the skin as gels, lotions, or sprays, allowing it to enter deeper into the tissue layers and circulate throughout the body.[6] The drug is currently available in: capsule, tablet, solution, injectable solution, suppository, and topical gel formulations.[7] Ketoprofen is intended to penetrate the skin to the underlying tissue layers and circulate throughout the body. Transdermal administration of ketoprofen is non invasive, painless, easy to administer, avoids contact with GI organs, and prevents first-pass liver metabolism. This technique may improve the bioavailability and

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predictability of ketoprofen.[8] One major disadvantage of these dose formulations is their difficulty to swallow. The condition affects around 35% of the population, leading to substantial non-compliance and inefficient therapy2. This is especially challenging for pediatric and geriatric patients, as well as those who are ill in bed, working, or traveling without access to water. It also affects those with conditions such as Parkinsonism, Motion sickness, unconsciousness, and mental disabilities.[9] Therefore, it must be protected from both light and moisture. The plasma elimination half-life is 2–4 hours. It has a simple metabolism and does not accumulate with repeated dosages. These qualities enable quick start of action, adjustable dosage, and consistent tolerance and pharmacodynamic effects.[10]

II. PHYSICOCHEMICAL PROPERTIES OF KETOPROFEN

Ketoprofen is known as 2-(3-benzolphenyl)propionic acid. Figure 1 shows the molecular formula for ketoprofen (C16H14O3). The molecular weight is 254.3 (13, 18). ketoprofen has a pKa of 5.94 in methanol: water (3:1) and n-octanol water partition coefficient of 0.97 at buffer pH 7.4.[11]

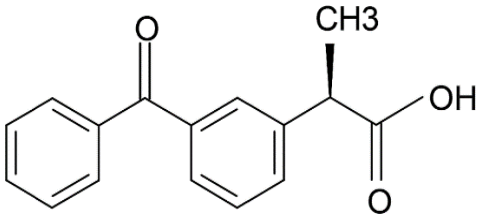

Fig. 1: Ketoprofen

Ketoprofen is odorless, white or nearly white crystalline powder that melts at 93-96°C. It is highly soluble in acetone, ethanol, methylene chloride, and strong alkaline pH (4, 8, 12, 13, 19). It has low solubility in water and acidic environments due to its pH-dependent solubility profile. Poor solubility decreases bioavailability and poses a significant challenge in drug development [12]. Ketoprofen is classified as class II by the Biopharmaceutical Classification Systems (BCS), indicating that its low water solubility limits absorption and bioavailability. This class has strong permeability, poor solubility, and low dissolution rate compared to the supplied dose ketoprofen is a photolabile medication. Therefore, Ketoprofen must be protected from both light and moisture. Exposing aqueous ketoprofen solutions (e.g. sodium salt) to visible light and ultraviolet radiation at 254 nm or daylight for an hour at room temperature produces (3- benzoylphenyl) ethane, which is then converted to (3-benzoylphenyl) ethanol and (3-benzoylphenyl) ethanone and analyzed using thin layer chromatography and high- performance liquid chromatography. Samples maintained in darkness exhibit minimal degradation after 24 months. [13]

Physical mixes of Ketoprofen were created using several excipients, including lactose, mannitol, polyvinylpyrolidone sorbitol, K30, beta-cyclodextrin, polyethyleneglycol 20.000, and urea in a 2:1 ratio (drug/excipient) [14]. Samples and KP were stored in sealed glass vials at 40, 50, and 60°C for 12 weeks. KP, alone or in combination with lactose, mannitol, sorbitol, or beta- cyclodextrin, was physically stable at 60°C for 12 weeks. KP in polyvinylpyrolidone K30, polyethyleneglycol 20.000, or urea were unstable when stored at 40°C, 50°C, and 60°C.[15]

