Anti-Inflammatory Drugs

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ABSTRACT

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Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages and is a protective phenomenon of the body to external or internal trauma. The treatment of patients with inflammation involves two primary goals. First, the relief of pain, which is often the presenting symptom, and secondly slowing or arrest of the tissue damaging process. The anti inflammatory drugs belong to either steroidal group or non steroidal group. The glucocorticosteroid agents (steroids) are very effective anti-inflammatory agents clinically used. Unfortunately the toxicity associated with chronic corticosteroid therapy limits their use as anti- inflammatory agents except in the control of acute flare- ups of joint diseases. They act by inhibition of the release of prostaglandins by preventing the activation of Phospholipase A2. But t steroidsdo not come in the purview of this article.

The other group of anti-inflammatory drugs is the non steroidal anti inflammatory drugs (NSAIDs) which play a significant role in treatment of inflammatory conditions.

Keywords: Inflammation, NSAIDs

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INTRODUCTION

Inflammation and pain are characteristic of a variety of medical disorders. Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages and is a protective phenomenon of the body to external or internal trauma. Foreign organism or antigenic substances liberated during injuries will lead to inflammation. Chronic inflammation involves the release of a number of mediators that are not prominent in the acute response. The treatment of patients with inflammation involves two primary goals. First, the relief of pain, which is often the presenting symptom, and secondly slowing or arrest of the tissue damaging process.

The anti inflammatory drugs belong to either steroidal group or non steroidal group. The glucocorticosteroid agents (steroids) are very effective anti-inflammatory agents clinically used. Unfortunately the toxicity associated with chronic corticosteroid therapy limits their use as anti- inflammatory agents except in the control of acute flare- ups of joint diseases. They act by inhibition of the release of prostaglandins by preventing the activation of Phospholipase A_2 (figure 1). But t steroidsdo not come in the purview of this article.

The other group of anti-inflammatory drugs is the non steroidal anti inflammatory drugs (NSAIDs) which play a significant role in treatment of inflammatory conditions.

NSAIDs are clinically diverse, most of them are organic acids, despite this structural heterogeneity, NSAIDs posses a single common mode of action. The anti inflammatory and analgesic effect of NSAIDs are due to the non specific inhibition of COX in the peripheral tissues and CNS. There are many products of NSAIDs in the market and the anti inflammatory property of different compounds roughly corresponds with their potency to inhibit Cycloxygenase (COX) enzyme.

Details of Cycloxygenase Enzyme

COX it is a microsomal enzyme existing as dimer (2 units linked together) in the lumen and membrane of endoplasmic reticulum. COX I is found in the gastrointestinal tract, kidneys and platelets and COX II enzymes are found in the kidney. The sensitivity of COX in different tissues is different. COX I is a constitutive enzyme ("house keeping") and is a protector of GIT mucous membrane, the enzyme is usually present in a very low concentration and is upregulated during inflammation by the proinflammatory agents like cytokines, endotoxins and tumour promoters, It has also a role in renal haemostasis. COX II enzyme

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is produced due to the stimulus at the site of inflammation and is inhibited selectively by some NSAIDs. COX III is found more in the CNS.

Groups of Anti inflammatory Drugs

A. COX I + II inhibitors – good anti-inflammatory action
   1. Salicylates – Acetyl salicylic acid (Aspirin), Sodium salicylate Methyl salicylate (oil of wintergreen), Salicylamide.
   2. Propionic acid derivatives Ibuprofen, Naproxen Ketoprofen, Flurbiprofen
   3. Anthralinic acid derivatives Mephenamic acid
   4. Aryl acetic acid derivatives Diciofenac, aceclofenac.
   5. Oxicam derivatives Piroxicam, tenoxicam
   6. Pyrrolone derivatives ketoralc
   7. Indole derivatives Indomethacin, sulindac
   8. Pyrozolone derivatives Oxyphenbutazone and phenyl butazone

B. COX I and high COX II inhibitors Nimesulide, meloxicam, nabumetone

C. COX II inhibitors
   Celecoxib and etoricoxib, valdecoxib

D. Mild anti inflammatory, analgesic & antipyretic Paracetamol, Propiphanezone, metamizol, nefopam Acetyl salicylic acid. (ASPIRIN)

Aspirin is considered as a prototype drug with which all NSAIDs are compared.

