**PHARMACOLOGY-III**

**AUTACOIDS**

The word autacoid comes from the Greek: ¨autos (self) & ¨akos (medicinal agent, or remedy)

**INTRODUCTION:**

 Histamine, serotonin, prostaglandins, & some vasoactive peptides belong to a group of compounds called

autacoids .

 They all have the common feature of being formed by the tissues on which they act so they function as local

hormones

 The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in

specific endocrine glands.

**TYPES**: The important autacoids include:

• Histamine,

• Hydroxytryptamine (5-HT, serotonin),

• Prostaglandins,

• Leukotrienes, and

• Kinins.

HISTAMINE

Histamine (Beta-aminoethyl-imidazole) is formed from decarboxylation of Imidazole ring containing amino

acid histidine. Histamine is a basic amine, stored in mast cell and basophil granules, and secreted when C3a and

C5a interact with specific membrane receptors or when antigen interacts with cell-fixed immunoglobulin E.

Histamine plays a central role in immediate hypersensitivity (Type 1) and allergic responses.

The actions of histamine on bronchial smooth muscle and blood vessels account for many of the symptoms of the

allergic response. In addition, certain clinically useful drugs can act directly on mast cells to release histamine,

thereby explaining some of their untoward effects.

Histamine has a major role in the regulation of gastric acid secretion and also modulates neurotransmitter release.

Stimulation of IgE receptors also activates phospholipase A2 (PLA2), leading to the production of a host of

mediators, including platelet-activating factor (PAF) and metabolites of arachidonic acid. Leukotriene D4, which

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is generated in this way, is a potent contractor of the smooth muscle of the bronchial tree.

Kinins also are generated during some allergic responses. Thus the mast cell secretes a variety of inflammatory

mediators in addition to histamine, each contributing to the major symptoms of the allergic response.

Epinephrine and related drugs that act through b2 adrenergic receptors increase cellular cyclic AMP and

thereby inhibit the secretory activities of mast cells. So are given in anaphylactic shock treatment.

However, the beneficial effects of b adrenergic agonists in allergic states such as asthma are due mainly to their

relaxant effect on bronchial smooth muscle.

Cromolyn or Cromoglicate sodium is used clinically because it inhibits the release of mediators from mast

and other cells in the lung.

Drug which release histamine: Tubocurarine, succinylcholine, morphine, Polymyxin B, bacitracin,

Vancomycin-induced "red-man syndrome" involving upper body and facial flushing and hypotension may be

mediated through histamine release. Bradykinin is a poor histamine releaser, whereas kallidin (Lys-bradykinin)

and substance P, with more positively charged amino acids, are more active.

 Histamine produces effects by acting on H1, H2 or H3 (and possibly H4) receptors on target cells.

 The main actions in humans are:

o Stimulation of gastric secretion (H2)

o Contraction of most smooth muscle, except blood vessels (H1)

o Cardiac stimulation (H2)

o Vasodilatation (H1)

o Increased vascular permeability (H1).

 Injected intradermally, histamine causes the 'triple response': reddening (local

vasodilatation), weal (direct action on blood vessels) and flare (from an 'axon'

reflex in sensory nerves releasing a peptide mediator).

 The main pathophysiological roles of histamine are:

o as a stimulant of gastric acid secretion (treated with H2-receptor antagonists)

o as a mediator of type I hypersensitivity reactions such as urticaria and hay fever

(treated with H1- receptor antagonists).

 H3 receptors occur at presynaptic sites and inhibit the release of a variety of neurotransmitters.