It has one asymmetric carbon and a chiral center, resulting in two enantiomers: R (-) and S (+). Figure 2 shows the stereochemistry of KP. Both enantiomers exhibit distinct biological functions. KP has enantiomeric selectivity, with the S (+)-enantiomer responsible for the pharmacological and pharmacodynamic actions. The R (-) enantiomer has lower or no therapeutic activity (20). Some enzymes and microorganisms can cause the inactive R (-)- enantiomer (distomer) to undergo configurational inversion and become the active enantiomer. The R(-)-enantiomer-enzyme complex reacts with endogenous triacylglycerols in fatty tissues, producing some profen residues. The R (-) enantiomers do not reduce COX activity. They can mitigate the negative gastrointestinal symptoms associated with racemic versions. R (-)-enantiomers can alter neutrophil activity and intestinal permeability. [16]

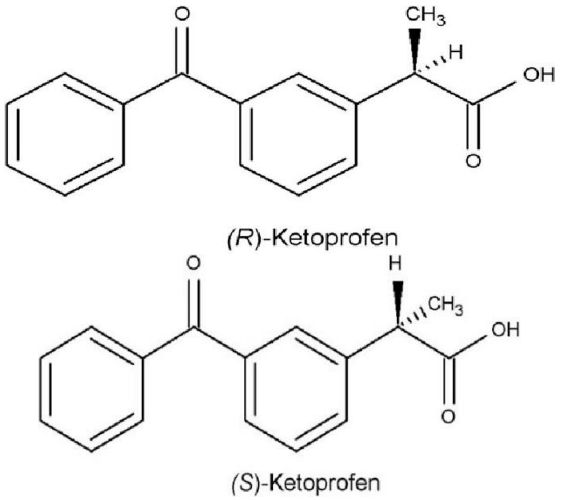

Fig: 2 shows the stereochemistry of KP

III. PHARMACOLOGY (MECHANISM OF ACTION OF KETOPROFEN)

Ketoprofen is an NSAID with both analgesic and antipyretic effects. KP, like other NSAIDs, inhibits the cyclooxygenase route of arachidonic acid metabolism, which is responsible for its pharmacodynamic effects. Arachidonic acid is the primary precursor to eicosanoids. Arachidonic acid is released from membrane phospholipids through enzymatic activation of phospholipid A2[17]. It is

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Volume-3 Issue-6 || December 2024 || PP. 41-50

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subsequently transformed into several types of prostaglandins. KP effectively inhibits cyclooxygenase at therapeutic plasma concentrations (EC50 = 2 µg/L).
In guinea pig lung preparations perfused with arachidonic acid, Ketoprofen inhibits prostaglandin synthesis 6 and 12 times more effectively than naproxen and indomethacin, respectively. Ibuprofen, phenylbutazone, and aspirin are supposedly 800-1500 times less powerful than ketoprofen. The antipyretic action involves resetting the hypothalamus thermoregulatory region, while the anti-inflammatory and analgesic benefits stem from inhibiting prostaglandin synthesis.[18]

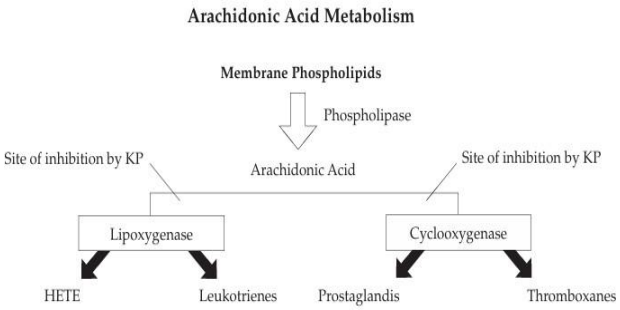

Figure 3. Schematic diagram of arachidonic acid metabolism (3).

IV. USES AND ADMINISTRATION

Ketoprofen is used to treat musculoskeletal and joint problems, including ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, as well as peri-articular illnesses including bursitis and tendonitis. It can treat postoperative pain, inflammatory illnesses like gout or soft tissue disorders, and lower fever. It is also recommended for treating acute painful shoulder syndrome and juvenile rheumatoid arthritis.[19]

It is comparable to aspirin, indomethacin, and ibuprofen in rheumatoid arthritis and to aspirin in osteoarthritis. KP can be applied in the following conditions.

