A overview: non-steroidal anti-inflammatory drugs and mechanisms

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ABSTRACT

The inflammatory response represents a generalized response to infection or tissue damage and is designed to remove cellular debris, to localize invading organisms and arrest the spread of infection. NSAIDs are metabolized primarily in the liver. They vary in their half-lives and bioavailability. Given the multitude of available NSAIDs, the variability of their half-lives allows for different dosing regimens. The fluid in the inflamed area is known as inflammatory exudates, commonly called as pus. These exudates contain dead cells and debris in addition to body fluids. The inflammatory response is characterized by the following symptoms: Reddening of the localized area, swelling, pain and elevated temperature. Reddening results from capillary dilation that allows more blood to flow to the damaged tissue. Elevated temperature results from capillary dilation which permits increased blood flow through these vessels, with associated high metabolic activities of neutrophils and macrophages. The release of histamine from mast cells during antigen antibody reactions is well known, as is its involvement in the inflammatory response to skin injury. The present review focused on list and precautions of NSAID with its typed and classification, Analgesic activity study, histamine.

Introduction

The inflammatory response represents a generalized response to infection or tissue damage and is designed to remove cellular debris, to localize invading organisms and arrest the spread of infection. The inflammatory response is characterized by the following symptoms: Reddening of the localized area, swelling, pain and elevated temperature. Reddening results from capillary dilation which permits increased blood flow through these vessels, with associated high metabolic activities of neutrophils and macrophages. The dialation of blood vessels is accompanied by increased capillary permeability causing swelling as fluid accumulates in the spaces surrounding tissue and cells. Pain in the case of inflammation is due to the lysis of blood cells that trigger the production of bradykinin and prostaglandins. The area of inflammation also becomes walled off as a result of the development of fibrinous clots. The deposition of fibrin isolates the inflamed area, cutting off normal circulation. The fluid in the inflamed area is known as inflammatory exudates, commonly called as pus. These exudates contain dead cells and debris in addition to body fluids. After the expulsion of the exudates, the inflammation may terminate and tissues may return to their normal state (Atlas, 1995). Pain belongs to a basic sensory abnormality associated with inflammation. Pain develops when nerve fiber terminals of polynodal nociceptors become sensitized by mediators of inflammation. The pain producing inflammatory mediators are bradykinin, prostaglandins (PGE1 and PGE2) and leukotrienes, especially LTB4. Pain becomes evoked by the synergistic action of bradykinin and prostaglandins (Antoni, 1991). Based on visual observation, the ancients characterised inflammation by five cardinal signs, namely redness (rubor), swelling (tumour), heat (calor; only applicable to the body'extremities), pain (dolor) and loss of function (junctio laesa). The first four of these signs were named by Celsus in ancient Rome (30–38 B.C.) and the last by Galen (A.D 130–200). Inflammation is a complicated and not fully understood communication between cellular and humoral elements. More recently, inflammation was described as “the succession of changes which occurs in a
living tissue when it is injured provided that the injury is not of such a degree as to at once destroy its structure and vitality. Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals or microbiological agents. The inflammatory response is characterized by the following symptoms: Reddening of the localized area, swelling, pain and elevated temperature. Reddening results from capillary dilation that allows more blood to flow to the damaged tissue. Elevated temperature results from capillary dilation which permits increased blood flow through these vessels, with associated high metabolic activities of neutrophils and macrophages. The dilation of blood vessels is accompanied by increased capillary permeability causing swelling as fluid accumulates in the spaces surrounding tissue and cells. Pain in the case of inflammation is due to the lysis of blood cells that trigger the production of bradykinin and prostaglandins. The area of inflammation also becomes walled off as a result of the development of fibrinous clots. The deposition of fibrin isolates the inflamed area, cutting off normal circulation. The fluid in the inflamed area is known as inflammatory exudates, commonly called as pus. These exudates contain dead cells and debris in addition to body fluids. After the expulsion of the exudates, the inflammation may terminate and tissues may return to their normal state (Atlas, 1995). Pain develops when nerve fiber terminals of polynodal nociceptors become sensitized by mediators of inflammation. The pain producing inflammatory mediators are bradykinin, prostaglandins (PGE1 and PGE2) and leukotrienes, especially LTB[1-9]. Pain becomes evoked by the synergistic action of bradykinin and prostaglandins.

