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Review Article

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

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Keywords

Classification, Mechanism, Structure-activity relationship (SAR), Synthesis, Pharmacokinetics, Uses, Adverse effects.

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.[1,2]
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. [3]
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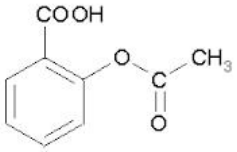
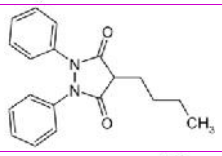
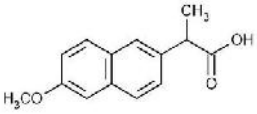
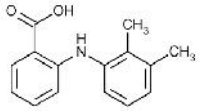
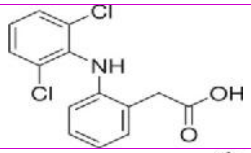
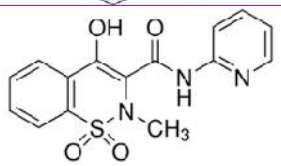
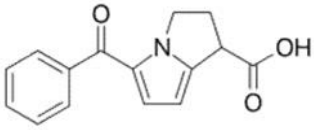
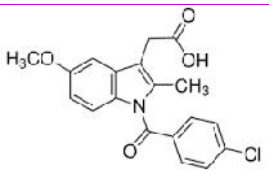
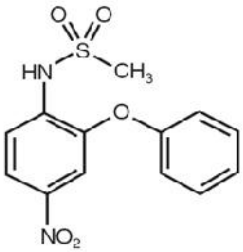
Structure-based classification of the NSAIDs: Based on their structures, they are classified as follows: [4,5]

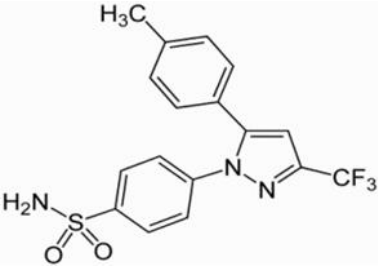
A. Non-selective COX inhibitors (i.e. traditional NSAIDs):

Sl. No.	Class	Example	Structure
1.	Salicylate derivative	Aspirin	
2.	Pyrazolone derivative	Phenylbutazone	
3.	Propionic acid derivative	Naproxen	
4.	Anthranilic derivative	Mephenamic acid	
5.	Aryl-acetic acid derivative	Diclofenac	
6.	Oxicum derivative	Piroxicam	
7.	Pyrrolo-Pyrrole derivative	Ketorolac	
8.	Indole derivative	Indomethacin	

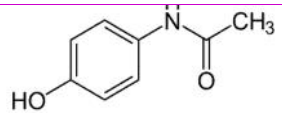
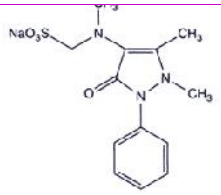
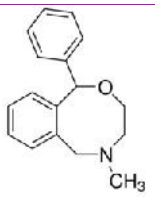
B. Preferential COX-2 inhibitor: Nimesulide



C. Selective COX-2 inhibitor: Celecoxib



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

Sl. No.	Class	Example	Structure
1.	Para-aminophenol derivative	Paracetamol	
2.	Pyrazolone derivative	Metamizole	
3.	Benzoxazocin derivative	Nefopain	

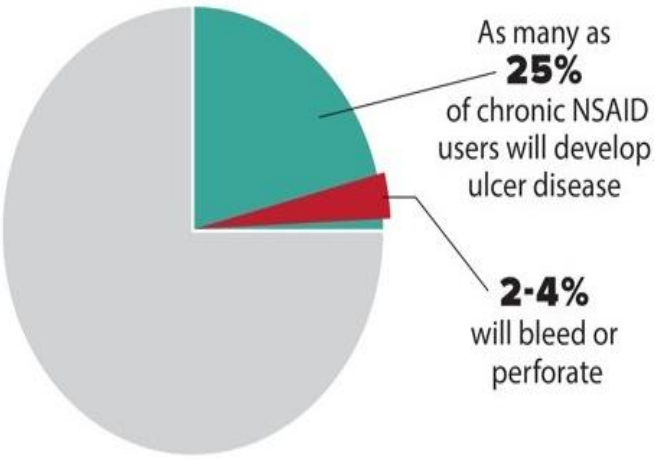


Figure 1: The Effects of chronic NSAIDs use among Americans: [5]