- Prevention and treatment of migraine headaches.
- For sports injuries, orthopedic manipulations, and dental extractions, analgesia is necessary
- during surgical or stressful conditions.
- Infectious disorders necessitate analgesic, anti-inflammatory, and anti-pyretic properties.
- Manages dysmenorrhea after IUD implantation, as well as uterine relaxation and analgesia in post-partum, non-nursing women.[20]

In a trial of 240 patients with severe postoperative pain following cesarean section, single doses of 100 mg or 50 mg KP, a combination of 650 mg acetaminophen and 10 mg oxycodone hydrochloride, 650 mg acetaminophen, or placebo were evaluated for effectiveness and safety. Multiple doses of 100 mg or 50 mg KP, as well as a combination of 325 mg acetaminophen and 5 mg oxycodone, were evaluated for up to 7 days. The dosage- dependent impact of KP was seen, with 100 mg providing much more analgesia than the lower dose. KP (100 mg) was equally effective as the combination and provided longerlasting analgesia, except for hour 1, where the combination was superior. Significantly more patients who took repeated doses of the combination (84%) than those who took either dose of KP (70%) had adverse effects. KP at both dose levels was shown to be effective, longlasting, and well tolerated. It should be considered to be a drug of choice for the management of moderate to severe postoperative pain.[21]

Ketoprofen is available in several forms worldwide, including capsules, tablets, solutions, injectables, suppositories, and topical gels. The recommended oral dose is 150 mg twice daily with a meal; however, 200 mg commercially controlled release formulations can be taken once daily Several topical Ketoprofen formulations have been successful. Additionally, it eliminates the negative side effects of oral Ketoprofen. Ketoprofen cream has been applied to the gingiva to treat periodontal disease. Ketoprofen cream and intra-oral gel can treat osteopenia, tension-type headaches, and migraines, as well as alleviate postoperative sore throats. Administering gel to oral surgery sites resulted in better analgesic effects. A transdermal KP delivery device has been explored to reduce delayed onset muscular pain [22]. The efficacy of KP topical preparations, dissolution rate of ketoprofen nanoparticle gels, transdermal delivery of KP microemulsions, and drug delivery from a new soya-lecithin aggregate have been studied using various ointment bases [23].

Precautions and adverse effect

Ketoprofen is contraindicated in the following medical conditions:

i. Bronchospasm.

Patients with aspirin-related rhinitis, nasal polyps, and asthma may have cross-sensitivity to other NSAIDs, such as KP. KP may worsen asthma in vulnerable people by inhibiting prostaglandins and increasing leukotriene levels (24).

ii. Peptic Ulceration

Patients with active peptic ulcers, recurrent ulcers, or persistent dyspepsia should not get KP. KP causes irritation in the gastrointestinal tract (GIT) through both local and systemic actions. Upper GIT damage is primarily caused by systemic actions that impede preventive prostaglandins (24), despite potentially viable local prevention.

iii. severe renal insufficiency.

Prostaglandins synthesised in kidneys are potent vasodilators that balance the effects of vasoconstrictive stimuli (norepinephrine, angiotensin II and renin) on renal blood flow. Preventing their formation can impact renal function in some conditions.
During Ketoprofen treatment, patients may exhibit

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Volume-3 Issue-6 || December 2024 || PP. 41-50
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pathologic conditions such congestive heart failure, high renal status, cirrhosis, renal disease propensity, and renal ischaemia.

Patients with these risks rely heavily on prostaglandins to regulate renal flow.[24]

Ketoprofen is quickly removed from the bloodstream after use. To maintain therapeutic plasma levels without significant changes, regular administration is required. Frequent dose delivery may contribute to patient non-compliance. Using a sustained-release dose form once day offers pharmacokinetic and therapeutic benefits in NSAID therapy.