Causes of inflammation

The numerous causes of inflammation may be classified as follows:

- Microbes—e.g. bacteria, viruses, protozoa, fungi,
- Physical agents—e.g. heat, cold, mechanical injury, ultraviolet and ionising radiation.
- Chemical agent—organic: e.g: microbial toxins, organic poison—-inorganic: e.g: acids, alkalis[Ross n Wilson P.N.371]

Types of inflammation

Acute Inflammation

These inflammation having short duration process E.g: days to a few weeks, and may range from mild to a very severe. The cardinal signs of inflammation are, redness, heat, pain, swelling, loss of function. The acute inflammatory response is described as a collection of overlapping events, increased blood flow, accumulation of tissue fluid, migration of leucocytes, increased core temperature, pain and suppuration. some of the most important substances released in inflammation as shown in table:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Made by</th>
<th>Trigger for release</th>
<th>Main pro inflammatory action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>mast cells (in most tissue), basophils (blood), stored in cytoplasmic granules</td>
<td>Binding of antibody to mast cell and basophils</td>
<td>Vasodilation, itching, increase vascular permeability, degranulation, smooth muscle contraction (e.g. bronchoconstriction)</td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>Platelet mast cell and basophils (stored in granules) also in CNS (acts as</td>
<td>When platelets are activated, and when mast cells/basophils</td>
<td>Vasoconstrictions, increases permeability</td>
</tr>
</tbody>
</table>

Table 1: Acute Inflammation
neurotransmitter) degranulate

<table>
<thead>
<tr>
<th>Prostaglandins (PGs)</th>
<th>Nearly all cells not stored but made from cell membrane as required</th>
<th>Many different stimuli e.g. drugs, toxins, other inflammatory mediators, hormones</th>
<th>Diverse, sometimes opposing e.g. fever, pain, vasodilation or vasoconstriction, increases vascular permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Liver, mast cell, basophils, (stored in cytoplasmic granules)</td>
<td>Released when cells degranulate</td>
<td>Anticoagulant (prevents blood clotting), which maintains blood supply (nutrients, O2) to injured tissue and washes away microbes and wastes</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Tissue and blood</td>
<td>When blood clots, in trauma and inflammation</td>
<td>Pain, vasodilation</td>
</tr>
</tbody>
</table>

**Figure 2: Acute Inflammation**

**Chronic Inflammation**

- Lymphocyte, macrophage, plasma cell (mononuclear cell) infiltration
- Tissue destruction by inflammatory cells
- Attempts at repair with fibrosis and angiogenesis (new vessel formation)
- When acute phase cannot be resolved
  - Persistent injury or infection (ulcer, TB)
  - Prolonged toxic agent exposure (silica)
  - Autoimmune disease states (RA, SLE)

**Figure 3: Chronic Inflammation**
This process having a longer duration of action, considerably more tissue is likely to be destroyed. The process involved is same as the acute inflammation. The inflamed tisselles are mainly lymphocytes instead of neutrophils and fibroblasts are activated, leading to the laying down of collagen, and fibrosis. If the body defences are unable to clear the infection, they may try to wall it off instead, forming nodules called as granulomas, within which are collection of defensive cells. Tuberculosis is an example of an infection that frequently becomes chronic, leading to granuloma formation. The causative agent is mycobacterium tuberculosius resistant to body defences and so pockets of organisms are sealed up in granulomas within the lungs.

