A Review on Systematic Study of Aryl Propionic Acid and Derivatives

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In aryl propionic acid most common drugs are ibuprofen, ketoprophen and naproxen. These are available over-the-counter in United States. A consumer report noted that ibuprofen, naproxen, and salsalate are less expensive than other NSAIDs, and essentially as effective and safe when used appropriately to treat osteoarthritis and pain. Ibuprophen (Motrin®, Advil®, Motrin IB®) is considered to be among the safest NSAIDs and is generally well tolerated but can, nevertheless, rarely cause clinically apparent and serious acute liver injury. Ketoprophen (Orudis,Oruvail) topical plasters are being extensively used for treatment of musculoskeletal pain. Ketoprofen is used for its antipyretic, analgesic, and anti-inflammatory properties. Naproxen (Naprosyn®, Aleve®) is commonly used for the reduction of pain, fever, inflammation and stiffness caused by conditions including migraine, osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis and bursitis.

In general, there exists virtually very little difference between the therapeutic efficacy of different NSAIDs, as certain patients would respond to one 'drug' better than another. In reality, it is almost difficult to predict the best suitable drug for a patient; thus, it invariably necessitates to arrive at the best-fit-drug *via* trial and error only. By studying these drugs we can get the knowledge about these drugs like how these drugs are useful and harmful for us.

Keywords: Aryl propionic acid, Ibuprofen, Ketoprofen,Neproxen, Non-steroidal anti-inflammatory drugs (NSAIDs) and Inflammation.

1. Introduction:

Inflammation may be defined as the series of changes that occur in living tissues following injury. The injury which is responsible for inflammation may be brought about by a variety of conditions such as physical agents like mechanical trauma, ultra-violet or ionizing radiation; chemical agents like organic and inorganic compounds, the toxins of various bacteria;intracellular replication of viruses, hypersensitivity reactions like reaction due to sensitized lymphocytes with antigenic material *viz.*, inhaled organic dusts or invasive bacteria and necrosis of tissues whereby inflammation is induced in the surrounding tissues.

Almost three decades ago, steroids namely prednisolone, dexamethasone, betamethasone, triamcinoline 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 non-steroidal anti-inflammatory drugs (NSAIDs).

Nonsteroidal anti-inflammatory drugs usually abbreviated to NSAIDs but also referred to as nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines are a class of drugs that provides analgesic and antipyretic (fever-reducing) effects and in higher doses, anti-inflammatory effects.Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications worldwide. They relieve pain and inflammation in many disorders.

According to Medilexicon's medical dictionary, nonsteroidal antiinflammatory drugs (NSAIDs) are "a large number of drugs exerting antiinflammatory (and also usually analgesic and antipyretic) actions; examples include aspirin, acetaminophen, diclofenac, indomethacin, ketorolac, ibuprofen, and naproxen. A contrast is made with steroidal compounds (hydrocortisone or prednisone) exerting anti-inflammatory activity."

NSAIDs block the Cox enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support the platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding [1].

Nonsteroidal anti-inflammatory drugs have anti-inflammatory, analgesic, and antipyretic effects and inhibit thrombocyte aggregation. NSAIDs are used primarily to treat inflammation, mild-to-moderate pain, and fever. NSAIDs are also included in cold and allergy preparations.

Non-steroidal anti-inflammatory drugs (NSAIDs) are medications used regularly in the treatment of arthritis and intermittently for fever, pain and headache. They are most commonly used systemically, usually as an oral formulation but can also be used as a suppository or administered by intramuscular injection. Topical gels and creams containing NSAIDs may be applied to sports injuries, painful joints and, most recently, for the treatment of solar (actinic) keratoses (sun spots) [2].

NSAIDs are usually used for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer.

NSAIDs are generally used for the symptomatic relief of the following conditions:

- Migraine, Acute gout, Dysmenorrhoea (menstrual pain),Metastatic bone pain and Ileus [3].
- Postoperative pain, Muscle stiffness and pain due to Parkinson's disease, Pyrexia (fever),Renal colic [3].
- They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth [3].

- Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis and Reiter's syndrome), Tennis elbow and Headache [4].
- Mild-to-moderate pain due to inflammation and tissue injury [4].
- Osteoarthritis [4,5].
- Rheumatoid arthritis [6].
- Low back pain [4,7].

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane A_2.

2.About of NSAIDs:

2.1. Types of NSAIDs

There are many different types of NSAIDs, which are categorized according to their chemical structures. Types of NSAIDs are as shown in Figure 1.