Ketoprofen can cause haematological side effects including as anemia, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. KP may cause kidney damage, including interstitial nephritis and nephrotic syndrome. KP may cause renal failure, especially in patients with pre-existing renal impairment. Fluid retention may lead to heart failure in older persons. Other side effects include photosensitivity, eczema, alveolitis, and pancreatitis [25]

The majority of the adverse responses are minor upper gastrointestinal issues such as nausea, dyspepsia, or epigastric discomfort. Subjective nervous system symptoms (e.g. headache, fatigue, dizziness) and lower gastrointestinal tract complaints (e.g. diarrhea, gastritis, ulcerations, abdominal burning, constipation, flatulence) are less common.

Side effects connected to the central nervous system may include headaches, vertigo, dizziness, anxiousness, tinnitus, depression, drowsiness, or sleeplessness. Hypersensitivity reactions can cause fever, angioedema, bronchospasm, and rashes.[26]

V. PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

Ketoprofen absorption has been examined in several dose forms, including solid dispersions, oral tablets, extended-release tablets, topical gels, microspheres, microemulsions, nanocapsules, and rectal suppositories.[27]

Human pharmacokinetic studies indicate that KP is quickly absorbed, processed, and eliminated after oral administration. It is almost fully absorbed by the gastrointestinal tract. Total bioavailability is dose proportionate between 75-200 mg. Plasma half-life is around 2-4 hours in healthy young volunteers. Absorption is more than 90% complete, with peak plasma levels (tmax) occurring within 1-2 hours. At a single dose of 150 mg, KP plasma concentrations can reach 15-25 µg/ml, significantly greater than therapeutic levels [27-28]. Synovial fluid KP concentrations peak at 2 hours after peak plasma levels and gradually fall, surpassing plasma levels after 4 hours of PO delivery. Taking KP with a meal does not affect its bioavailability, but it reduces Cmax by half and increases mean time to peak concentration. Circadian shifts in absorption can affect plasma peak fluctuations. KP is quickly removed from the bloodstream after dosage. To maintain therapeutic plasma levels without significant changes, regular administration is required. Frequent dose delivery may contribute to patient non-compliance. Using a sustained-release dose form once day offers pharmacokinetic and therapeutic benefits in NSAID therapy. Sustained-release pellets are recommended for daily use. [28]

Distribution

KP binds to plasma proteins at around 99%.

Therefore, it is predominantly restricted to the plasma compartment, as seen by its tiny apparent volume of distribution. KP is excellent for treating localized musculoskeletal problems as it penetrates the skin sufficiently. This study examines the bioavailability of KP in a photostabilized gel formulation without photoprotection utilizing a new dermatopharmacokinetic tape-stripping model and an established ex vivo penetration method on human skin. Analysis of the stratum corneum revealed that the formulations absorbed around 12µg/cm2 KP into the skin within 45 minutes. KP penetrates isolated skin at about 0.2 µg/cm2h for both formulations.[29]

A study examined the distribution of KP in the cerebrospinal fluid (CSF) of children aged 4–144 months. Samples of venous blood and CSF were obtained from each child 7-67 minutes after KP administration. KP concentration ratios in CSF to total plasma were consistently less than
0.01 in children. After a dosage of 1 mg/kg, the KP concentration in the CSF ranged from 1.4 to 24 ng/ml, with a median of 6.6.[29-30]

Another study utilized a synthetic triglyceride prodrug of KP (1,3-diacetyl-2-ketoprofen glyceride, DAKG) as a model for CNS delivery. KP has minimal permeability from the brain to the plasma due to full carboxyl group ionization at physiological pH and modest lipophilicity. KP's physicochemical and physiological properties limit its distribution in the brain. The addition of diacetylglyceride to the KP carboxylic group increases its lipophilicity but prevents ionization of the acid group. DAKG boosted KP transport to the brain by increasing permeability through the Blood Brain Barrier (BBB) and facilitating fast hydrolysis within the brain .[30]

