



An Extensive Overview of Topical Anti-inflammatory Drugs

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Abstract : To treat acute musculoskeletal pain conditions Topical NSAIDs are used. The NSAIDs are used widely because they gives relief to the pain without causing major side effects to a person consuming orally or applying it topically. Non-steroidal anti-inflammatory Drugs (NSAIDs) applied topically are effective in great pain relief in chronic and acute musculoskeletal diseases like muscular sprain, tendon inflammation (inflammation of thick fibrous cords that attach muscle to bone.) and Degenerative joint disease. There are number of topical NSAIDs are available in market which has essential difference in their formulations. It is essential to consider and summarize the authentication of their effectiveness and safety. NSAIDs constitute a class of pharmaceutical agents that treats multiple common health concerns like fever, pain, and other inflammatory conditions like swelling, rheumatoid arthritis, abdominal pain, menstrual cramps, joint pain etc. This review article describes the introduction of musculoskeletal pain, information about topical NSAIDs , mechanism of action of NSAIDs, properties, role, classification, pharmacology, pharmacokinetics and important points regarding Topical NSAIDs.

IndexTerms - non-steroidal anti-inflammatory drugs (NSAIDs), Topical, musculoskeletal pain, inflammation

INTRODUCTION-

The most recommended drugs in the world by physicians for inflammatory conditions like pain, fever, swelling, and inflammation are non-steroidal anti-inflammatory drugs. [1] The most effective drug for musculoskeletal pain is NSAIDs. They are widely used to treat acute or chronic musculoskeletal pain. [2]. To treat patients suffering from inflammatory conditions like pain, osteoarthritis, rheumatoid arthritis, and menstrual cramps NSAIDs are mainly used. They are widely used as antipyretics and analgesics [3, 4]

NSAIDs when administered orally or intravenously, they circulate throughout the body via bloodstream. Relatively high blood levels are necessary to concentrate effectively at the site of pain and inflammation. However, these elevated concentrations throughout the body can cause various side effects, it can cause uncomfortable side effects such as indigestion, and can also cause severe side effects such as bleeding in the gastrointestinal tract. [8] Medications applied directly to the body's exterior, such as skin or mucous membranes, for treating musculoskeletal conditions are known as topical medications. These are available in the market in various types, including creams, sprays, gels, lotions, ointments, and patches. The desired rate of drug absorption often influences the choice of formulation. When slow absorption into the bloodstream is necessary to maintain low drug levels and potentially avoid significant first-pass metabolism in the liver, drug reservoir patches may be employed. This approach is used for transdermal opioids and contraceptive steroids. For quick absorption, formulations are enhanced with ingredients that boost skin penetration, sometimes aiming for high concentrations in the skin rather than the blood. Gel formulations are particularly effective for this purpose, which explains their frequent use in topical NSAIDs. Topical preparations are the preparation that is applied locally to the affected area, it provides effective concentrations in the target tissue without causing the systemic effects associated with common side effects. Topical preparations are different from transdermal drug forms that deliver a full systemic concentration of the drug through the skin into the circulations. [5]

Theoretically, a topically administered NSAID could reach therapeutic concentrations near the site of application while maintaining low, relatively safe serum levels. This approach would minimize gastrointestinal side effects, bypass first-pass metabolism, and decrease the risk of adverse reactions associated with the high serum drug concentrations typically required for efficacy in systemic oral formulations. [6]

Topical NSAIDs are formulated in such a way that they can be used to direct application to the area of pain, they produce a localized pain-relieving effect at the same time they avoid body-wide distribution of drugs in physiologically active concentrations. The method of topical administration is limited to painful medical conditions specifically sprains, strains, and tendon or muscle soreness. They are not be used for open wounds be they accidental or surgical, so they are not suitable for broken skin.[8]

Topical NSAIDs were developed to ease musculoskeletal pain and lessen or mitigate the frequency of adverse effects associated with parenteral or oral NSAIDs, which can be severe sometimes and associated with mortality. [7]