Classification of NSAIDs

A. Non selective COX inhibitors (traditional NSAIDs)
   1. Salicylates: Aspirin
   2. Propionic acid derivatives: Ibuprofen
   3. Anthranilic acid derivatives: Mephenamic acid
   4. Aryl-acetic acid derivatives: Diclofenac, Acetofenac
   5. Oxicam derivatives: Piroxicam, Tenoxicam
   6. Pyrrolo-pyrrole derivatives: Ketorolac
   7. Indole derivatives: Indomethacin
   8. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone

B. Preferential COX-2 inhibitors
   1. Nimesulide, Meloxicam, Nabumetone

C. Selective COX-2 inhibitors
   1. Celecoxib, Etoricoxib, Parecoxib

D. Analogic Antipyretic with poor inflammatory action
   2. Paraaminophenol derivatives: paracetamol
   3. Pyrazolone derivatives: Metamizol, Propiphenazone
   4. Benzoxazocine derivatives: Nefopam

Marketed preparations and dose[2-5]

A. Nonselective COX-2 inhibitors
1. Salicylates
   - Aspirin-
   - Ecospirin 75,150,325 mg tablets
   - Disprin 350 mg tablets
   - Aspirin 350 mg tablets
   - An injectable preparation has been made available recently:
     - Biospirin:Lysine acetylsalicylate 900 mg+ glycine 100mg/vial for dissolving 5 ml water and i.v. injection

2. Propionic acid derivatives
   - Ibuprofen:
     - Ibugeic plus tablets
   - Combination of aspirin(650mg) and codeine(60mg) in reliving dental surgery pain
   - Naproxen:
     - In acute gout dose 750 mg stat followed by 250 mg 8 hourly till attack subsides
     - Ketoprofen:
     - Ketorol DT tablet
     - Flurbiprofen:
       - Ocuflox, Flur, Flurbiflurin, 0.03% eyedrops, 1 drop of 6 hourly

3. Anthranilic acid derivatives
   - Mephanamic acid:
     - Dose: 250-500 mg, Medol 250-500 mg capsule, Meftal 250,500 mg tablet, 100 mg/5 ml suspension, Ponstan 125,250,500 mg tablet, 50 mg/ml syrup

4. Aryl acetic acid derivatives
   - Diclofenac sodium:
     - Dose: 50 mg TDS, then BD oral, 75 mg deep i.m.
     - Voveran, Diclonac, monovac 50 mg enteric coated tablet, 100 mg S.R. tablet, 25 mg/ml in 3 amp. for i.m.inj.
     - Diclimax 25,50 mg tablet,
   - Diclofenac potassium:
     - Voltarflam 25,50 mg tablets, Ultra-k 50 mg tablets, Voveran 1% topical gel, Diclonac 0.1% eye drops

5. Oxicam Derivatives
   - Piroxicam:
     - Dose: 20 mg BD for two days followed by 20 mg OD, Dolonex, pirox 10,20 mg capsule, 20 mg dispersible tablets, 20 mg/ml injection in 1 and 2 ml amps.
     - Piricam 10,20 mg Capsule
   - Tenoxicam:
     - Tobitil 20 mg tablets, dose 20 mg OD

6. Pyrrolo-pyrrole derivatives
   - Ketorolac:
     - Ketorol, zorovon, ketanov, torolac 10 mg tablets, 30 mg in 1 ml amp.
     - Ketlur, acular 0.5% eye drops, 1-2 drops 2-4 times a day for noninfective ocular inflammatory conditions

7. Indole derivatives
   - Indomethacin:
     - Dose: 25-50 mg BD-QID, those not tolerating the drug orally may be given nightly suppository.
     - Idicin, Indocap 25 mg capsules, 75 mg SR capsules, Indoflam 25,75 mg capsules, 1% eye drops. Recticin 50 mg suppository

8. Pyrazolones derivatives
   - Phenyalbutazone
     - Esgipyrin tablets

B. Preferential COX-2 inhibitors
   - Nimesulide:
     - Dose: 100 mg BD, nimulid, nimgesic, nimoxy 100 mg tablet, 50 mg/5 ml suspension
   - Meloxicam:
     - Dose: 7.5-15 mg OD, melflam, mel OD, muvik, mcam 7.5 mg, 15 mg tablets
   - Nabumetone
     - Nabuflam 500 mg tablets; 1 tablet OD

