INTRODUCTION

Inflammation may be defined as the series of changes that occur in living tissues following injury. Injury may be caused due to various exogenous and endogenous stimuli, which in turn initiate protective response in the host cell [1-3].

The signs of inflammation are:
1. Rubor (Redness)
2. Tumor (Swelling)
3. Calor (Heat)
4. Dolor (Pain)
5. Futio leasa (Loss of functional activities).

The term non-steroidal anti-inflammatory drugs, in short NSAIDs, encompass all the heterogeneous group of compounds that possess analgesic, antipyretic (lowers elevated body temperature) and also anti-inflammatory properties [6-10]. The exception to this is Paracetamol and certain other drugs which are devoid of anti-inflammatory actions. The NSAIDs are also termed non-narcotic analgesic agents. However, the analgesic action produced by these agents is of relatively low degree than opioid analgesics.

Aspirin, is the prototype drug of NSAIDs. NSAIDs have attained the status of being the most commonly used OTC drugs. The traditional or conventional NSAIDs are liable to precipitate adverse gastrointestinal effects [11].

Almost three decades ago, steroids namely: prednisolone, dexamethasone, betamethasone, triamcinolone and hydrocortisone were considered to be the drug of choice as anti-inflammatory agents. Owing to the several adverse effects caused by either short-term or long-term steroid therapy, these have been more or less replaced by much safer and better tolerated nonsteroidal anti-inflammatory drugs (NSAIDs).

ABSTRACT

Inflammation can be well understood by its symptoms. The most common anti-inflammatory drug used is Aspirin. Gradually many anti-inflammatory drugs were discovered. All these were put under non-steroidal class for anti-inflammatory drugs. They possess certain general characteristics in terms of mechanism, adverse effects, therapeutic uses etc. which has been discussed in a systematic manner. The classes of NSAIDs is discussed with examples.
The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of non-steroidal anti-inflammatory drugs since he past three decades. A good number of these agents have been put into clinical usage widely and confidently thereby exhibiting therapeutic efficacy accompanied with fewer untoward reactions.[12-14]

General characteristic features of NSAIDs

1. They are non-steroidal compounds i.e., devoid of steroidal ring in their basic skeleton.
2. They possess analgesic, antipyretic and anti-inflammatory actions.
3. These NSAIDs are also termed non-narcotic, non-opioid analgesics as they do not interact with opioid receptors.
4. They do not produce CNS and respiratory depression, dependence, sleep etc., which are the characteristic features of opioid analgesics.
5. These drugs exert their therapeutic response by exerting an inhibitory effect on cyclo-oxygenases (COX-1 and COX-2), thereby inhibiting the generation of certain inflammatory prostaglandins (PGs).

General mechanism of action of NSAIDs

NSAIDs are potent inhibitors of cyclooxygenases enzymes (2 isoforms-COX1 and COX2). The non-selective NSAIDs inhibit both the isoforms, while the selective COX2 NSAIDs are inhibitors of COX2 enzyme only.

Arachidonic acid is released from the membrane phospholipids in response to disturbances of the cell membrane. This arachidonic acid undergoes metabolism to form various eicosanoids by four different pathways, only cyclooxygenase and lipoxygenase pathways are discussed here as the COX enzymes involved in this pathway are the major target for NSAIDs [15].

Prostaglandins and also thromboxanes so generated act as potent mediators of inflammation. Inflammation is brought about by inducing vasodilatation of vasculature, increasing the vascular permeability and also by sensitization of nociceptive receptors (PGE2).

NSAIDs exert their effect by inhibiting the enzyme cyclooxygenases, due to which the arachidonic acid cascade gets precluded. Such inhibition is effected by binding of drugs to the amino acid arginine, located at position 120 on the target, i.e., cyclooxygenases enzyme. The prototype NSAID i.e., aspirin and its congeners are irreversible inhibitors of COX enzyme. The non-selective COX inhibitors get bound at position 120 of both COX1 and COX2 hence are termed non selective in action. Inhibition on COX1 results in analgesic and antipyretic activity, while inhibition of COX2 results in anti-inflammatory activity [16,17].