MUSCULOSKELETAL PAIN-

To treat acute musculoskeletal pain in adults, topical non-steroidal anti-inflammatory drugs are used. Conditions like a sprained ankle or a muscle pull come under acute musculoskeletal pain. However, these conditions get better within two or three weeks without treatment but it can be truly painful while they last. Topical non-steroidal anti-inflammatory (NSAIDs) are in the form of gels, creams, sprays, or plasters. They are used on the undamaged skin where it hurts. Topical NSAIDs enter the skin, enter joints, and minimize processes causing pain in the joints. The concentration of drugs in the blood with topical NSAIDs is much lower than with the same drug administered orally. They reduce the risk of dangerous effects.[9] Musculoskeletal pain represents a considerable health issue, with approximately 20.33 of people comprehensively living with painful musculoskeletal conditions. The condition of musculoskeletal pain involves a wide range of health conditions affecting bones, joints, and muscles and rarer conditions of vulnerable systems. This includes lower back pain, osteoarthritis, neck pain, rheumatoid arthritis, gout, and lupus. Musculoskeletal pain conditions include various symptoms like loss of mobility, stiffness, etc. They constantly interrupt the normal routine of affected people. [10] Painful musculoskeletal conditions are common worldwide and affect a large number of people. The most common musculoskeletal pain is lower back pain and osteoarthritis. Approximately more than 10 million and 8.5 million UK citizens are affected

with lower back pain and osteoarthritis. [11]

MECHANISM OF ACTION –

The NSAIDs give their action by inhibiting the enzyme cyclooxygenase (COX). To convert arachidonic acid into thromboxanes, prostaglandin, and prostacyclins, cyclooxygenase is required. [12] Thromboxanes play a role in platelet aggregation, prostaglandin causes vasodilation, increases thermoregulatory set point, and plays a role as an analgesic. Two distinct cyclooxygenase enzymes exist: COX-1 and COX-2. Cox-1 gets naturally expressed in the body and plays a role in maintaining the filling of gastrointestinal mucosa, order function, and platelet adhesion.COX-2 is not typically produced in the body under normal conditions. It is produced in response to inflammation. Most of the NSAIDs inhibit both COX-1 and COX-2 as they are non-selective. Still, selective COX-2 NSAIDs (e.g. Celecoxib) only target COX-2 and give their action.[13]

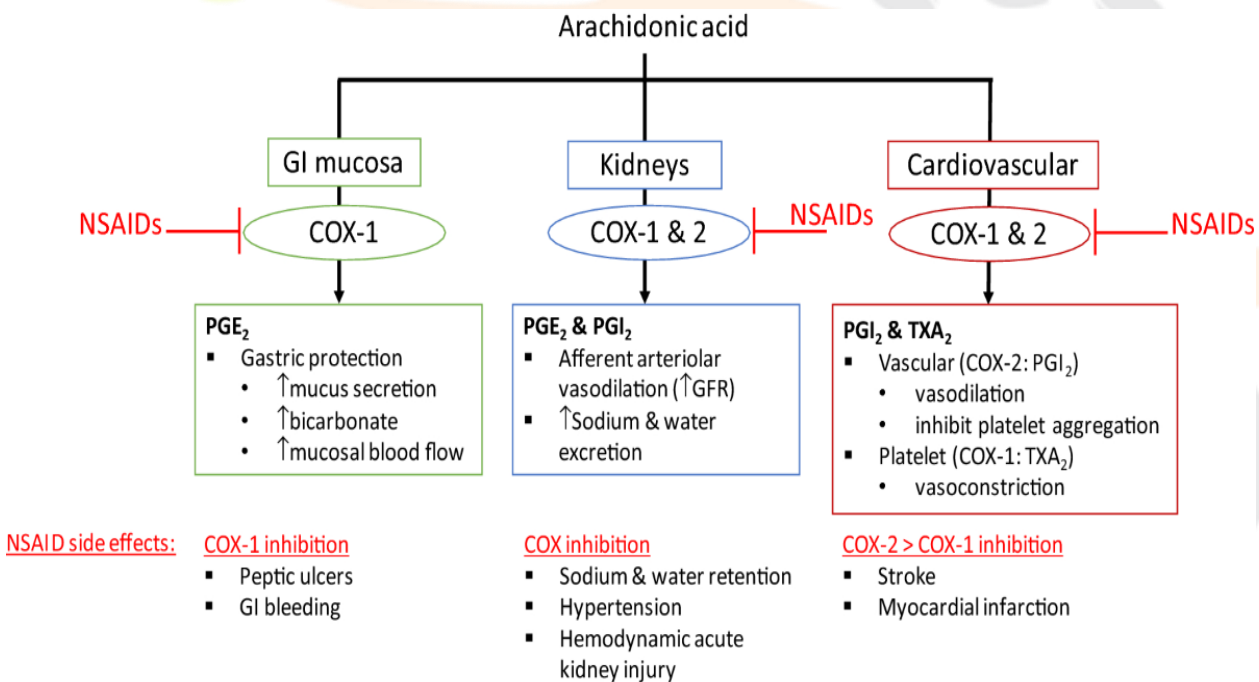


Fig NSAID- -intermediated COX inhibition

COX- Cyclooxygenase

NSAID – Non-steroidal anti-inflammatory Drugs.