Metabolism

The liver converts KP to inactive metabolites that are removed through renal excretion. KP, like other NSAIDs, is extensively metabolized to acyl-glucuronide conjugates by hepatic microsomal enzymes. Subjects' urine and bile contain little unaltered KP, independent of age or kidney function. Studies indicate that up to 80% of the dosage is retrieved in the form of glycoconjugate metabolites.[31] Other studies indicate that up to 50% of the administered dose is eliminated unaltered in urine. These findings are false because glucuronide acyl-

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conjugates easily hydrolyze to their parent molecule in vitro. [32]

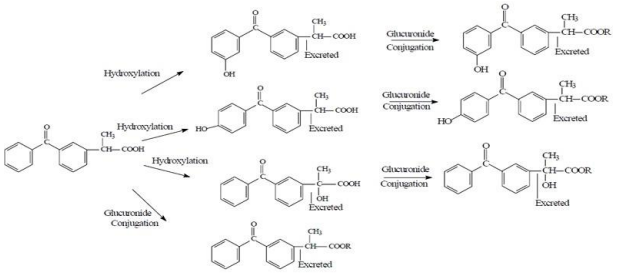

Figure 4 metabolism of ketoprofen

Elimination

KP is removed after an almost complete metabolism. Even after repeated dosing, there is minimal or no buildup in plasma due to rapid clearance. The medication is eliminated in urine in its unaltered form.

KP has a plasma clearance rate of 0.08 L/kg/h and a volume of distribution (Vd) of 0.1 L/kg following intravenous dosing. KP has an elimination half-life of 2.05 ± 0.58 hours for intravenous administration and 2 to 4 hours for capsules. Slow drug absorption affects the elimination rate, leading to a longer half-life (t1/2) compared to an intravenous dose. During a 24-hour period, roughly 80% of administered KP is eliminated in urine as glucuronide metabolites.[33]

Although enterohepatic recirculation of the medication is suspected, biliary levels have not been examined to corroborate this. Recently, it was discovered that the systemic clearance of KP is much lower in elderly patients. [34]

Drug Intrection of Ketoprofen

KP has 99% protein binding affinity, but does not affect the pharmacokinetics of other strong protein-binding medicines such oral antidiabetics or anticoagulants. KP's single-dose bioavailability remained unaltered whether administered with meal or antiacid. KP is influenced by the following medicines.

Paracetamol

KP and paracetamol combination results in a significant decrease in morphine requirement comparable to analgesic treatment alone (35).

The pharmacokinetic studies revealed that this synergistic (supra-additive) effect doesn't due to pharmacokinetic interaction, but might be associated with protein binding. This synergistic analgesic effect may be of great clinical interest, providing an alternative for pain management as lower doses of each component may cause fewer adverse effects (36)

Aspirin

In a study of 14 healthy volunteers, 13 doses of KP 50 mg every 6 hours were given with or without 975 milligrams of aspirin every 6 hours to investigate potential medication interactions. This combination results in a complicated pharmacological interaction. Salicylate pharmacokinetics remain unaltered by KP, likely because to the higher molar dosages of aspirin compared to ketoprofen Concurrent use of numerous NSAIDs should be avoided due to increased risk of adverse effect

VI. COMBINING KP AND ASPIRIN MAY LOWER SERUM KP LEVELS.[36]

Diuretics

Combining hydrochlorothiazide with KP lowers urine potassium and chloride excretion compared to using hydrochlorothiazide alone. Patients taking diuretics are more likely to develop kidney failure due to decreased renal blood flow caused by prostaglandin production suppression (37).

Warfarin

KP doesn't significantly interfere the effects of warfarin on prothrombin time. Multiple bleeding sites may be a complication of warfarin treatment and GI bleeding a complication of KP treatment. Because prostaglandins play an important role in haemostasis and KP has an effect on platelet function, concurrent therapy with KP and warfarin requires close monitoring of patients on both drug (37)

Methotrexate

Methotrexate's clearance may be altered by KP, resulting in higher serum KP levels and enhanced toxicity. KP competitively reduces methotrexate accumulation in rabbit kidney slices. This suggests that KP could increase the toxicity of methotrexate. When using KP with methotrexate, it should be administered with caution (37).