In 18th century Sir Edmund Stone brought out an article regarding the value of the extract of Willow bark for alleviating pain and fever. The bark contained the active principle salicin which was hydrolysed to salicylic acid responsible for the action. In 1897 Felix Hoffmann succeeded introducing acetyl salicylic acid which was useful as an analgesic. The exact mechanism of action of Acetyl salicylicacid (Aspirin) at the cyclooxygenase level of was established years later. In the succeeding years many new anti-inflammatory compounds were discovered with differences in their potency and adverse effects. Then came the discovery of the specific inhibitors of cyclooxygenase II which were claimed to have lesser side effects.

Salicylates Aspirin is taken as a prototype drug in narrating the actions of salicylates.

PHARMACODYNAMICS - Mechanism of action:

Aspirin binds irreversibly to the cyclooxygenase enzyme and acetylates COX I + II at the serene residue and causes irreversible inhibition (for long time till enzyme is re synthesised) of PG synthesis especially PGE2 (Figure1). All other NSAIDs inhibit the enzyme in a competitive & reversible manner. It also produces inhibition of TXA2 and exhibits antiplatelet action both due to PG inhibition in CNS and periphery.

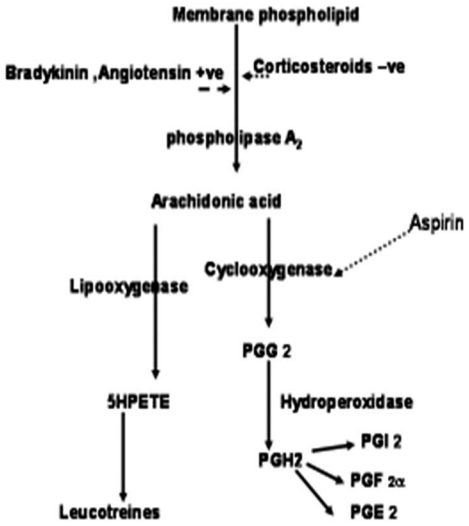

Figure 1. **Showing Cyclooxygenase inhibition**

Pharmacological actions

Anti-inflammatory action Aspirin by inhibition of the PGs decrease the local inflammatory reaction at the site of injury. Aspirin also decreases the sensitivity of vessels to bradykinin and histamine, affect lymphokine production from T lymphocytes, and reverse vasodilation. Hence the connective tissue and integumental inflammatory mediators are reduced.

Analgesic action: Aspirin produces analgesia by obtunding the peripheral pain receptors and reduce the PG mediated sensitivity to pain. It also raises the pain threshold in inflammation. It addition it inhibits central PG synthesis and so reduces the sensitivity of pain fibres in the brain and spinal cord.

Antipyretic action: PGs play a role in temperature regulation and aspirin by interfering with the hypothalamic PGs, set the temperature regulation at a higher level. So temperature dissipation by cutaneous vasodialatation occurs and it acts as anantipyretic.

Antiplateletaction: Aspirin prevent platelet aggregation in low doses. This is by preventing synthesis of thromboxane A2 (TXA2) This inhibition is irreversible and lasts till the life of the platelets (8-10days).

Gastrointestinal action: Aspirin is ulcerogenic. The inhibition ofPGI2increases the hydrochloric acid secretion and adds to the ulcerogenicproperty. Inhibiting the synthesis of PGE2 it reduces the production of mucin and reduces the protection to the secreted acid in the gastric mucosa. Aspirin is ionized in the gastric mucosa and the ionized molecule is not absorbed and this can irritate the gastric mucosa and is an added factor producing gastric irritation and necrosis and bleeding.

Respiratory system: Aspirin in higher doses canstimulate respiration and can produce alkalosis (Figure 2)

Metabolic actions: Celular metabolism is increased in skeletal muscles, glucose utilization is more and in diabetes can lead to hypoglycemia. In toxic doses hyperglycemia is seen due to the sympathetic stimulation. In larger doses the initial respiratory alkalosis is followed by metabolic acidosis as more and more HCO3 is excreted by the kidney.