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H1 antagonists

A. Sedating H1 antagonists (1st generation antihistaminics)

1. Chlorpheniramine , Clemastine

2. Diphenhydramine- Mainly used as a mild hypnotic, also show significant antimuscarinic effects

3. Cyproheptadine - Used also for migraine due to additional 5-hydroxytryptamine antagonist activity

4. Promethazine- Also used for motion sickness, Used for anaesthetic premedication

to prevent post- operative vomiting, , weak blockade at α1 adrenoceptors

5. Hydroxyzine – used also to treat anxiety

6. Alimemazine- Used for premedication

7. Doxylamine, Triprolidine - Mainly used as an ingredient of proprietary decongestant and other

medicines

B. Non-sedating H1 antagonists (2nd generation antihistaminics, Do not penetrate the

blood-brain barrier)

1. Desloratidine: Metabolite of loratidine

2. Fexofenadine: Metabolite of Terfenadine

3. Levocetrizine: Isomer of cetrizine

4. Terfenadine: Grapefruit juice inhibits metabolism; rare fatal

arrhythmias or QT interval prolongation as it blocks the K+

conduction in heart leading to ventricular tachycardia. The arrhythmiac

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potential increases when given with erythromycin, ketoconazole etc.

5. Mizolastine: May cause QT interval prolongation

6. Azelastine: in addition to inhibit histamine release, it also inhibits

inflammation triggered by leukotrienes and given as nasal spray for

rhinitis.

7. Acrivastine

8. Loratidine

Some important drugs:

I. Antihistaminic which increases the appetite and weight gain: Buclizine

II. (used for underweight children), Cyproheptadine, Astimazol

III. Appetite suppressant

While the adnergic drugs called anorectics like Fenfluramine and Desfluramine is appetite

suppressant.

IV. local anaesthetic property :

Mepyramine also have local anaesthetic property also or membrane stabilizing activity

(antiarrythimic)

V. Cinnarizine: is drug choice for vertigo, it is antihistaminic, anticholinergic, anti-5-

HT and vasodilator

It inhibits vestibular sensory nuclei, post-rotatary labyrinthine refluxes by reducing the

calcium influx from endolympth into vestibular sensory cells.

VI. Diphenhydramine is generally combined with Thecolic acid to reduce the sedative effect of

diphenhydramine.

H2 blockers: are used to treat ulcers and includes the drug like cimetidine, ranitidine etc.

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EICOSANOIDS

The cell damage associated with inflammation acts on cell membranes to cause leukocytes to release

lysosomal enzymes; arachidonic acid is then liberated from precursor compounds, and various eicosanoids

are synthesized.

The cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins, which have a

variety of effects on blood vessels, on nerve endings, and on cells involved in inflammation.

The discovery of cyclooxygenase isoforms (COX-1 and COX-2) led to the concepts that the constitutive

COX-1 isoform tends to be homeostatic in function, while COX-2 is induced during inflammation and

tends to facilitate the inflammatory response.

On this basis, highly selective COX-2 inhibitors have been developed and marketed on the assumption

that such selective inhibitors would be safer than nonselective COX-1 inhibitors but without loss of

efficacy.

The lipoxygenase pathway of arachidonate metabolism yields leukotrienes, which have a powerful

chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction

and alterations in vascular permeability.

Kinins, neuropeptides, and histamine are also released at the site of tissue injury, as are

complement components, cytokines, and other products of leukocytes and platelets. Stimulation of the

neutrophil membranes produces oxygen-derived free radicals.

Superoxide anion is formed by the reduction of molecular oxygen, which may stimulate the production of

other reactive molecules such as hydrogen peroxide and hydroxyl radicals. The interaction of these

substances with arachidonic acid results in the generation of chemotactic substances, thus perpetuating the

inflammatory process.

In mammals, the main eicosanoid precursor is arachidonic acid (5, 8, 11, 14-eicosatetraenoic acid), a

20-carbon unsaturated fatty acid containing four double bonds (hence eicosa, referring to the 20 carbon

atoms, and tetraenoic, referring to the four double bonds).

In most cell types, arachidonic acid is esterified in the phospholipid pool, and the concentration of the

free acid is low. The principal eicosanoids are the prostaglandins, the thromboxanes and the

leukotrienes, although other derivatives of arachidonate, for example the lipoxins, are also produced.

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In most instances, the initial and rate-limiting step in eicosanoid synthesis is the liberation of arachidonate,

either in a one-step process or a two-step process, from phospholipids by the enzyme phospholipase A2

(PLA2).