Lithium

NSAIDs increase plasma lithium levels while decreasing renal lithium clearance (37).

Antiacids

Taking magnesium hydroxide and aluminium hydroxide together does not affect the absorption of KP in capsules (38).

Probenecid

Probenecid increases both free and bound KP by reducing the plasma clearance of KP to about one-third, as well as decreasing its protein binding. Therefore, KP and probenecid combination is not recommended (39)

Product and development

KP is an NSAID that falls within the category of substituted 2-phenyl propionic acids [2-(3-benzoylphenyl)-propionic acid]. It was first synthesized in 1967 at Rhone-Poulenc Research Laboratories in Paris and approved for clinical usage as an oral formulation in France and the United Kingdom in 1973. It is currently available in over 100 countries globally. The clinical experience with KP is extensive, with an estimated 3 million patients treated annually8. Between 1998 and 2008, about 140 million patients were treated with KP gel.[40]

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KP 2.5% gel is primarily used for treating musculoskeletal pain and inflammation in muscles and joints, including contusions, distortions, strains, stiff neck, and lumbago. Topical release of active molecules is efficacious locally and has lower systemic bioavailability, leading to fewer adverse effects (AEs) compared to systemic formulations (1). To avoid irritation on mucosa and damaged skin, KP should only be applied to intact skin, either once or repeatedly. [41]

Efficacy

In controlled trials, KP gel was found to be more effective than placebo or other analgesic drugs like diclofenac or etofenamate in treating acute and chronic pain conditions, including sports injuries, low back pain, tendonitis, knee and hand osteoarthritis, and soft tissue rheumatic pain. In most studies, KP 2.5% gel was applied twice daily at dosages ranging from 40-600 mg (usually 100-300 mg) for 2-42 days (7-20 days). Several open trials (41-42) have looked into the effects of KP 1-5% gel. The study found significant improvements in pain intensity, mobility, and inflammation. The use of KP 2.5% and 5% gel resulted in considerable improvements compared to KP 1% gel. However, no statistical differences were found between the two higher concentrations for any of the assessed parameters. Another series of trials found similar results when using KP with physical therapy like iontophoresis and sonophoresis. Meta-analyses confirm the efficacy of topical NSAIDs, including KP. A quantitative systematic review of 86 randomised controlled studies including 10,160 patients found KP to be significantly more effective than placebo in reducing pain in both acute and chronic illnesses. Mason et al. (35) conducted a meta-analysis of 26 double-blind, placebo-controlled trials involving 2,853 patients to confirm the efficacy of KP. A recent Cochrane meta-analysis found that topical NSAIDs can effectively treat acute musculoskeletal conditions without causing systemic adverse events like oral NSAIDs.[42]

Safety and Tolerability

Overall, KP 2.5% gel is well tolerated (43). Meta-analyses across a diverse patient population indicate that adverse events related to KP administration are uncommon and often moderate (5, 34, 35). A 7-day double-blind, placebo-controlled research found no side effects. (44). Other trials have found that using KP did not result in any local or systemic adverse events (45). Mild pruritus and erythema were the only reported adverse events (AEs) in other trials (46). The administration of KP gel did not affect blood chemical parameters32. From January 2001 to July 2010, over 273 million patients treated with KP 2.5% gel reported 624 severe adverse reactions (SDRs) in 437 patients, with an incidence of 0.16/100,000 (data on file). Most adverse drug reactions (ADRs) were cutaneous, including hypersensitivity and photosensitivity reactions. KP gel treatment has been linked to photosensitivity, which can lead to persistent dermatitis (47). Topical administration is unlikely to cause drug interactions, and there have been no reports of overdosage.[48] Avoid using KP during pregnancy, nursing, and in children and adolescents under the age of 15. The main safety concern with KP gel is its association with skin problems, including photosensitivity responses.[48] To lessen the incidence of these events, patients should avoid exposing treated skin to sunlight during the application process and for two weeks thereafter. Avoid applying KP gel near or over wounds, and keep it away from the eyes. Based on extensive clinical experience, KP has a flavorable safety profile, with uncommon cases of skin problems (49]