CLASSIFICATION OF NSAIDs-

NSAIDs are generally divided into groups grounded on their chemical structure and selectivity acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acid (naproxen), ibuprofen, acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxiam), anthranillic acids (meclofenamate, mefenamic acids), naphthylamine (nabumetone) and

picky COX- 2 impediments (celecoxib, etoricoxib). Topical NSAIDs (diclofenac gel) are also available for use in acute tenosynovitis ankle sprains and soft towel injuries. [14,15,16,17]

A.Non-selective NSAID

1. Diclofenac
2. Diflunisal
3. Etodolac
4. Fenoprofen
5. Flurbiprofen
6. Ibuprofen
7. Indomethacin
8. Ketoprofen
9. Ketorolac
10. Mefenamic acid
11. Meloxicam
12. Nabumetone
13. Naproxen
14. Oxaprozin
15. Piroxicam
16. Sulindac
17. Tolmetin

B. Selective COX- 2 NSAIDs

1. Celecoxib
2. Rofecoxib
3. Valdecoxib

Still, rofecoxib and valdecoxib were withdrawn from the request in 2004 and 2005, independently.

PHARMACOLOGY OF NSAIDs –

More than 90 of the NSAIDs are largely bound to tube proteins. These drugs generally parade extensively well bioavailability in monogastric species upon oral, subcutaneous and intramuscular administration due to their moderate to high lipid solubility (an aspect that also allows their penetration of blood- brain barricade).[18]

Direct Urinary excretion of the parent drug is low due to high list with tube proteins; hepatic metabolism clears out the NSAIDs from the body as inactive metabolites that are excreted in urine and cattiness. Drug elimination by concurrence and terminal half- life is largely species specific.

The microsomal enzymes cytochrome P450 (CYP)- containing-mixed- function oxidase system is responsible for ultimate of the NSAIDs metabolism wherein CYP2C9 is the most important oxidase primarily responsible for metabolism. Especially, allelic variations in the protein (including CYP2C9 * 2 and CYP2C9 * 3) affect the pharmaco-therapeutic effectiveness of the medicine in case-specific manner.[19]

Hence, pharmacogenomics variability of P450 in a population also correlates well with varying degree of metabolism of the drugs among individualities or racial groups. [20]

Pharmacokinetics of Topical NSAID –

1. Penetration Through the skin –

There is the need to understand the anatomy of skin and physiochemical process involved in absorption across the skin barrier to formulate the topical dosage form and to efficiently administer an NSAID to the surrounding soft tissues and joints. The drugs are transported through the different skin layers to reach its site of action in bone, soft tissue or the systemic circulations are stratum corneum, the dermis, the basal membrane and the epidermis.[21]