Several species exist, but the most important is probably the highly regulated cytosolic PLA2. This

enzyme generates not only arachidonic acid (and thus eicosanoids) but also lysoglycerylphosphorylcholine

(lyso-PAF), the precursor of platelet activating factor, another inflammatory

mediator.

The free arachidonic acid is metabolised by several pathways, including the following.

 Fatty acid cyclo-oxygenase (COX). Two main isoform forms, COX-1 and COX-2,

transform arachidonic acid to prostaglandins and thromboxanes.

 Lipoxygenases. Several subtypes synthesize leukotrienes, lipoxins or other compounds

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The term prostanoids encompasses the prostaglandins and the thromboxanes.

 PGI2 (prostacyclin), predominantly from vascular endothelium, acts on IP receptors,

producing vasodilatation and inhibition of platelet aggregation.

 Thromboxane (TX) A2, predominantly from platelets, acts on TP receptors, causing

platelet aggregation and vasoconstriction.

 PGE2 is prominent in inflammatory responses and is a mediator of fever. Main effects are:

o EP1 receptors: contraction of bronchial and gastrointestinal tract (GIT) smooth muscle

o EP2 receptors: relaxation of bronchial, vascular and GIT smooth muscle

o EP3 receptors: inhibition of gastric acid secretion, increased gastric mucus

secretion, contraction of pregnant uterus and of GIT smooth muscle, inhibition of

lipolysis and of autonomic neurotransmitter release.

 PGF2α acts on FP receptors, found in uterine (and other) smooth muscle, and corpus luteum,

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producing contraction of the uterus and luteolysis (in some species).

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 PGD2 is derived particularly from mast cells and acts on DP receptors, causing

vasodilatation and inhibition of platelet aggregation.

Prostaglandins of the E series are also pyrogenic (i.e. they induce fever). High concentrations are found

in cerebrospinal fluid during infection, and there is evidence that the increase in temperature (attributed to

cytokines) is actually finally mediated by the release of PGE2. NSAIDs exert antipyretic actions by

inhibiting PGE2 synthesis in the hypothalamus.

Clinical uses of prostanoids

 Gynecological and obstetric

o termination of pregnancy: Gemeprost or misoprostol (a metabolically stable prostaglandin

(PG)

(PG E analogue)

o induction of labour: Dinoprostone (PGE2 analogue) or misoprostol

o Postpartum haemorrhage: Carboprost ( 15-α methyl PGF2α analogue)

 Gastrointestinal

o to prevent ulcers associated with non-steroidal anti-inflammatory drug use: misoprostol

 Cardiovascular

o to maintain the patency of the ductus arteriosus until surgical correction of the

defect in babies with certain congenital heart malformations: Alprostadil (PGE1)

o to inhibit platelet aggregation (e.g. during haemodialysis): Epoprostenol or

Cicaprost (PGI2 analogue ), especially if heparin is contraindicated

o Primary pulmonary hypertension: Epoprostenol.

 Ophthalmic

o Open-angle glaucoma: latanoprost (PGF2α analogue) eye drops.

Dinoprostone (PGE2 analogue)

Carboprost(15-αmethylPGF2α

latanoprost (PGF2α analogue)

Misoprostol (PGE1 analogue)

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Misoprostol is approved for use in the prevention of NSAID-induced gastric ulcers. It acts upon gastric

parietal cells, inhibiting the secretion of gastric acid via G-protein coupled receptor-mediated inhibition of

adenylate cyclase, which leads to decreased intracellular cyclic AMP levels and decreased proton pump

activity at the apical surface of the parietal cell.

Because other classes of drugs, especially H2-receptor antagonists and proton pump inhibitors, are more effective for

the treatment of acute peptic ulcers, Misoprostol is only indicated for use by people who are both taking NSAIDs and

are at high risk for NSAID-induced ulcers, including the elderly and people with ulcer complications.

Misoprostol is sometimes co-prescribed with NSAIDs to prevent their common adverse effect of gastric ulceration (e.g.

with Diclofenac in Arthrotec). Misoprostol may stimulate increased secretion of the protective mucus that lines the

gastrointestinal tract and increase mucosal blood flow, thereby increasing mucosal integrity—however, these effects are

not pronounced enough to warrant prescription of misoprostol at doses lower than those needed to achieve gastric acid

suppression

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**BRADYKININ**

BK is a nonapeptide 'clipped' from a plasma α-globulin, kininogen, by kallikrein.

