A Review on different types of the Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

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Abstract

The non-steroidal anti-inflammatory drugs (NSAIDs) are generally used among the patients for the treatment of different types of pain, acute pain (example: injury, low back pain, headache), and chronic pain (example: rheumatoid arthritis, osteoarthritis). Both traditional NSAIDs (non-selective COX inhibitors) and second-generation (cyclooxygenase-2 inhibitors) can show the activity against inflammation & fever. Some NSAIDs show adverse effects related to the gastrointestinal and renal complications.

Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) are usually prescribed medicines that help in relieving pain and inflammation and are commonly used for the treatment of conditions like arthritis and headaches. NSAIDs help in relieving pain in patients by blocking cyclooxygenase (COX) enzymes that lead to secretion of prostaglandins, which cause pain and inflammation. An estimated 70 to 100 million prescriptions are written annually for NSAIDs, with over the counter (OTC) use accounting for an additional use that may be up to sevenfold higher. Rheumatic diseases, which have been classified by the Arthritis foundation, are inflammatory disorders affecting more individuals than any chronic illness. The centers for Disease control and prevention estimates that more than 40 million Approximately 7 million Americans have some form arthritis or chronic joint disorder. Osteoarthritis is the most common form of arthritis in the United States, affecting about 12% of American between the age of 25 and 74. Rheumatoid arthritis is through to affect well over 2 million American (two to three times more female more than males), where as juvenile arthritis affects 71,000 children under 16 years of age, 61,000 of whom are females. In addition, non rheumatoid osteoporosis affects 24 million female half of all women older than 45 years and 90% of all women older than 7 years) and 16 million males. Because more than 80% of the U.S. populations older than 50 years have joint abnormalities that are detectable radio graphically, the use of NSAIDs will increase as American experience a greater life expectancy. It is not surprising therefore, that the development of new NSAIDs continue at a steady pace—a slowed down by the recent controversies surrounding selective cyclo-oxygenase (COX-2) inhibitors.
Structure-based classification of the NSAIDs: Based on their structures, they are classified as follows:

A. Non-selective COX inhibitors (i.e. traditional NSAIDs):

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Class</th>
<th>Example</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Salicylate derivative</td>
<td>Aspirin</td>
<td><img src="image1.png" alt="Structure" /></td>
</tr>
<tr>
<td>2.</td>
<td>Pyrazolone derivative</td>
<td>Phenylbutazone</td>
<td><img src="image2.png" alt="Structure" /></td>
</tr>
<tr>
<td>3.</td>
<td>Propionic acid derivative</td>
<td>Naproxen</td>
<td><img src="image3.png" alt="Structure" /></td>
</tr>
<tr>
<td>4.</td>
<td>Anthranilic derivative</td>
<td>Mephenamic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
</tr>
<tr>
<td>5.</td>
<td>Aryl-acetic acid derivative</td>
<td>Diclofenac</td>
<td><img src="image5.png" alt="Structure" /></td>
</tr>
<tr>
<td>6.</td>
<td>Oxicum derivative</td>
<td>Piroxicam</td>
<td><img src="image6.png" alt="Structure" /></td>
</tr>
<tr>
<td>7.</td>
<td>Pyrrolo-Pyrrole derivative</td>
<td>Ketorolac</td>
<td><img src="image7.png" alt="Structure" /></td>
</tr>
<tr>
<td>8.</td>
<td>Indole derivative</td>
<td>Indomethacin</td>
<td><img src="image8.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

B. Preferential COX-2 inhibitor: Nimesulide

![Structure](image9.png)
C. Selective COX-2 inhibitor: Celecoxib

![Celecoxib molecule]

B. Analgesic and anti-pyretic but poor anti-inflammatory:

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Para-aminophenol derivative</td>
<td>Paracetamol</td>
<td>![Paracetamol structure]</td>
</tr>
<tr>
<td>2.</td>
<td>Pyrazolone derivative</td>
<td>Metamizole</td>
<td>![Metamizole structure]</td>
</tr>
<tr>
<td>3.</td>
<td>Benzoxazocin derivative</td>
<td>Nefopain</td>
<td>![Nefopain structure]</td>
</tr>
</tbody>
</table>

Figure 1: The Effects of chronic NSAIDs use among Americans. (5)
Figure 2: Time dependent hazard analysis of risk of death for various NSAIDs was reported: (6)

Figure 3: Relative risk of acute myocardial infarction for various NSAIDs compared to no NSAIDs, as reported in the meta-analysis: (6)

**Mechanism of action (MOA) of NSAIDs:**

**Figure 4:** Cyclooxygenase pathways and pharmacological actions of paracetamol and other non-steroidal anti-inflammatory drugs (COX = cyclooxygenase, NSAIDs = non-steroidal anti-inflammatory drugs, PGE2 = prostaglandin E2). (7)
A. Analgesic drugs:

1. Aspirin: Aspirin is the analgesic drug, the active constitute of Aspirin is salicylic acid, which reduce the acidity in stomach.