C. Selective COX-2 inhibitors
   - Celecoxib
Celact, revibra, colcibra 100,200 mg capsule
- **Etoricoxib**
  Dose: 60-120 mg OD; Etody, torocoxia, etoxib, nucoxia 60,90,120 mg tablets
- **Parecoxib**
  Dose: 40 mg oral/i.m/i.v. repeated after 6-12 hours. Revaldo, valto-p 40 mg/vial inj., paroxib 40 mg tablet

D. Analgesic Anti pyretics with poor anti inflammatory action
- Paraaminophenol derivatives
  a. Paracetamol
  Metacin, paracin 500 mg tablets, 125mg/5 ml syrup,
  Crocin pain relief 650 mg + caffeine 50 mg tablets
- Pyrazolone Derivatives
  a. Propiphenazone
  Pyrlfil tablet
- Benzoxazocine derivatives
  Nefopam

Dose: 30-60 mg TDS oral, 20 mg i.m. 6 hourly. Nefomax 30 mg tablets, 20 mg in 1 ml ampule.

**Mechanism of action of NSAIDs**

**Anti inflammatory**
The most important mechanism of anti inflammatory action of NSAIDs is considered to be inhibition of PG synthesis at the site of injury. The antiinflammatory potency of different compounds roughly corresponds with their potency to inhibit COX. However, nimesulide is a potent anti-inflammatory but relatively weak COX inhibitor. PGs are only one of the mediators of inflammation; inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines etc. Inflammation is the result of concerted participation of large number of vasoactive, chemotactic and proliferative factors at different stage, and there are many targets for inflammatory action[8-11].

Features of non selective COX inhibitors and selective COX-2 inhibitors:

**Table 2: COX inhibitors and selective COX-2 inhibitors**

<table>
<thead>
<tr>
<th>Action</th>
<th>COX-1/COX-2 inhibitors</th>
<th>COX-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Analgesic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2. Antipyretic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3. Antiinflammatory</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4. Antiplatelet aggregatory</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5. Gastric mucosal damage</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6. Renal salt/water retention</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7. Delay/prolongation of labour</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8. Ductus arteriosus closure</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>9. Aspirin sensitive asthma precipitation</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**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.

**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 no receptors to respond to stimuli that are normally painless. In particular, it is believed that inflammation leads to a lowering of the response threshold of poly modal no receptors.

**Pharmacokinetic**

NSAIDS are metabolized primarily in the liver. They vary in their half-lives and bioavailability. Given the multitude of available NSAIDs, the variability of their half-lives allows for different dosing regimens. Although decreased frequency of dosing improves compliance as a general rule, consideration must be given to the increase in renal dysfunction associated with longer-acting NSAIDs. It has also been speculated that use of daily dosed medications, by improving compliance, may increase the risk for GI bleeding. Variability in susceptibility to adverse effects of various NSAIDs does not seem to be due to difference in pharmacokinetics. Hepatic function, renal function, and age must be considered before prescribing and dosing.
Catabolic pathway of AA

![Catabolic pathway of AA](image)

**Figure 4: Catabolic pathway of AA**

Mediators

**Mediators of acute inflammation**

**Effector-cell-derived factors preformed in secretory granules:**
- Mast cell: Histamine
- Neutrophil/Macrophage: Lysosomal enzymes
- Platelet: Serotonin

**Newly synthesized**
- Prostaglandins
- Leukotrienes
- Platelet activating factor
- Oxygen radicals
- NO
- Cytokines

**Figure 5: Mediators**

**Table 3-7. MOST LIKELY MEDIATORS IN INFLAMMATION**

<table>
<thead>
<tr>
<th>Vasodilation</th>
<th>Prostaglandins</th>
<th>Nitric oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased vascular permeability</td>
<td>Vasoactive amines</td>
<td>C5a and C5a (through liberating amines)</td>
</tr>
<tr>
<td>Bradycinins</td>
<td>Leukotrienes</td>
<td>C4, D4, E4</td>
</tr>
<tr>
<td>PAF</td>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Chemotaxis, leukocyte activation</td>
<td>C5a</td>
<td>Leukotriene B4</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Bacterial products</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>IL-1, IL-6, TNF</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Pain</td>
<td>Prostaglandins</td>
<td>Bradycinins</td>
</tr>
<tr>
<td>Tissue damage</td>
<td>Neutrophil and macrophage lysosomal enzymes</td>
<td>Oxygen metabolites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitric oxide</td>
</tr>
</tbody>
</table>