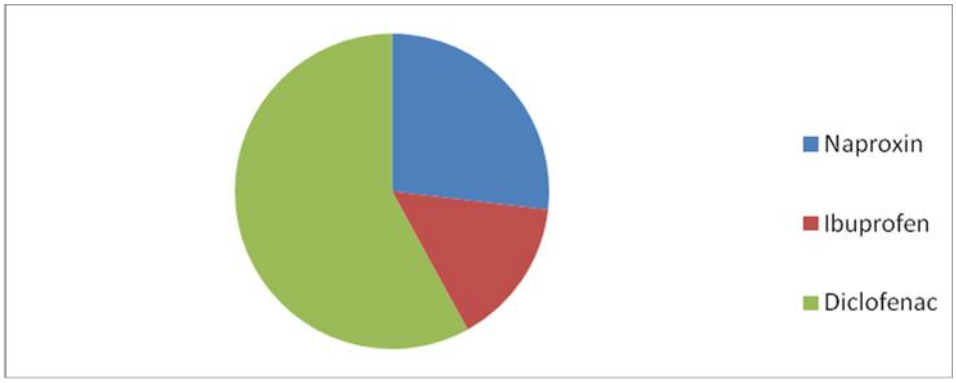


Figure 2: Time dependent hazard analysis of risk of death for various NSAIDs was reported: [6]

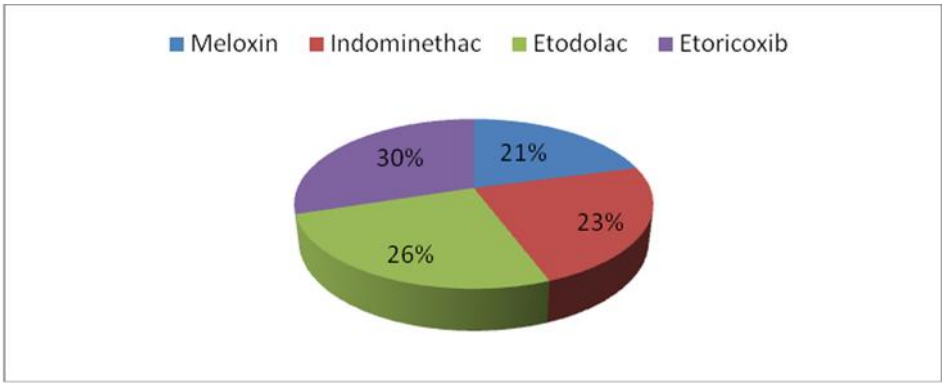


Figure 3: Relative risk of acute myocardial infarction for various NSAIDs compared to no NSAIDs, as reported in the meta–analysis: [6]

Mechanism of action (MOA) of NSAIDs:

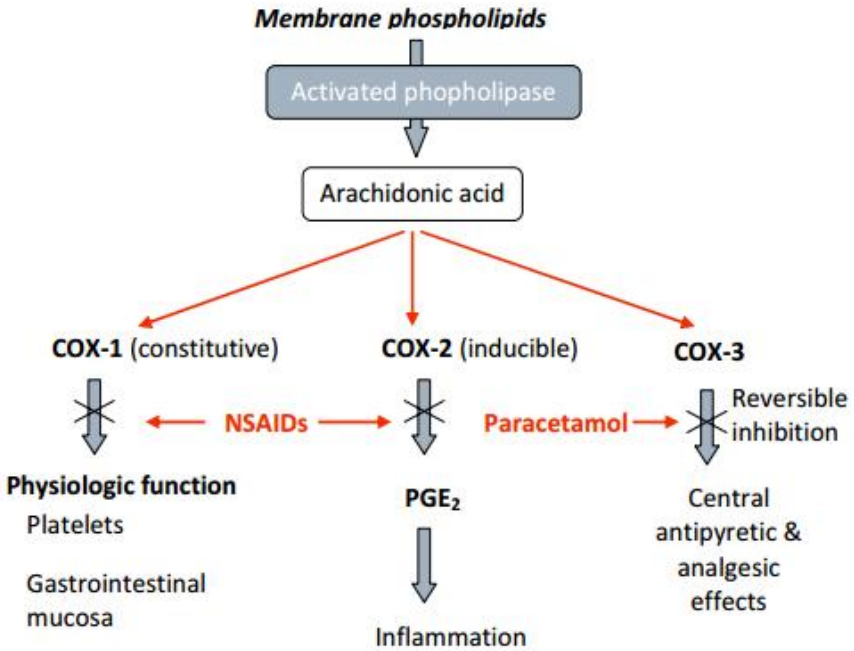
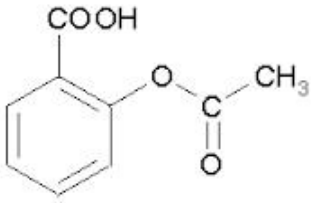