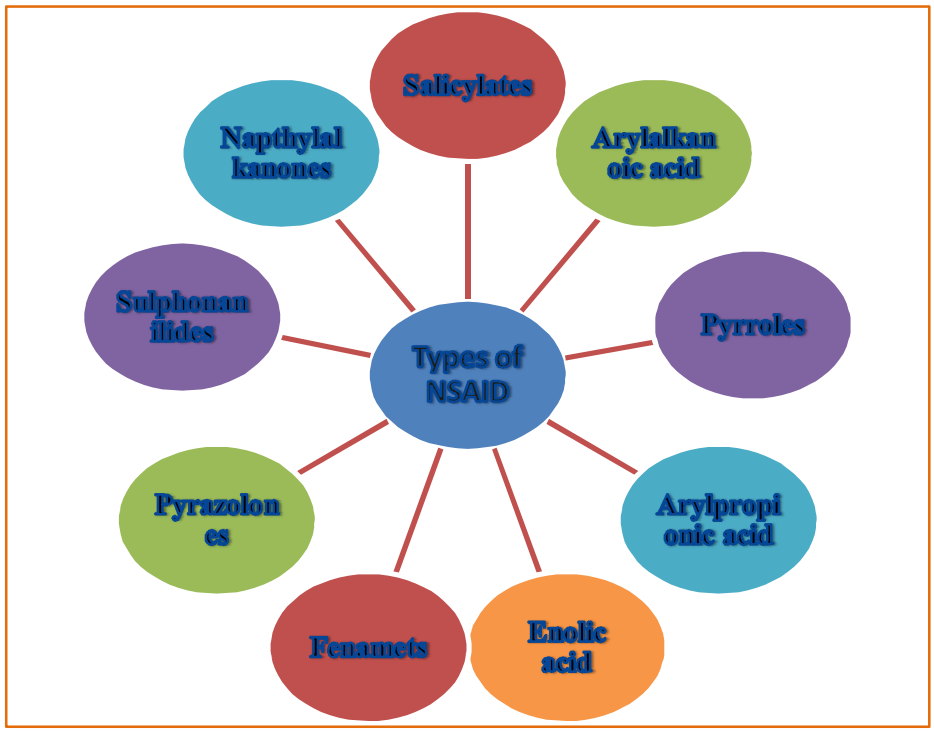

Fig. 1: Name of types of NSAIDs according to their Chemical structures.

2.2 Mechanism of action of NSAIDs

The mechanism of action of NSAIDs can be divided into their effects on inflammation, pain, and fever.

2.2.1. Anti-inflammatory effect

NSAIDs exert their anti-inflammatory effect through inhibition of prostaglandin G/H synthase, or cyclooxygenase, which is the enzyme catalyzing the transformation of arachidonic acid to prostaglandins and thromboxanes [8]. This enzyme has two recognized forms: cox-1 and cox-2. Selective inhibition of cox-2 leads to decreased GI side effects. Recent work suggests that activation of endothelial cells and expression of cell adhesion molecules play a role in targeting circulating cells to inflammatory sites. NSAIDs may inhibit expression of these cell adhesion molecules and may directly inhibit activation and function of neutrophils [9].

2.2.2. Analgesic effect

Although they are classified as mild analgesics, NSAIDs have a more significant effect on pain resulting from the increased peripheral sensitization that occurs during inflammation and leads nociceptors to respond to stimuli that are normally painless. In particular, it is believed that inflammation leads to a lowering of the response threshold of polymodal nociceptors [10].

2.2.3. Antipyretic effect

NSAIDs exert their antipyretic effect by inhibition of prostaglandin E2 (PGE2) synthesis, which is responsible for triggering the hypothalamus to increase body temperature during inflammation [10]. NSAIDs work by preventing an enzyme (a protein that triggers changes in the body) from doing its job.

The enzyme is called cyclooxygenase, or COX, and it has two forms. COX-1 protects the stomach lining from harsh acids and digestive chemicals. It also helps maintain kidney function. COX-2 is produced when joints are injured or inflamed. Traditional NSAIDs block the actions of both COX-1 and COX-2, which is why they can cause stomach upset and bleeding as well as ease pain and inflammation.

Generic and Brand names of some common traditional NSAIDs are summerised in Table 1.

Table1: Some common traditional NSAIDs.

Generic Name	**Brand Names**
IBUPROFEN	Motrin®, Advil®, Motrin IB®
KETOPROPHEN	Orudis,Oruvail
NAPROXEN	Naprosyn®, Aleve®

NSAIDs come in different strengths and formulas. Some may work better for you than others. Your physician can help you find the dose and medication that works best for you. Generally, you should take NSAIDs with food or a glass of milk and should avoid drinking alcohol while you are taking NSAIDs.

2.3. RISKS

Tell your physician if you are pregnant, have high blood pressure, asthma, or a history of kidney or liver disease, or have had ulcers in the past. People older than 65 years of age must be especially careful when taking NSAIDs. Also tell your doctor about other medications you are taking. NSAIDs may intensify or counteract the effects of some medications. Both the risk and the severity of side effects increase the longer you take NSAIDs [11].