**Figure 6: Mediators**
Histamine

The release of histamine from mast cells during antigen antibody reactions is well known, as is its involvement in the inflammatory response to skin injury. Also, increased numbers of mast cells are present in the rheumatoid synovium and in the asthmatic lung, correlated with raised levels of histamine. The advent of non sedating H1 antihistamines has allowed them to be tested in much higher doses than ever before, and some evidence suggests that histamine may play a role in allergic asthma[11-15].

Bradykinin

Small amounts of bradykinin cause pain, vasodilatation, and edema, all contributing to inflammation. Bradykinin-like immunoreactivity has been detected in rat pleural inflammatory exudates. Kinins are also present in nasal secretions after immunological challenge, and a kininogenase is released from human lung mast cells. Inhaled bradykinin causes bronchoconstriction in normal and asthmatic individuals, but not through release of PGs.

Thromboxane A2 and prostacyclin

The anti platelet effects of aspirin could not be explained by inhibition of the synthesis of PGE2 or PGF2α because these PGs do not affect platelet aggregation to any great extent. Prostacyclin, as it was later termed, relaxes blood vessels and inhibits aggregation of platelets. Its synthesis in endothelial cells of blood vessel walls is of special importance.

Interleukin-1

IL-1 is a polypeptide produced by activated macrophages that mimics the symptoms of chronic inflammation. It has had other names, including endogenous pyrogen. IL-1-like activity (equivalent to 1.69 U/ml) has been detected in synovial fluids from patients with rheumatoid arthritis. Its actions include activation of lymphocytes and production of fever, the latter being mediated by release of PGE2.

The prostaglandins

Apart from non nucleated erythrocytes, all cells are capable of synthesizing PGs, which are released in response to many kinds of trauma or any disturbance of the cell membrane. In other words, the pathological release of PGs that contributes to inflammation, fever, and pain is inhibited by aspirin and other NSAIDs. The aspirin like drugs also share, to a greater or lesser extent, certain side effects, such as a propensity to irritate the stomach, nephrotoxicity in high concentrations, and interference with the birth process. It was suggested that these side effects resulted from the inhibition of the physiological release of a protective PG.

Platelet-activating factor (PAF)

The phospholipid PAF-ac ether is released by the action of phospholipase A2 from most pro inflammatory cells, as well as by vascular endothelial cells and platelets .It induces inflammatory reactions in various animal species and in human skin. PAF also mimics themain clinical features of asthma and is particularly effective in producing hyper reactivity and accumulation of eosinophils in lung tissue. Asthmatic patients have high levels of circulating PAF and their eosinophils make more PAF than those of normal controls. The anti asthmatic glucocorticoids, by suppressing phospholipase A2, will thus reduce the formation of PAF. Furthermore, PAF antagonists, such as the ginkgolides, are currently being investigated for the treatment of asthma.
Histamine and Serotonin
induce vasodilation and increased vascular permeability

Mast cell:
- richest source of histamine
- located in connective tissue
- adjacent to blood vessels
- Degranulation through receptors for IgE, IgG, histamine, bacterial products and anaphylatoxin C5a, physical injury, cold, heat
- release of PAF (platelet activating factor) leads to serotonin and histamine release from activated platelets
- Mast cells are very important effector cells in hypersensitivity reactions (anaphylactic reactions)