Uric acid metabolism: Aspirin produces a dose dependent action on uric acid. In smaller doses it produces retention of uric acid by increasing the renal tubular reabsorption of urates. But in larger doses it can increase the excretion of urates and be of use in gout, but it is usually not preferred.

All other NSAIDs with nonspecific inhibition have almost similar action and uses as aspirin. They differ mainly in kinetics, metabolism and adverse drug reactions (ADR).

Pharmacokinetics

Aspirin is rapidly absorbed from the stomach and intestine. As it is less water soluble absorption is reduced in gastric pH. Alkalinisation can increase the solubility and increases absorption but food does not substantially change the biovailability. Although its concurrent administration with antacids may slow its absorption rate, it will not significantly reduce the bioavailability. Aspirin after absorption is metabolized to salicylic acid in the gut wall which exerts its pharmacological action. It is highly bound to plasma proteins, it enters the brain at a slow rate but placental penetration is good. NSAIDs can be found in synovial fluid after repeated dosing and drugs with short half lives remain in the joints longer. Most of the NSAIDs are highly metabolized, some by phase I followed by phase II mechanisms and other by direct glucuronidation (phase II) alone. Aspirin is metabolized by glucorinidation Metabolism of most NSAIDs proceeds, in part, by way of the CYP3A or CYP2C families of P450 enzymes in the liver and excreted by the kidney by glomerular filtration and tubular secretion. One tenth of salicylic acid is excreted as free drug and this can be increased by administration of alkalies. Sodium bicarbonate given will increase the alkalinity of urine and produces ionization of aspirin preventing tubular reabsorption of aspirin. Elimination is dose dependent and will be increased in poisoning and alkalinisation will enhance excretion.

Indications

1. Anti inflammatory Aspirin and other NSAIDs are particularly effective in conditions like rheumatoid arthritis, osteoarthritis, acute musculoskeletal pain, ankylosing spondylitis. Aspirin in high dose is very effective in controlling the inflammation and swelling in rheumatic fever.
2. Analgesic As an analgesic it can be used in headache, tooth ache, arthritis and acute musculoskeletal pain. But it is not effective in visceral pain or pain due to myocardial infarction.
3. Antipyretic. Aspirin is used in adult having fever. But it should be avoided in children below 2 years with fever as it can produce Rye's syndrome.
4. Antiplatelet. Aspirin in small dose daily is used in Myocardial infarction and other thrombotic conditions. (It will not relieve pain).
5. Alzheimers (ALZ) disease Aspirin can delay the progress in Alzheimers as COX is involved in the inflammatory mechanism in ALZ .
6. Pregnancy induced hypertension .and pre eclampsia. The production of thrombus and necrosis of placenta are reduced and can control hypertension.
7. Colorectal Ca Over expression of COX 2 enzyme is thought to be a factor in this condition and so use of aspirin can reduce the incidence.

Most of the NSAIDs can be used for these conditions though the effectiveness varies. The antiplatelet action is seen with aspirin and indomethacin.

Adverse Drug Reactions (ADR)

Gastric irritation characterized by epigastric distress, anorexia, peptic ulceration, are very common. Taking the drug with, antisecretory drugs like proton pump inhibitors or histamine 2 antagonists or antacids can reduce the incidence. Haematemesis and malena can occur and can even end fatally. Allergic reactions, bronchospasm due to over expression of leukotreins is also seen. The non salicylate anti-inflammatory drugs are prone for more adverse effects than aspirin.

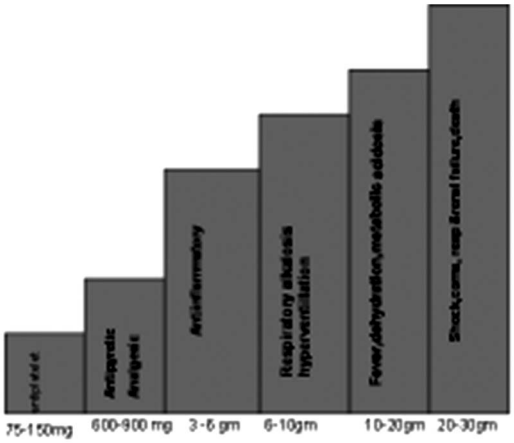

Figure 2. **Showing the effect of various doses of aspirin**

Poisoning with aspirin is uncommon now as the administration is limited mainly to the lowest dose. Still accidental consumption by children can occur. It is characterized by respiratory alkalosis, metabolic acidosis and later leads to coma. (Figure 2) Gastric lavage and administration of sodium bicarbonate and supportive measures have to be followed.