NSAIDs can be used for a number of conditions. While some OTC medications, others can only be accessed with a prescription. Typically, NSAIDs are used to treat the following symptoms and conditions:

- *Pain and discomfort*:for example muscle strain/sprain, headaches, migraines, and dysmenorrhoea (painful cramps during menstruation).
- *Fever*: NSAIDs are effective at reducing body temperature.
- *Inflammation*: NSAIDs are often used for the treatment of inflammation, as may occur in rheumatoid arthritis.
- *Some other conditions*:sometimes NSAIDs are recommended for the treatment of menorrhagia (heavy menstrual periods).

2.4. NSAIDs may be taken

- *Orally (by mouth)* - available in tablet, capsule or liquid form.
- *Intravenously* - by injection
- *Rectally* - as a suppository through the rectum
- They are also available as eye-drops
- Topical NSAIDs also exist, which are applied directly onto the skin in the form of creamsorgels.

3. Aryl propionic acid Drugs:

3.1. Ibuprophen (orlbuprofen)

Ibuprofen is considered to be among the safest NSAIDs and is generally well tolerated but can, nevertheless, rarely cause clinically apparent and serious acute liver injury [12].

3.2. Ketoprophen

Ketoprofen topical plasters are being extensively used for treatment of musculoskeletal pain[13,14,15].Ketoprofen is used for its antipyretic, analgesic, and anti-inflammatory properties by inhibiting cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes reversibly, which decreases production of proinflammatory prostaglandin precursors [16].

3.3. Naproxen

Naproxen is commonly used for the reduction of pain, fever, inflammation and stiffness caused by conditions including migraine, osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis and bursitis. It is also used for the treatment of primary dysmenorrhea [17]. It became available OTC in British Columbia in late January 2010 [18].

Naproxen may have anti-viral activity against influenza. Specifically, it blocks the RNA-binding groove of the nucleoprotein of the virus, thereby preventing formation of the ribonucleoprotein complex, thus taking the vital nucleoproteins out of circulation [19]. Naproxen has been utilized to differentiate between infectious fevers and those with neoplastic or connective tissue disease related fevers [20].

In general, there exists virtually very little difference between the therapeutic efficacy of different NSAIDs, as certain patients would respond to one ‘drug’ better than another. In reality, it is almost difficult to predict the best suitable drug for a patient; thus, it invariably necessitates arriving at the best-fit-drug *via* trial and error only.

Keeping in view the innumerable adverse side effects caused by the NSAIDs, their clinical usefulness are restricted drastically. Therefore, patients who are taking such drugs for a relatively longer period should have periodic white-blood cell counts as well as determinations of serum creatinine levels, besides hepatic enzyme activities [21].

4. OTHERS SURVEY:

Derived from willow bark, salicin was used by Maclagan in 1874 to treat inflammation in rheumatic fever. Later, a more efficacious and better tolerated synthetic derivative, aspirin, was produced by Felix Hoffman of the Bayer Company[22].

In 1963, Indomethacin was introduced to treat rheumatoid arthritis, and this was followed by the development of manyother anti-inflammatory agents. The poor gastrointestinal (GI) tolerabilityof this class of drugs, coupled with their widespread use, led to the developmentof selective agents known as COX-2 inhibitors [23].

In 1987 Giordano *et al.* of Italy prepared optically active alpha-arylalkanoic acid &itsnovel intermediates. He got U.S. Patent on this research activity [24].

In 1989 Claudio Giordano *et al.* of chemistry research institute Italy developed a sterio-convergent strategy for the synthesis of pure naproxen [25].

In 1994 Mr.Harikisan R.S. *et al.* of NCL, Pune study photochemical rearrangement of alpha cloro-propiophinone to alpha aryl propionic acid and synthesis of ibuprophen and ketoprophen [26].

In 1999Zimmerman H.J. of Germany studiedhyper toxicity and its adverse effect of drugs and chemicals used to treat rheumatic and musculospastic diseases on liver [27].

In 2003 Vane JR and Botting RM developed a mechanism of action of asprin [28].

In 2005 Mazieres*et al.* studies topical ketoprophen in the treatment tendinities[29].

In 2006 Brunton L et al in his book the pharmacological basis of therapeutics wrote that NSAIDs exert their anti-inflammatory effect through inhibition of prostaglandin G/H synthase, or cyclooxygenase, which is the enzyme,catalyzing the transformation of arachidonic acid to prostaglandins and thromboxanes [30].

In 2011 Reacherdkjonaass et al. developed a method for the synthesis of ibuprophen and standardised the process for its manufacture [31].

5. CONCLUSION

On the basis of various literature surveys, aryl propionic acid derivatives are known as NSAIDs and show various type of applicationsantipyretic, analgesic, and anti-inflammatory,neoplastic and anti-viral activity against influenza. The possible improvements in the following activity and other also can be further achieved by slight modifications in the substituents on the basic aryl propionic acid derivatives.

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