General adverse effects of NSAIDs

a) Gastro intestinal manifestations
b) Renal manifestations
c) Renal manifestations
d) CNS manifestations
e) Hepatic manifestations
f) Hypersensitive reactions

General therapeutic uses of NSAIDs

a) Analgesics-
reduction of pain
b) Antipyretics-
lowering of body temperature when this is raised in disease (i.e. fever).
c) Anti-inflammatory agents-
modification of the inflammatory reaction

CLASSIFICATION

NSAIDs may be classified on the basis of their basic chemical structures.
a) Hetero aryl acetic acid analogues
b) Aryl propionic acid analogues
c) Aryl acetic acid analogues

d) Naphthalene acetic acid analogues

e) Gold compounds

The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of non-steroidal anti-inflammatory drugs since he past three decades. A good number of these agents have been put into clinical usage widely and confidently thereby exhibiting therapeutic efficacy accompanied with fewer untoward reactions [12-14].

General characteristic features of NSAIDs

1. They are non-steroidal compounds i.e., devoid of steroidal ring in their basic skeleton.
2. They possess analgesic, antipyretic and anti-inflammatory actions.
3. These NSAIDs are also termed non-narcotic, non-opioid analgesics as they do not interact with opioid receptors.
4. They do not produce CNS and respiratory depression, dependence, sleep etc., which are the characteristic features of opioid analgesics.
5. These drugs exert their therapeutic response by exerting an inhibitory effect on cyclo-oxygenases (COX-1 and COX-2), thereby inhibiting the generation of certain inflammatory prostaglandins (PGs).

General mechanism of action of NSAIDs

NSAIDs are potent inhibitors of cyclooxygenases enzymes (2 isoforms-COX1 and COX2). The non-selective NSAIDs inhibit both the isoforms, while the selective COX2 NSAIDs are inhibitors of COX2 enzyme only.

Arachidonic acid is released from the membrane phospholipids in response to disturbances of the cell membrane. This arachidonic acid undergoes metabolism to form various eicosanoids by four different pathways, only cyclooxygenase and lipoxygenase pathways are discussed here as the COX enzymes involved in this pathway are the major target for NSAIDs [15].

Prostaglandins and also thromboxane’s so generated act as potent mediators of inflammation. Inflammation is brought about by inducing vasodilation of vasculature, increasing the vascular permeability and also by sensitization of nociceptive receptors (PGE2).

NSAIDs exert their effect by inhibiting the enzyme cyclooxygenases, due to which the arachidonic acid cascade gets precluded. Such inhibition is effected by binding of drugs to the amino acid arginine, located at position 120 on the target, i.e., cyclooxygenases enzyme. The prototype NSAID i.e., aspirin and its congeners are irreversible inhibitors of COX enzyme. The non-selective COX inhibitors get bound at position 120 of both COX1 and COX2 hence are termed non selective in action. Inhibition on COX1 results in analgesic and antipyretic activity, while inhibition of COX2 results in anti-inflammatory activity [16,17].

General adverse effects of NSAIDs

a) Gastro intestinal manifestations
b) Renal manifestations
c) Renal manifestations
d) CNS manifestations
c) Hepatic manifestations
f) Hypersensitive reactions

General therapeutic uses of NSAIDs

a) Analgesics- reduction of pain
b) Antipyretics- lowering of body temperature when this is raised in disease (i.e. fever).

c) Anti-inflammatory agents- modification of the inflammatory reaction

**CLASSIFICATION**

NSAIDs may be classified on the basis of their basic chemical structures.

a) Hetero aryl acetic acid analogues

b) Aryl propionic acid analogues

c) Aryl acetic acid analogues

d) Naphthalene acetic acid analogues

e) Gold compounds

f) Misc. anti-inflammatory drugs

g) Salicylic acid analogues

h) Pyrazolones and pyrazolodiones

**Hetero aryl acetic acid analogues**

This constitutes an important class of NSAIDs which have gained importance in the recent past. A few classical examples of this group are, Indomethacin; sulindac; tolfmetin sodium; zomepirac sodium [18]. Eg: Indomethacin (Figure 1). Indomethacin is a non-steroid drug possessing anti-inflammatory, anti-pyretic and analgesic properties. It is usually used for the treatment of rheumatoid arthritis, spondylitis, gouty arthritis and osteoarthritis [19]. It is not an ordinary simple analgesic and owing to its reasonably serious untoward effects should be used with great caution.