Contraindications & Precautions

Acid Peptic diseases, history of bleeding diseases, chronic liver disease are absolute contraindications. It should not be administered in chicken pox and other viral diseases in children. Aspirin must be stopped one week before elective surgery. If this is not possible adequate measures should be taken to cope up with bleeding during surgery. In case of pregnancy if there are no absolute indications it is better to avoid aspirin as postpartum bleeding can occur. It can also result in low birth weight babies and closure of the patent ductus arteriosus

In case of patients with bronchial asthma or history of allergy it should be administered with caution.

Non Salicylate NSAIDS

Paracetamol

It is the de ethylated product of phenacetin (banned). It is a drug with more analgesic and antipyretic effect and less anti-inflammatory property. The action is more central and so it can be used more for controlling hyperpyrexia It acts as an analgesic and mild anti-inflammatory agent by its peripheral action. It inhibits the COX III enzymein CNS and that may be the reason for the antipyresis.

PARACETAMOL is given orally and I/M. It is well absorbed from GIT. Gastric irritation is far less with this drug. It has no antiplatelet action and has no effect on uric acid excretion.

Paracetamol is metabolized by CYP2E1 enzyme to N-acetyl-p-benzoquinoneimine. (NABQI) It is detoxified by liver by conjugating with glutathione. Leucopenia and nephropathy have been reported in some cases. The most important precaution to be taken during administration of this drug is to prevent over dosage as it can result in acute liver damage. This can occur in small children and those with decreased liver function. When there is overloading of the liver, the glucorinidation capacity is saturated and the metabolite bind to the liver proteins causing necrosis .The protein binding occurs in the kidney also and renal tubular necrosis can occur. In chronic alcoholics large doses of paracetamol taken for a few days induce the metabolising enzymes and can result in hepatic toxicity.

Treatment is by early gastric lavage and administration of activated charcoal and supportive measures. The specific antidote is N-acetyl cysteine which replenishes the hepatic glutathione is given I/ V or orally.

It is a drug notorious for over the counter (OTC) use. It is used for headache, tooth ache, musculoskeletal pain, dysmenorrhoea and the analgesic potency is equal to aspirin.

ADRs. Mild gastric irritation and liver damage can occur.

NEFOPAM It is an analgesic without inhibition of PGs. It is used for musculoskeletal pain, dental pain . It has anti cholinergic adverse effects like dry mouth, urinary retension and blurred vision and adrenergic ADRs like tachycardia and nervousness.

DICLOFENAC SODIUM. It has good analgesic, anti-inflammatory and mild antipyretic effect and acts by decreasing PG production. In addition, it can reduce neutrophil chemotaxis and superoxide production at the site. It is available as oral tabs of 50&100 mg. Slow release tablets, eye drops and injection containing 25mg/ml are also available. It is highly protein bound and so good duration of action is seen. Penetration to the tissues is good and attain good concentration in synovial fluid& sites of inflammation which makes it a preferred drug for arthritis, musculoskeletal pain and inflammations of the eye.

ADR. Gastric irritation is the most important one and can decrease the excretion of lithium and can precipitate lithium toxicity.

PIROXICAM It is a drug with similar analgesic and

anti-inflammatory properties and antiplatelet action. It has added actions of decreasing the production of IgM rheumatoid factor, and decrease leucocyte chemotaxis. It is well absorbed and after glucorinidation enterohepatic circulation of the drug occurs. So the dose of the drug is less -only 20 mg. It is used mainly in arthritis and musculoskeletal pain.

INDOMETHACIN. It is a potent anti- inflammatory drug with antipyretic action. In addition to inhibition of PG synthesis it suppresses neutrophil motility. The dose is 25-75mg orally, Eye drops and suppositories are available. It is absorbed well orally and minimally by rectal route. The drug is highly protein bound and so has good duration of action.