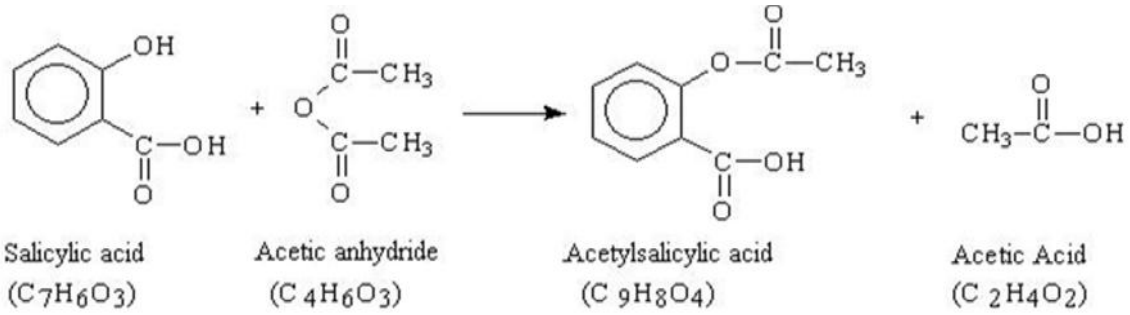
Figure 4: Cyclooxygenase pathways and pharmacological actions of paracetamol and other non-steroidal anti-inflammatory drugs (COX = cyclooxygenase. NSAIDs = non-steroidal anti-inflammatory drugs. PGE2 = prostaglandin E2). [7]

A. Analgesic drugs:

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



Synthesis of aspirin: The reaction that is used for the synthesis is shown below. In this reaction, an excess of acetic anhydride ($C_4H_6O_3$) is added to a measured mass of salicylic acid ($C_7H_6O_3$) in the presence of a catalyst, sulfuric acid (H_2SO_4). The mixture is heated to form the acetyl salicylic acid ($C_9H_8O_4$) and acetic acid ($C_2H_4O_2$). 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]



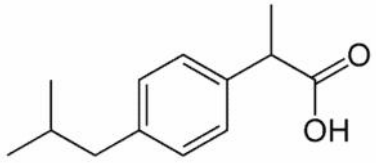
Structure-activity relationship (SAR): Reducing the acidity of this group maintains the analgesic actions of salicylic acid derivatives but eliminates the anti-inflammatory properties. Substitution on either the carboxyl or phenolic hydroxyl groups meta or para to the carboxyl group abolishes this activity. [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 (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.

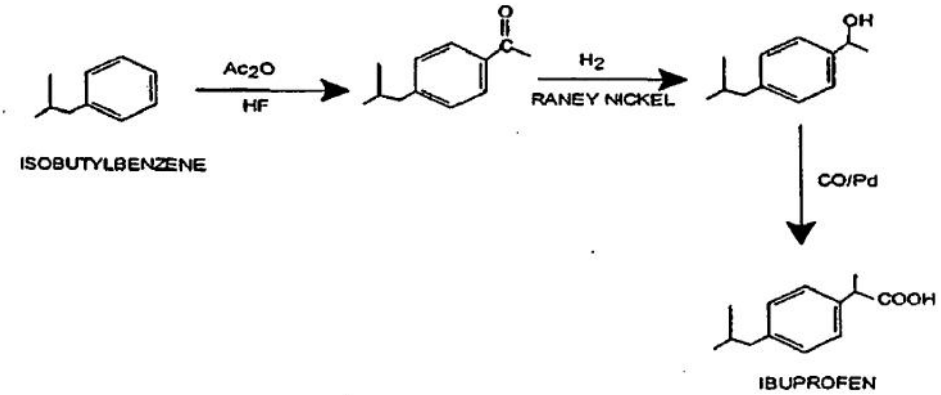
Adverse effects: The most observed side effects associated with the use of salicylic acid relate to disturbance of GI tract. Nausea, vomiting, epigastria, discomfort, intensification of peptic ulcer disease, gastric ulceration, erosive gastritis, and GI hemorrhage occur in indivisibles on high doses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



Synthesis of ibuprofen: [14]



Structure-activity relationship (SAR): The function of acetic acid must be co-planar. [14]