![View of aspirin](image)

Synthesis of aspirin: The reaction that is used for the synthesis is shown below. In this reaction, an excess of acetic anhydride ($\text{C}_4\text{H}_6\text{O}_3$) is added to a measured mass of salicylic acid ($\text{C}_7\text{H}_6\text{O}_3$) in the presence of a catalyst, sulfuric acid ($\text{H}_2\text{SO}_4$). The mixture is heated to form the acetyl salicylic acid ($\text{C}_9\text{H}_8\text{O}_4$) and acetic acid ($\text{C}_2\text{H}_4\text{O}_2$). After the reaction takes place, water is added to destroy the excess acetic anhydride and cause the product to crystallize. The aspirin is then collected, purified by recrystallization, and its melting temperature measured. (8)

![Structure of aspirin](image)

Structure-activity relationship (SAR): Reducing the acidity of this group maintains the analgesic actions of salicylic acid derivatives but eliminates the anti-inflammatory properties. Substitution on either the carboxyl or phenolic hydroxyl groups meta or para to the carboxyl group abolishes this activity. (9) Substitution of aromatic ring enhances potency and toxicity. Substitution of aromatic ring at the 5-position of salicylic acid increases anti-inflammatory activity. (10)

Pharmacokinetics: Most of salicylic are rapidly and perfectly absorb on oral administration with the rate of absorption and bioavailability being dependent on a number of factor ,including dose of formulation, gastric $p^H$, food contents in the stomach ,gastric emptying time ,the presence of buffering agents or antacid ,and particle size. Because salicylic acid is weak acid ($\text{pK}_a$-3.5), absorption generally takes place primarily from the stomach by the process of passive diffusion of un-ionized molecules across the epithelial membranes of the GI tract. (11) Tablet formulation consisting of small particle size are absorbed faster than large particle. Because, small particle surface area maximum drug distribution maximum absorb maximum.

Adverse effects: The most observed side effects associated with the use of salicylic acid relate to disturbance of GI tract. Nausea, vomiting, epigastria, discomfort, intensification of peptic ulcer disease, gastric ulceration, erosive gastritis, and GI hemorrhage occur in indivisibles on high doses of aspirin. (12)

Drug interactions: Because of the widespread use of salicylates, it is not surprising that interaction with many other drugs used in therapeutic combination have been observed .Salicylic acid is a weak acid that is highly bound to plasma proteins (50-80%), and it will complete for this plasma protein binding sites with other drugs that are highly to these sites. The interaction that’s result from the combination of salicylates with oral anti-coagulants represents one of the most widely documented clinically significant of drug interaction. (13)
2. **Ibuprofen:** Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) available in greater strength by prescription. It aims to relieve pain in a variety of cases, including fevers, headaches, toothaches, menstrual cramps, joint pain and backaches. It is prescribed to relieve the symptoms of osteoarthritis such as stiffness, tenderness and swelling, though it cannot cure arthritis. It works by blocking the body’s enzymes that make chemicals that signal pain.

![Ibuprofen structure](image)

**Synthesis of ibuprofen:**

![Ibuprofen synthesis](image)

**Structure-activity relationship (SAR):** The function of acetic acid must be co-planar.  

**Pharmacokinetics:**

- Well absorbed orally.  
- Highly bound to the plasma protein (90-99%).  
- Similar to other NSAIDs, they are likely to decrease diuretic and anti-hypertensive action of thiazides, furosemide and β-blockers.  
- They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as bile.  
- Oral ibuprofen is rapidly absorbed and has an onset of action of approximately 40 to 80 minutes with duration of action of six to eight hours.

**Clinical uses:**

- Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders.  
- They are indicated in soft tissue injuries, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation.

**Adverse effects:**

- Ibuprofen and all its congeners are better tolerated than aspirin.  
- Side effects are milder and their incidence is lower.  
- Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects.  
- Gastric erosion and occult blood loss are rare.  
- CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression.  
- Rashes, itching and other hypersensitivity phenomena are infrequent.  
- They are not to be prescribed to pregnant woman and should be avoided in peptic ulcer patient.
3. Diclofenac: These NSAIDs has more significant analgesic and lower anti-inflammatory effect than ibuprofen. The drugs is used is extensively to manage traumatic pain and pain associated with rheumatoid arthritis. The drugs are readily absorbed from the GIT following oral administration.