VII. VARIOUS DRUG DELIVERY OF KETOPROFEN

Ketoprofen is a nonsteroidal anti-inflammatory medication (NSAID) that is often used to relieve pain, reduce inflammation, and lower fevers. Different drug delivery systems (DDS) for ketoprofen are intended to improve therapeutic efficacy, increase bioavailability, and lessen side effects, particularly gastrointestinal irritation. Here are several different medication administration routes for ketoprofen:[50]

- ***Oral Delivery Systems:***
  - Conventional Tablets or Capsules:
    - Traditional oral formulations are the most common form. They deliver ketoprofen directly into the gastrointestinal system for absorption.
    - Disadvantages: Poor bioavailability due to extensive first-pass metabolism in the liver, leading to gastrointestinal side effects.
  - Modified-Release Formulations:
    - Extended-Release (ER) or Sustained-Release (SR) Tablets:
      - These formulations release ketoprofen gradually over time, maintaining therapeutic plasma concentrations and reducing the frequency of dosing.
      - Benefits: Reduces the risk of GI side effects and provides longer-lasting pain relief.
  - Enteric-Coated Tablets:
    - The enteric coating protects ketoprofen from being released in the acidic environment of the stomach, ensuring it is released in the small intestine, where absorption is more flavorable.
    - Benefits: Reduces GI irritation and ulcers, which is a common issue with traditional NSAIDs.
  - Effervescent Tablets:
    - These are designed to dissolve in water before administration, improving solubility and speed of absorption.
    - Benefits: Quicker onset of action and potentially better absorption.[51]
- ***Topical Delivery Systems:***
  - Creams, Gels, or Ointments:
    - Ketoprofen can be incorporated into topical

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preparations to be applied directly to the skin over the affected area. This local delivery reduces systemic side effects.
- Benefits: Ideal for localized pain (e.g., joint or muscle pain) and minimizes systemic exposure, reducing the risk of GI or cardiovascular side effects.
- Transdermal Patches:
- Ketoprofen patches provide controlled, sustained delivery of the drug through the skin, providing long-term pain relief.
- Benefits: Steady drug release over time with reduced side effects, ideal for chronic pain management.
- Iontophoretic Delivery:
- Uses a small electric current to enhance the penetration of ketoprofen through the skin.
- Benefits: Allows for deeper tissue penetration and localized treatment of pain with fewer systemic side effects.[52]

- ***Parenteral (Injectable) Delivery Systems:***
- Intravenous (IV) or Intramuscular (IM) Injection:
- Ketoprofen can be administered directly into the bloodstream for rapid pain relief, especially in acute settings like surgery or severe pain.
- Benefits: Provides fast onset of action, bypassing the gastrointestinal system and first-pass metabolism.
- Liposome-Encapsulated Ketoprofen:
- Liposomes are lipid-based vesicles that can encapsulate ketoprofen and target it to specific tissues or release it over time.
- Benefits: Enhanced drug delivery to target tissues, reduced side effects, and better control over the drug's release.

- ***Inhalation Delivery Systems:***
- Nebulized Ketoprofen:
- Aerosolized ketoprofen delivered via nebulizers may be useful in treating localized inflammation in the respiratory tract or in patients who cannot take oral medications.
- Benefits: Fast absorption via the lungs, offering a rapid onset of action for certain conditions.[53]

- ***Nano systems:***
- Nanoparticles or Nanocarriers:
- Ketoprofen can be encapsulated in nanoparticles or other nanocarriers like dendrimers or micelles. These systems can enhance the solubility, stability, and bioavailability of ketoprofen.
- Benefits: Improved drug targeting, sustained release, and reduced side effects.
- Nanostructured Lipid Carriers (NLCs):
- These lipid-based nanoparticles can increase the solubility of ketoprofen, leading to better absorption and controlled release.
- Benefits: Enhanced bioavailability and sustained release, with reduced gastrointestinal irritation.