Pharmacokinetics:

- Well absorbed orally. [14]
- Highly bounded to the plasma protein (90-99%). [14]
- Similar to other NSAIDs, they are likely to decrease diuretic and anti-hypertensive action of thiazides, furosemide and β-blockers. [14]
- They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as bile. [14]
- 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. [15]

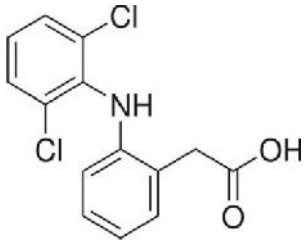
Clinical uses:

- Ibuprofen is used as a simple analgesic and antipyretic in the same way as low dose of aspirin. It is particularly effective in dysmenorrhoea. In which the action is clearly due to PG synthesis inhibition. [14]
- Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders. [14]
- They are indicated in soft tissue injuries, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation. [15]

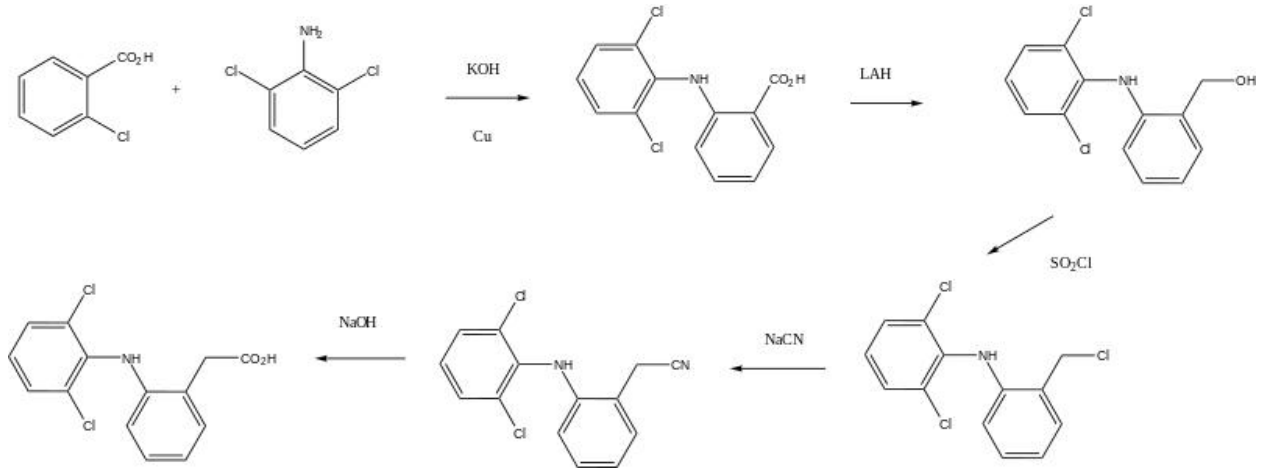
Adverse effects:

- Ibuprofen and all its congeners are better tolerated than aspirin. [14]
- Side effects are milder and their incidence is lower. [14]
- Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects. [14]
- Gastric erosion and occult blood loss are rare. [14]
- CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression. [15]
- Rashes, itching and other hypersensitivity phenomena are infrequent. [15]
- They are not to be prescribed to pregnant woman and should be avoided in peptic ulcer patient. [15]

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.



Synthesis of diclofenac: [16]



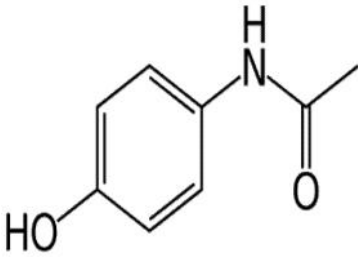
Structure-activity relationship (SAR): Function of 2 ortho chloro groups is to force aniline phenyl ring out of plane of the phenyl acetic portion. [17]

Pharmacokinetics: 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. [18]