\[
\begin{align*}
\text{Diclofenac:} & \quad \text{These NSAIDs has more significant analgesic and lower anti-inflammatory effect than ibuprofen. The drugs is used is extensively to manage traumatic pain and pain associated with rheumatoid arthritis. The drugs are readily absorbed from the GIT following oral administration.}
\end{align*}
\]

\[
\begin{align*}
\text{Synthesis of diclofenac:} & \quad \text{(16)}
\end{align*}
\]

\[
\begin{align*}
\text{Structure-activity relationship (SAR):} & \quad \text{Function of 2 ortho chloro groups is to force aniline phenyl ring out of plane of the phenyl acetic portion.} \quad \text{(17)}
\end{align*}
\]

\[
\begin{align*}
\text{Pharmacokinetics:} & \quad \text{Diclofenac is readily absorbed after oral administration and undergoes a considerable first pass metabolism, its bioavailability ranging from 54 to 90% in humans. Diclofenac is highly bound to serum proteins (≥99.5%) and it has a relatively small volume of distribution in humans.} \quad \text{(18)}
\end{align*}
\]

\[
\begin{align*}
\text{Drug interactions:} & \quad \text{The drug is extensively protein bound in systemic circulation and may displace other protein-bound drugs from their binding sites leading to concentration of the free drugs. It may increase free aspirin levels when administer aspirin. Since this aggravates the risk of the adverse effect, simultaneous administer of diclofenac to patients on chronic treatment with aspirin is not recommended.} \quad \text{(18)}
\end{align*}
\]

\[
\begin{align*}
\text{B. Anti-pyretic drug:}
\end{align*}
\]

\[
\begin{align*}
\text{Paracetamol:} & \quad \text{Paracetamol has almost no anti-inflammatory action and therefore some American authors put this drug in a category separated from NSAIDs. It (paracetamol) has analgesic and antipyretic effect. Therefore it is “a non-narcotic analgesic”. Opioids are narcotic analgesics. Narcotic analgesics cause physical dependence and tolerance while paracetamol does produce them.} \quad \text{(19)}
\end{align*}
\]

\[
\begin{align*}
\text{HO}
\end{align*}
\]
Synthesis of paracetamol: \(^{(20)}\)

\[
\begin{array}{c}
\text{OH} \\
\text{Ac}_2\text{O} \\
\text{HF} \\
\text{OH} \\
\text{NH}_2\text{OH} \\
\text{HO} \\
\text{CF}_3\text{COOH} / \text{SOCl}_2 \\
\text{NH} \\
\text{NO} \\
\text{N} \\
\text{O}
\end{array}
\]

Mechanism of action (MOA): Paracetamol inhibits prostaglandin synthesis in the CNS but not in the periphery. Therefore, by its CNS effects:

1. It reduces pain sensation,
2. It produces anti-pyrexia by exerting its action on the hypothalamic heat regulating centre and analgesia but has virtually,
3. It is having no affect on inflammation,
4. It produces no hemorrhage. \(^{(21)}\)

Pharmacokinetics:

i) Paracetamol is given by orally; after that it is absorb satisfactorily. It undergoes some intestinal and hepatic first pass effect. \(^{(22)}\)

ii) After oral ingestion peak blood level is reached between 30-60 minutes. It is metabolized and excreted as follows: \(^{(23)}\)

- A small portion (<5%) is excreted unchanged via kidney.
- A substantial portion is converted into sulfates and glucuronides excreted via urine.

Structure-activity relationship (SAR):

- Esterification of the phenolic function with methyl or propyl produces derivatives with greater toxic side effects than ethyl groups. \(^{(24,25)}\)
- The substituent on the nitrogen atom which reduces basicity also reduces activity except for acetyl which is metabolically labile. \(^{(26,27)}\)

Clinical uses:

- Paracetamol is indicated where analgesia and anti-pyrexia are desired. \(^{(28,29)}\)
- Paracetamol virtually does not produce gastritis therapy or does not interfere with platelet aggregation. \(^{(30,31)}\)
- Paracetamol, by itself is not much effective in rheumatoid arthritis but in combination with a classical NSAIDs. \(^{(32,33)}\)

Adverse effects:

- With usual therapeutic doses, the adverse effects are skin rashes in allergic reactions person, minor rise of hepatic enzymes. \(^{(34,35)}\)
- In heavy doses, toxic symptoms appear. \(^{(36)}\)

Conclusion

The non steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from arthritis. A number of these drugs possess anti-pyretic activity in addition to having analgesic and anti-inflammatory actions and thus have utility in the treatment of fever. Their inhibition of physiologic processes such as prostaglandin, prostacyclin and thromboxane formation shows the target area responsible for inflammation. That means most of these drugs show their therapeutic actions by inhibition of prostaglandin biosynthesis. The combination of ibuprofen and paracetamol drugs is having greater effect due to synergism effects.
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