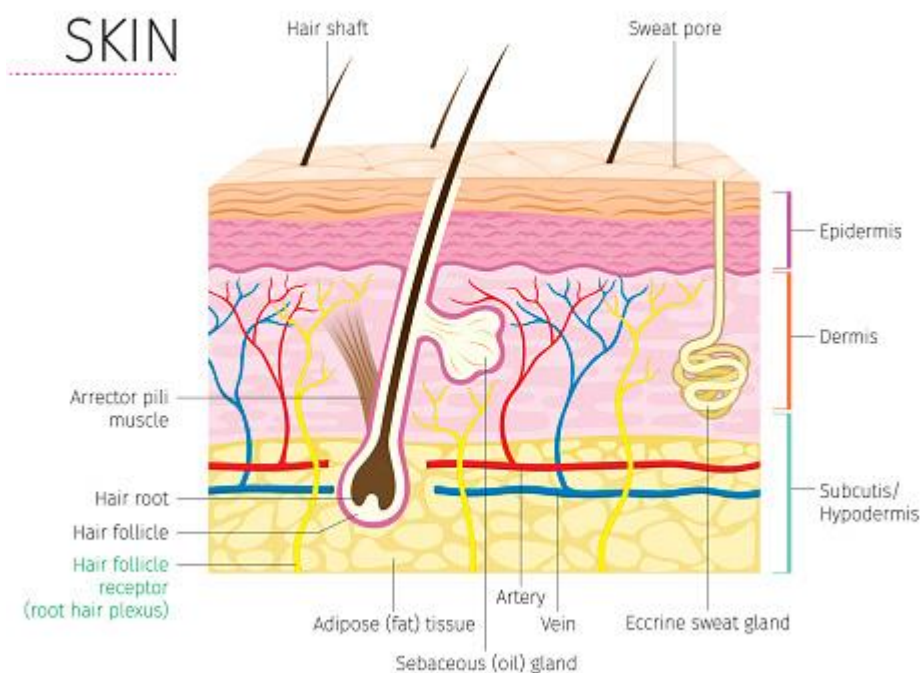


Fig. Representation of the skin layers through which medicine must be transported to reach its point of action

2. Differences in Formulation –

The topical NSAID expression may greatly impact its immersion and penetration through the skin. Differences in the expression may be grounded on the formulations of topical NSAIDs greatly influence their absorption and penetration through the skin.

The formulations differ based on

- The form of dosage - (e.g. gel v/ s result in v/ s patch)
- Different salt of same molecule – (e.g. diclofenac sodium v/s diclofenac potassium v/s diclofenac epiolamine)
- Facilitated transport (e.g. lipid conflation v/ s solid nanoparticles)
- Penetration enhancement styles, either chemical (e.g. addition of penetration enhancer like menthol v/s dimethyl sulfoxide (DMSO) or Physical (e.g. addition of penetration enhancer similar to iontophoresis) [23]

Administration of topical ketoprofen 110 mg twice a day produced a mean through tube attention of 81.2(range 4.6 – 6.77) ng/ml [24], which is only 0.1- 17 of the tube attention achieved following oral administration of 50 mg ketoprofen four times daily. [25]

PROPERTIES OF TOPICAL NSAIDs-

- Topical non-steroidal anti-inflammatory medicines (NSAIDs) give original analgesic and anti-seeditious effects with minimum systemic uptake –**

NSAIDs inhibit the cyclooxygenase enzyme, which gives action by reducing inflammation and pain. In contrast to oral administration, topical NSAIDs act locally, with only about 5% absorbed into the bloodstream. [26]

- Topical NSAIDs give similar pain relief to oral NSAIDs in cases with specific painful conditions-**

Meta-analyses have shown that topical NSAIDs handed analogous pain relief to oral NSAIDs for cases with chronic osteoarthritis and for cases with acute musculoskeletal pain. [26,27]

- Topical NSAIDs are effective for targeting certain painful conditions.**

For acute strains, muscular sprains, topical diclofenac, and ketoprofen are used.[26]

- Topical NSAIDs are more safe than oral NSAIDs –**

Substituting topical NSAIDs for oral NSAIDs reduces the prevalence of severe gastrointestinal adverse events, with 1 study showing a drop from 26 to 17. [27,28]

4. Topical NSAIDs have a part in the operation of mild to moderate musculoskeletal pain –

NSAIDs are more effective than other pharmacological approaches in the operation of pain associated with different musculoskeletal conditions. Still, when used as oral treatment they may be associated with systemic (especially gastrointestinal).