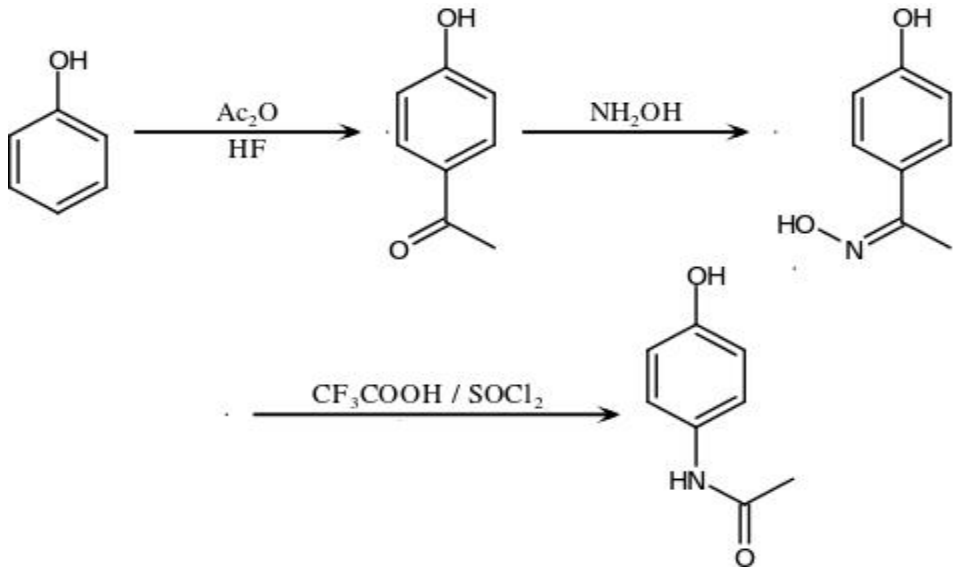
Drug interactions: The drug is extensively protein bound in systemic circulation and may displace other protein-bound drugs from their binding sites leading to concentration of the free drugs. It may increase free aspirin levels when administer aspirin. Since this aggravates the risk of the adverse effect,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

B. Anti-pyretic drug:

Paracetamol: 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. [19]



Synthesis of paracetamol: [20]



Mechanism of action (MOA): Paracetamol inhibits prostaglandin synthesis in the CNS but not in there 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.

References

1. Tripathi KD; Non-steroidal anti-inflammatory drugs; Essentials of medical pharmacology; 2012; 5; 167-170.
2. Am JM;Quantifying the impact of NSAID-associated adverse events; The *American Journal of Managed Care;*2013;19(14); 267-272.
3. Abraham NS, El-Serag HB, Hartman C, Richardson P, Deswal; Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident; Alimentary *Pharmacology* & Therapeutics; 2007; 25(8); 913-924.
4. Andersohn F, Schade R, Suissa S, Garbe E; Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study; Stroke; 2006; 37(7); 1725-1730.
5. http://www.theatlantic.com/health/archive/2015/06/the-evolution-of-alternative-medicine/396458/; Access online from 2016.
6. Arber N, Eagle CJ, Spicak J, Rácz I, Dite P, Hajer J, Zavoral M, Lechuga MJ, Gerletti P, Tang J, Rosenstein RB, Macdonald K, Bhadra P, Fowler R, Wittes J, Zauber AG, Solomon SD, Levin B; Celecoxib for the prevention of colorectal adenomatous polyps;The New England Journal of Medicine; 2006; 355(9); 885-895.
7. Bak S, Andersen M, Tsiropoulos I, García Rodríguez LA, Hallas J, Christensen K, Gaist D; Risk of stroke associated with nonsteroidal anti-inflammatory drugs: a nested case-control study; Stroke; 2003; 34(2); 379-386.
8. Joe T, Emily B, Rima D, Zeljko M, Robert N, David T; Paracetamol and Ibuprofen for Paediatric Pain and Fever; Journal of Pharmacy Practice and Research; 2009; 39(3); 223-225.
9. Brater DC; Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition; The *American Journal of Managed Care*; 1999; 107(6); 65-70.
10. Brophy JM, Levesque LE, Zhang B; The coronary risk of cyclo-oxygenase-2 inhibitors in patients with a previous myocardial infarction; Heart; 2007; 93(2); 189-194.
11. Buneo H, Bardaji A, Patrignani P, Martin-Merino E, Garcia Rodriguez L; Use of non steroidal anti-inflammatory drugs and type-specific risk of acute coronary syndrome; The *American Journal of Cardiology*; 2010; 105(8); 1102-1116.
12. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodringuez LA; Non-Steroidal Anti-inflammatory Drugs and the Risk of Acute Myocardial Infarction; Basic Clinical Pharmacology and Toxicology; 2006; 98(3); 266-274.
13. Nidhi M, Ranjit J, Wagh A, Aparna S, Manjeeta G;Prescription pattern monitoring of non steroidal anti-inflammatory drugs in urban health centre in talegaon: a retrospective study;International Journal of Pharma and Bio Sciences; 2015; 6(2); 596-602.
14. Padmaja UK; Nonsteroidal anti-inflammatory drugs (NSAIDs); Medical Pharmacology; CBS Publishers and Distributors Pvt. Ltd.; 2011; 3; 251-263.
15. Gislason G, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbol EL, Sorensen R, Folke F, Buch P, Gadsboll N, Rasmussen S, Poulsen H, Kober L, Madsen M, Torp-Pedersen C; Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure; Archives of Internal Medicine; 2009; 169(2); 141-149.
16. Ku EC, Wasvary JM, Cash WD; Diclofenac sodium (GP45840, Voltaren), a potent inhibitor of prostaglandin synthetase; Biochemical Pharmacology; 1975; 24(3); 641.
17. Jack DJ; Non-steroidal antiinflammatory drugs (NSAIDS); Principles of Drug Action; Auburn University; 2012; 2; 1-24.
18. Kar A; Medicinal Chemistry; Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); New Age International Publishers; 4; 2007; 522-543.