**Figure 8: Histamine**

**NSAID (List of non steroidal anti-inflammatories)**
- **Aspirin** (Anacin, Ascriptin, **Bayer**, Bufferin, Ecotrin, **Excedrin**)
- Choline and magnesium salicylates (CMT, Tricosal, Trilisate)
- Choline salicylate (Arthropan)
- Celecoxib (Celebrex)
- Diclofenac potassium (Cataflam)
- Diclofenac sodium (Voltaren, Voltaren XR)
- Diclofenac sodium with misoprostol (Arthrotec)
- Diflunisal (Dolobid)
- Etorofac (Lodine, Lodine XL)
- Fenoprofen calcium (Nalfon)
- Flurbiprofen (Ansaid)
- **Ibuprofen** (Advil, Motrin, Motrin IB, Nuprin)
- Indomethacin (Indocin, Indocin SR)
- Ketoprofen (Actron, Orudis, Orudis KT, Oruvail)
- Magnesium salicylate (Arthritab, Bayer Select, Doan's Pills, Magan, Mobidin, Mobogesic)
- Meclofenamate sodium (Meclomen)
- Mefenamic acid (Ponstel)
- Meloxicam (Mobic)
- Nabumetone (Relafen)
- Naproxen (Naprosyn, Naprelan*)
- Naproxen sodium (**Aleve**, Anaprox)
- Oxaprozin (Daypro)
- Piroxicam (Felldene)
- Rofecoxib (Vioxx)
- Salsalate (Amigesic, Anaflax 750, Disalcid, Marthritic, Mono-Gesic, Salflex, Salsitab)
- Sodium salicylate (various generics)
- Sulindac (Clinoril)
- Tolmetin sodium (Tolectin)
- Valdecoxib (Bextra)

Note: Some products, such as Excedrin, are combination drugs (Excedrin is acetaminophen, aspirin, and caffeine). Note that **acetaminophen** (Paracetamol; Tylenol) is not on this list. Acetaminophen belongs to a class of drugs called analgesics (pain relievers) and antipyretics (fever reducers). The exact mechanism of action of acetaminophen is not known. Acetaminophen relieves pain by elevating the pain threshold, that is, by requiring a greater amount of pain to develop before it is felt by a person. It reduces fever through its action on the heat-regulating center of the brain. Specifically, it tells the center to lower the body's temperature when the temperature is elevated. Acetaminophen relieves pain in mild arthritis but has no effect on the underlying inflammation, redness and swelling of the joint Paracetamol, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties, and so it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs.
Latest anti-inflammatory drugs

Table 3: Latest anti-inflammatory drugs

<table>
<thead>
<tr>
<th>Recent drug</th>
<th>Dosage form</th>
<th>Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acecloflam</td>
<td>Tablet</td>
<td>Acelofenac 100 mg, Paracetamol 325 mg, Serratiopeptidase 10mg</td>
</tr>
<tr>
<td>Etocoxiv</td>
<td>Tablet</td>
<td>Etoricoxib30, 60,120 mg</td>
</tr>
<tr>
<td>Fleura D</td>
<td>Soft gel.capsule</td>
<td>Diclofinac 50 mg, Metaxalone 400mg</td>
</tr>
<tr>
<td>Muvera</td>
<td>Tablet</td>
<td>Meloxicam 15,30mg</td>
</tr>
</tbody>
</table>

NSAIDs should never be combined

Preferentially inhibitors of cyclo-oxygenase-2 (cox 2) such as meloxicam and the specific cox 2 inhibitor celecoxib are approved for pain relief in osteoarthritis (OA). Although their analgesic efficacy has been established their ability to significantly reduce gastrointestinal (GI) side effects has not been convincingly proven. They should also be used with caution in patients with renal or heart failure. Recent evidences on the relative safety of oral NSAIDs have indicated differences in the risk of serious upper gastro intestinal side effects as per following scale[5-21]:

**Lowest Risk**
Ibuprofen

**Intermediate Risk**
Diclofenac, Indomethacin, Ketoprofen, Naproxen, Nimesulide, Piroxicam, Celecoxib. Higher in the case of nimesulide, And possibly higher in the case of piroxicam

**Highest Risk**
Azapropazone. It is suggested that NSAIDs should generally be preferred to start at lowest recommended dose not to use more than one oral NSAIDs at a time and to remember that all NSAIDs are contraindicated in patients with peptic ulceration.