![Figure 1: Indomethacin.](image)

**Aryl propionic acid analogues:**

These analogues exhibit potent anti-inflammatory properties besides usual antipyretic and analgesic characteristics [20]. A few examples of this category of compounds are flurbiprofen, ketoprofen, indoprofen, fenoprofen calcium. Eg: Ketoprofen (Figure 2). It acts by inhibiting the synthesis of leukotriens and their migration to inflamed joints [21]. It is used in the treatment of rheumatoid arthritis and osteoarthritis.

![Figure 2: Ketoprofen.](image)
Aryl acetic acid analogues

Eg: Ibuprofen (Figure 3).

Napthalene acetic acid analogues

The recent intensive quest for NSAIDs and aryl acetic acids in particular offer a brighter scope that the napthalene acetic acid analogues might turn out to be the leading compounds of an extensive series of promising clinical agents \[22-26\]. Eg: Naproxen (Figure 4).

Miscellaneous Anti-Inflammatory Drugs

Antimalarial Agents

Chloroquine and hydroxyl chloroquine belonging to the class of 4-amino-quinoline antimalarials are being used in clinical practice in the cure and treatment of rheumatoid arthritis since 1957 \[27\].

Disadvantages: Slow onset of therapeutic effect and significant ocular toxicity seemed to have shadowed the clinical supremacy of these drugs.

Uricosiric Agents

Such drugs that help in the enhanced excretion of excess uric acid through urination and thus reduce the urea concentration in the plasma are known as uricosiric agents \[28-33\]. There are 2 important agents which are frequently used in hyperuricemia viz., sulfinpurazone and probenecid both of which enhance the level of pencilllin in plasma by inhibiting its secretion. Eg: Probenecid (Figure 5).
Salicylic acid analogues

A good number of salicylic acid analogues have also been found to possess anti-inflammatory actions, e.g., aspirin, salol, salsalate, sodium salicylate, salicylamide, benorilate, choline salicylate, flufenisal etc., in addition to their antipyretic analgesic property. Among them Aspirin is the most commonly used over the counter drug (Figure 6).

![ASPIRIN](image.png)

Figure 6: Aspirin.

GOLD COMPOUNDS

As the name denotes, drugs in this class are derived from the heavy metal gold (Au). They are the synthetic disease modifying antirheumatic drugs (DMARDs). Examples are: Auranofin, Aurothioglucose, Auruthioglucanide, sodium Aurothiomalate (Figure 7,8).

![Mercaptosuccinic acid](image.png)

Figure 7: Sodium Aurothiomalate.

![Synthesis of Sodium Aurothiomalate](image.png)

Figure 8: Synthesis of Sodium Aurothiomalate.

Structure activity relationship (SAR)

1. Compounds with the presence of aurous ion attached to ligand having sulfur possess pharmacological activity.
2. The gold compounds which are monovalent i.e., having aurous ion (Au\(^+\)) are more active than trivalent (auric ion, Au\(^{3+}\)) or colloidal gold compounds\(^{[38,40]}\).

**General adverse effects**

1. Dermatological manifestations like exfoliative dermatitis, vesicular dermatitis, erythema and popular dermatitis.
2. Hematological disorders like thrombocytopenia, purpura, aplastic anaemia, eosinophilia and blood dyscrasias.

**General therapeutic uses**

1. Treatment of rheumatoid arthritis and progressive joint disease.
2. Treatment of atypical form of tuberculosis and bacterial endocarditis.

**CONCLUSION**

Non-steroidal anti-inflammatory drugs have been discussed briefly citing an example for each class. Gold compounds also have been discussed giving emphasis on its SAR; adverse effects; therapeutic effects as well synthesis of gold compounds. Use of gold compounds as inflammatory drugs has risen. Non-selective NSAIDs are indicated in the relief of all grades of pain and inflammation in a wide range of conditions, and are important treatments for arthritic conditions, acute musculo-skeletal disorders and other painful conditions resulting from trauma\(^{[41,42]}\). The adverse event profile of NSAIDs, including Cox-2 inhibitors, is known. Gastrointestinal adverse events, including serious events of PUB (perforation, ulcer, bleeding) are one main reason for discontinuation of treatment with NSAIDs. Other events such as hypersensitivity or skin reactions, cardiorenal effects and hepatotoxicity are class effects, although the exact incidence may vary between products. The CHMP noted that although the benefits of NSAIDs outweighed their risks, they should be used at the lowest effective dose and for the shortest possible treatment duration. All the chemical structures were drawn using software Chemdraw 8.0.

**REFERENCES**