5. Topical NSAIDs are more safe than oral NSAIDs –

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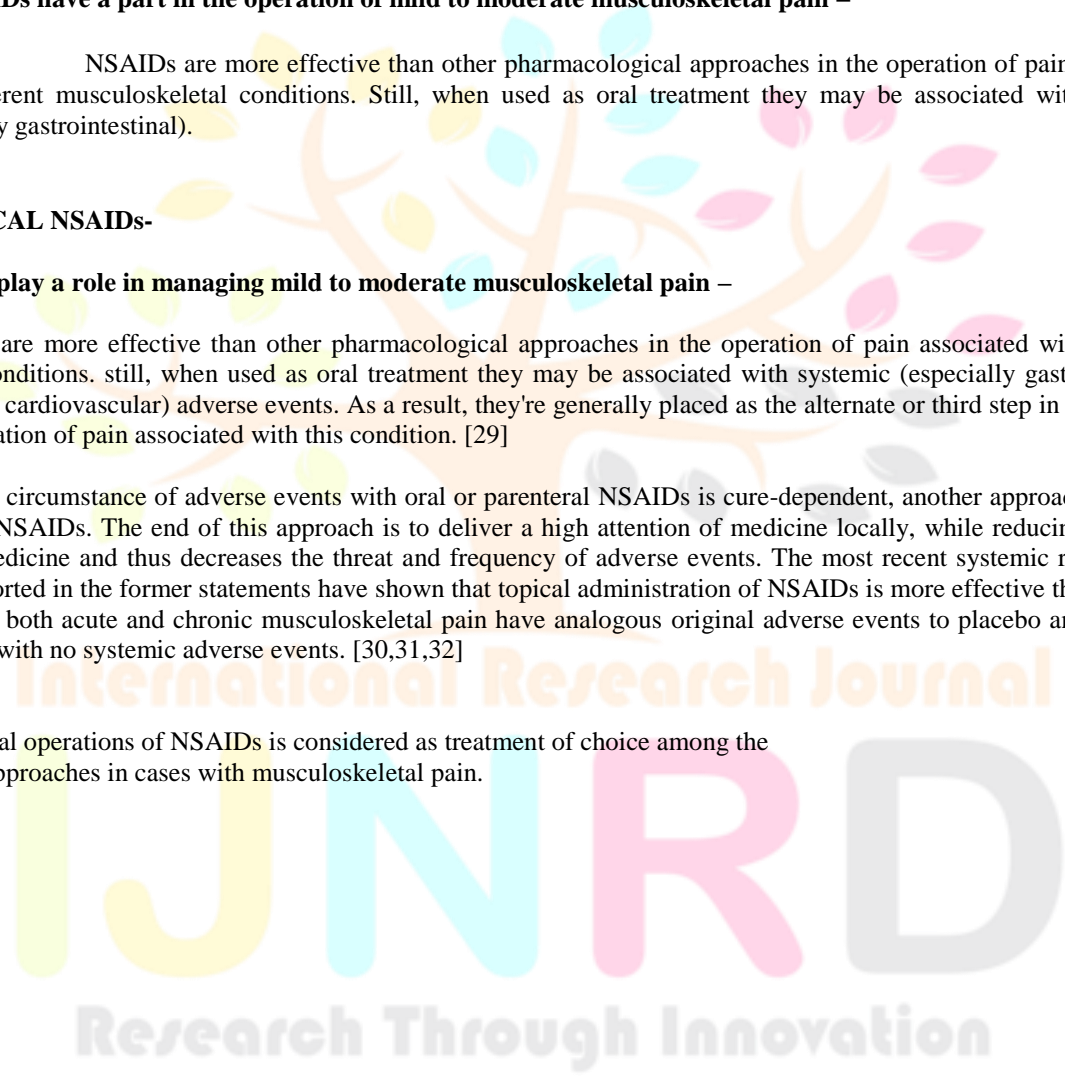
ROLE OF TOPICAL NSAIDs-

Topical NSAIDs play a role in managing mild to moderate musculoskeletal pain –

NSAIDs are more effective than other pharmacological approaches in the operation of pain associated with different musculoskeletal conditions. still, when used as oral treatment they may be associated with systemic (especially gastrointestinal and less constantly cardiovascular) adverse events. As a result, they're generally placed as the alternate or third step in the scale or algorithms of operation of pain associated with this condition. [29]

Since the circumstance of adverse events with oral or parenteral NSAIDs is cure-dependent, another approach has been the use of topical NSAIDs. The end of this approach is to deliver a high attention of medicine locally, while reducing systemic exposure to the medicine and thus decreases the threat and frequency of adverse events. The most recent systemic reviews and meta- analysis reported in the former statements have shown that topical administration of NSAIDs is more effective than placebo in the treatment of both acute and chronic musculoskeletal pain have analogous original adverse events to placebo and are safer than oral NSAIDs with no systemic adverse events. [30,31,32]

In summary, topical operations of NSAIDs is considered as treatment of choice among the pharmacological approaches in cases with musculoskeletal pain.



RESULT-

The review article presents a comprehensive analysis of various topical anti-inflammatory drugs, mainly non-steroidal anti-inflammatory drugs (NSAIDs)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Topical NSAIDs, such as diclofenac and ibuprofen, demonstrate effective pain relief and inflammation reduction with a favorable side effect profile compared to oral NSAIDs. They are particularly beneficial for localized pain and inflammatory conditions.

CONCLUSION -

The review underscores the essential role of topical anti-inflammatory drugs in managing various inflammatory skin conditions. NSAIDs and emerging therapies are valuable alternatives, particularly for patients at risk of corticosteroid-related side effects. Overall, a personalized approach, considering patient-specific factors and preferences, is crucial for achieving optimal therapeutic outcomes in the management of inflammatory conditions.

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