**Opioids**
Weak opioids such as codeine or dihydrocodeine, used alone or in combination with paracetamol may be effective option if paracetamol does not relieve pain or NSAIDs are unsuitable. Constipation is common, especially in the elderly but it may be minimised by encouraging a high fibre diet and plenty of fluids prescribing prophylactic laxatives.

**Other Drugs:**
Topical analgesic such as NSAIDs, capsaicin, or rubefacients may also provide some degree of pain relief in OA. [P.N.147,148. MIMS volume 34 number 4. April 2004]

**Analgesic activity study[8-19]**

**Hot-plate method (Thermal stimulus)**
The mice selected were weighted (25-30g) and groups into eight of six in each and the normal basal reaction time were taken by repeating for 5 times. Group-3 to Group-5 received chloroform extract and Group-6 to Group-8 received methanol extracts respectively at a dose of 50mg/kg, 100 mg/kg and 200mg/kg body weight (p.o.). Group-2 received Morphine sulphate 5mg/kg body weight (s.c.) and served as standard. Group-1 administrated 1% DMSO in the dose of 10ml/kg body weight (p.o.) served as control. All animals were lowered onto the surface of a hot plate (50±1.00C) enclosed with cylindrical glass and the time for the animal to jump or lick the fore limb was noted as the reaction time (RT). Cut off time in the absence of a response was 15 sec to prevent the animals from being burnt. The observations were made before and after administration of respective drugs at 30 min, 60 min, 120 min, and at the end of 180 min.

**Tail immersion Test (Thermal stimulus)**
The Swiss albino mice were selected by immersing the tail in hot water at temperature 55°C ±5°C and the basal reaction time was noted. The mice which showed a positive response within a span of 5 seconds for withdrawal of the tail clearly out of water were selected for further studies. The mice selected were weighted (25-30g) and groups into eight of six in each and the normal basal reaction time were taken by repeating for 5 times. Group 3 to Group 5 received chloroform extract and Group 6 to Group 8 received methanol extract respectively at a dose of 50mg/kg, 100 mg/kg and 200mg/kg body weight. Group 2 received Morphine sulphate 5mg/kg body weight (s.c.) and served as a positive control. Group 1 served as solvent control (1% DMSO) and received the dose of 10ml/kg body weight. The observations were made before and after administration of respective drugs at 30 min, 60 min, 120 min, and at the end of 180 min.

**Writhing Test (Chemical stimulus)**
Aspirin like non-narcotic analgesic activity of the test extracts was investigated by the ability to protect a painful writhing syndrome in mice. The syndrome is characterized by abdominal torsion, drawing up of hind limbs to the abdominal wall, marked contraction of the abdominal area and periodical arching of the back to rub the abdominal wall on the glazed surface on which the mouse is kept. Writhing was consistently produced in mouse by an intra peritoneal injection of 0.6% aqueous acetic acid. Overnight fasted, healthy adult male albino Swiss mice weighing between 18 to 25gm in groups of
six each were taken for present investigation. DMSO 1% solution of the test extracts were administered orally in a dose of 50mg/kg, 100mg/kg and 200mg/kg body weight respectively to the test groups animal. The control group of animals were given only DMSO 1% solution in the dose of 10ml/kg body weight. One group of animal was administered with Diclofenac sodium as standard, orally in a dose of 5mg/kg (b.w). After a gap of 30 minutes of the administration of the test extracts, all the groups of mice were given the writhing agent, 0.6% aqueous acetic acid, in a dose of 1ml/100gm (b.w) intra peritoneally. Five minutes after administration of acetic acid the number of writhing produced in these animals were counted for next 10 minutes and the number of writhing produce in the treated groups were compared with those in the control group and the percentage protection was calculated as show below,

Percentage protection = [(No.of writhes in control - No. of writhes in test)/ No. of writhes in control] x 100

Conclusion

These suggestions are very helpful for most people with inflammatory conditions such as sprains, strains, bursitis, tendonitis, arthritis, etc. and can be used in conjunction with supplementation. Most people find that eating this way also often lowers blood lipids, smooths out blood sugar variations, helps with weight management, reduces digestive problems, increases energy, and more.

Conflict of interest statement

We declare that we have no conflict of interest.

References