Indomethacin has been used in resistant cases of rheumatoid arthritis, gouty arthritis, ankylosing spondylitis, psoriatic arthritis and acute exacerbations of arthropathies.

In addition, it can be used in closure of patent ductusarteriosis in children and resistant fever in malignancy.

Adverse effects are gastric irritation, gastric bleeding and diarrhea. Frontal lobe headache mental confusion and hallucinations can occur which can sometimes be neglected by physicians.

IBUPROFEN, NAPROXEN & OTHERS

They are drugs with less anti-inflammatory action than aspirin. Antiplatelet action is also seen. They are well absorbed and highly protein bound. Good penetration occurs to the brain, synovial fluid and it crosses the placenta. They are conjugated in the liver and excreted through urine mainly and also through bile. Ibuprofen is given as 400mg tabs. This group of drugs has been popularly used for arthritis, post operative anti-inflammatory action, after tooth extraction, soft tissue injuries etc.

ADR. Gastric irritation and allergic reactions occur.

INTER ACTIONS of Aspirin and NSAIDs

Aspirin displaces sulphonylureas, phenytoin, methotrexate and warfarin from binding sites on plasma and can increase their ADR.

In gouty arthritis when probenecid is co-administered with aspirin the uricosuric action of probenecid is reduced. Aspirin can displace ketorolac from plasma proteins and then increases the blood level of ketorolac and so should not be given together. Ibuprofen group will decrease the diuretic and antihypertensive action of thiazides, frusemide and beta blockers ACE inhibitors. NSAIDs inhibit the renal excretion of lithium and produce high levels and toxicity. With K+ sparing drugs NSAIDs cause potassium retention and hyperkalemia. NSAIDs reduce the clearance of methotrexate and aminiglycoside drugs and produce respective ADRs. High doses of NSAIDs exert a hypoglycemic effect and can alter the response to other oral hypoglycemics. Indomethacin reduces the natriuresis produced by Triamterine and nephrotoxicity is produced.

COX II inhibitors. They inhibit the COX IIenzyme Some of them have no action on COX I enzyme at all and they are the selective inhibitors of COX II enzyme.

Some of these drugs were preferential inhibitors of the enzyme and some are selective inhibitors. The greatest advantage of COX II inhibitors claimedover COX I inhibitors is that they produce less gastricirritation, still abdominal pain and diarrhea have been reported by some. Another advantage is that they do not have antiplatelet effect and so bleeding tendency is not seen. Although these drugs were brought out with much enthusiasm some of them were with drawn after their introduction and some are still used with caution

The different drugs are tabulated in the table.

Table 1. Comparative properties of COX II inhibitors

Drug		Actions	Dose	Specific ADR	Remarks	
Nemesulide	COX II more	Analgesic, antipyretic Anti-inflammatory (AAA)	100 mg	Hepatic necrosis	Withdrawn in most countries	Still used in India in fever
Meloxicam	COX II more	Anti-inflammatory analgesic	7.5mg	Gastric ulcer		Used in osteoarthritis
Nabumetone	COX II more	AAA	500mg	Gastric erosions		Arthritis
Celicoxib	Cox II only 20 times	Analgesic, antiinflammatory	100-300mg	Oedema thrombosis	Less gastric ulcers	Rheumatoid arthritis, osteoarthritis
Rofecoxib		Analgesic, antiinflammatory	12.5mg	Oedema Hypertension	GIT less antiplatelet less	Osteoarthritis
Valdecoxib	Cox II only	Analgesic, antiinflammatory	10mg	GIT upset	antiplatelet less caution in sulpha sensitive	Rheumatoid arthritis, osteoarthritis gouty arthritis musculo skeletal pain
Etericoxib	MAX COX II	Analgesic, antiinflammatory	60-90mg	Liver toxicity	Very long acting	Rheumatoid arthritis, osteoarthritis dysmenorrhoea dental surgery

Combinations of various anti-inflammatory compounds are now marketed claiming lesser dose of individual drug and so lesser toxicity.

As days go more and more analgesics will be tested and marketed, but their exact efficacy, safety and economic advantages over the others will be fully known only after a few years.

END NOTE

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