19. Whelton A, Schulman G, Wallemark C, Drower EJ, Isakson PC, Verburg KM, Geis GS; Effects of celecoxib and naproxen on renal function in the elderly; Archives of Internal Medicine; 2000; 160(10); 1465-1470.
20. Hinz B,Cheremina O, Brune K;"Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man; The FASEB Journal; 2008; 22(2); 383-390.
21. Whelton A; Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications; The American Journal of Medicine; 1999; 106(5); 13-24.
22. Blaser JA, Allan GM; Acetaminophen in pregnancy and future risk of ADHD in offspring; Canadian Family Physician; 2014; 60(7); 642.
23. Fays L, Van M, De S, Sawchik J, Verlinden V, Hamdani J, Dogné JM, Dan B; Use of paracetamol during pregnancy and child neurological development; Developmental medicine and child neurology; 2015; 57(8); 718–724.
24. White WB, Kent J, Taylor A, Verburg KM, Lefkowith JB, Whelton A; Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors; Hypertension; 2002; 39(4); 929-934.
25. Van der Linden MW, van der Bij S, Welsing P, Kuipers EJ, Herings RM; The balance between severe cardiovascular and gastrointestinal events among users of selective and non-selective non-steroidal anti-inflammatory drugs; Annals of the Rheumatic Diseases; 2009; 68(5); 668-673.
26. Van Staa TP, Reitbrock S, Setakis E, Leufkens HG; Does the varied use of NSAIDs explain the differences in the risk of myocardial infarction?; Journal of Internal Medicine; 2008; 264(5); 481-492.
27. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS; Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study; The Journal of the American Medical Association; 2000; 284(10); 1247-1255.
28. Solomon DH, Avorn J, Stürmer T, Glynn RJ, Mogun H, Schneeweiss S; Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk;Arthritis & Rheumatology; 2006; 54(5); 1378-1389.
29. Solomon DH, Glynn R, Rothman K, Schneeweiss S. Setoguchi S, Mogun H, Avorn J, Sturmer T. Sub-group analyses to determine cardiovascular risk associated with non-steroidal antiinflammatory drugs and coxibs in specific patient groups; Arthritis & Rheumatology; 2008; 59(8); 1097-1104.
30. Solomon DH, Schneeweiss S, Levin R, Avorn J; Relationship between Cox-2 specific inhibitors and hypertension; Hypertension; 2004; 44(2); 140-145.
31. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M; Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention; The New England Journal of Medicine; 2005; 352(11); 1071-1080.
32. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, Kivitz A, van Ingen H, Brabant T, Fort JG; Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT) Investigators. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis and type 2 diabetes; Archives of Internal Medicine; 2005; 165(2); 161-168.
33. Suissa S, Bernatsky S, Hudson M; Antirheumatic drug use and the risk of acute myocardial infarction; Arthritis & Rheumatology; 2006; 55(4); 531-536.
34. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Jüni P; Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis; British Medical Journal; 2011; 342(110); 7086.
35. Van der Linden MW, van der Bij S, Welsing P, Kuipers EJ, Herings RM; The balance between severe cardiovascular and gastrointestinal events among users of selective and non-selective non-steroidal anti-inflammatory drugs; Annals of the Rheumatic Diseases; 2009; 68(5); 668-673.

36. Abdel H, Suleiman M; A rapid and sensitive high-performance liquid Chromatographic method for the determination of diclofenac sodium in serum and its use in pharmacokinetic studies; Journal of Pharmacy and Pharmacology; 1988; 40(14); 727–729.

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