- ***Mucosal Delivery Systems:***
- Buccal or Sublingual Tablets:
- Ketoprofen can be delivered via the buccal or sublingual route, where it rapidly dissolves and is absorbed through the mucosal membranes directly into the bloodstream.
- Benefits: Quick onset of action, bypassing the gastrointestinal tract and first- pass metabolism.
- Nasal Sprays:
- Ketoprofen can be delivered as a nasal spray for rapid systemic absorption through the nasal mucosa.
- Benefits: Rapid absorption and onset of action with a lower risk of gastrointestinal side effects.

- ***Ocular (Eye) Delivery Systems:***
- Eye Drops or Gels:
- Ketoprofen is used in the treatment of eye conditions such as inflammation or post-surgical pain, where it is delivered directly to the site of action.
- Benefits: Localized treatment of eye inflammation, reducing systemic side effects.

- ***Implants or Intra-Articular Injections:***
- Depot Injections or Implants:
- Ketoprofen can be administered via slow-release implants or injections directly into joints or tissues.[54]
- Benefits: Provides prolonged local pain relief for conditions like osteoarthritis without systemic side effects.

VIII. CONCLUSION

Ketoprofen is a popular nonsteroidal anti-inflammatory medicine (NSAID) that effectively relieves pain and inflammation in a wide range of therapeutic contexts, including musculoskeletal illnesses such as osteoarthritis, rheumatoid arthritis, and acute pain. Its capacity to effectively relieve pain, inflammation, and fever stems mostly from its suppression of cyclooxygenase (COX), which reduces the formation of prostaglandins—chemicals implicated in the inflammatory response.

Efficacy tests have shown that ketoprofen has strong analgesic and anti-inflammatory properties, which are generally equivalent to other NSAIDs. It is effective for both acute pain relief, such as after surgery or injury, and chronic inflammatory disorders. One of the benefits of ketoprofen is its rapid beginning of action, which makes it especially useful for acute pain attacks. Furthermore, its availability in a variety of formulations, such as oral tablets, topical gels, and injectable forms, allows for more flexible treatment approaches and more targeted therapies, particularly for localized pain or patients who may have difficulty tolerating systemic side effects.However, ketoprofen, like all NSAIDs, can have a variety of side effects, the most serious of which are gastrointestinal (GI) disorders. These include the risk of

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Volume-3 Issue-6 || December 2024 || PP. 41-50

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peptic ulcers, GI bleeding, and perforation, which are more common with long-term or high-dose treatment. Patients with a history of gastrointestinal issues, older persons, and those taking concurrent drugs such as corticosteroids or anticoagulants are more likely to experience these side effects. Furthermore, ketoprofen has been linked to renal impairment, cardiovascular risks, and allergic reactions, making it important to exercise caution in individuals with pre-existing diseases such as hypertension, kidney disease, or heart disease.The risk profile of ketoprofen, especially in long-term usage, warrants caution. Healthcare providers must carefully analyze each patient's health status, taking into account factors such as age, comorbidities, and the possibility of drug interactions. Patients receiving prolonged or high-dose ketoprofen medication must be closely monitored for evidence of side effects, particularly GI bleeding and renal function. To summarize, while ketoprofen is an efficient and diverse therapeutic choice for pain and inflammation, its usage must be carefully monitored to reduce potential hazards. It remains an important tool in the treatment of acute and chronic pain, but the advantages must be balanced against the danger of major side effects, particularly in individuals with risk factors for gastrointestinal, renal, or cardiovascular issues. A patient-centered strategy is required for optimal outcomes with any NSAID, including adequate dose, regular monitoring, and, when necessary, the use of protective co-therapy (e.g., proton pump inhibitors).

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