 It is converted by kininase I to an octapeptide, BK1-8 (des-Arg9-BK), and inactivated by kininase II

(angiotensin-converting enzyme) in the lung.

 Pharmacological actions:

o vasodilatation (largely dependent on endothelial cell nitric oxide and prostaglandin I2)

o increased vascular permeability

o stimulation of pain nerve endings

o stimulation of epithelial ion transport and fluid secretion in airways and gastrointestinal tract

o Contraction of intestinal and uterine smooth muscle.

 There are two main subtypes of BK receptors: B2, which is constitutively present, and B1,

which is induced in inflammation.

Leukotrienes

 5-Lipoxygenase oxidises arachidonate to give 5-hydroperoxyeicosatetraenoic acid (5-

HPETE), which is converted to leukotriene (LT) A4. This, in turn, can be converted to either

LTB4 or to a series of glutathione adducts, the cysteinyl-leukotrienes LTC4, LTD4 and LTE4.

 LTB4 mainly involves in inflammatory cells, acting on specific receptors, causes adherence,

chemotaxis and activation of polymorphs and monocytes, and stimulates proliferation and

cytokine production from macrophages and lymphocytes.

 The cysteinyl-leukotrienes cause:

o Contraction of bronchial muscle mainly LTC4, LTD4

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o Vasodilatation in most vessels, but coronary vasoconstriction.

o LTB4 is an important mediator in all types of inflammation; the cysteinyl-leukotrienes

are of particular importance in asthma.

o The CysLT-receptor or leukotriene antagonist zafirlukast and montelukast are

now in use in the treatment of asthma. Cysteinyl-leukotrienes may mediate the

cardiovascular changes of acute anaphylaxis.

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**ASTHMA**

Asthma is defined as recurrent reversible airway obstruction, with attacks of wheeze, shortness of breath

and often nocturnal cough. Severe attacks cause hypoxaemia and are life-threatening. Essential features

include: airways inflammation, which causes bronchial hyper-responsiveness, which in turn results in

recurrent reversible airway obstruction. Pathogenesis involves exposure of genetically disposed individuals

to allergens; activation of Th2 lymphocytes and cytokine generation promote:

o Differentiation and activation of eosinophils

o IgE production and release

o Expression of IgE receptors on mast cells and eosinophils.

o Important mediators include leukotriene B4 and cysteinyl leukotrienes (C4 and D4);

interleukins IL- 4, IL-5, IL-13; and tissue-damaging eosinophil proteins.

DRUGS USED TO TREAT ASTHMA

There are two categories of antiasthma drugs: bronchodilators and anti-inflammatory agents.

Bronchodilators reverse the bronchospasm of the immediate phase; anti-inflammatory agents inhibit or

prevent the inflammatory components of both phases.

Theophylline and leukotriene antagonists, such as montelukast, also exert a corticosteroid-sparing effect

Cromoglicate (see below) has only a weak effect and is now seldom used.

BRONCHODILATORS

The main drugs used as bronchodilators are β2-adrenoceptor agonists; others include xanthines, cysteinyl

leukotriene receptor antagonists and muscarinic receptor antagonists.

β-Adrenoceptor agonists

Two categories of β2-adrenoceptor agonists are used in asthma.

 Short-acting agents: Salbutamol and Terbutaline, duration of action is 3-5 hours.

 Longer-acting agents: e.g. Salmeterol and Formoterol, the duration of action is 8-12 hours.

 Others are Adrenaline, Ephedrine, Isoprenaline

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Xanthine drugs

There are three pharmacologically active, naturally occurring methylxanthines: theophylline , theobromine

and caffeine . Theophylline (1,3-dimethylxanthine), which is also used as theophylline ethylenediamine

(known as aminophylline ), is the main therapeutic drug of this class.

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Actions

Antiasthmatic. Methylxanthines have long been used as bronchodilators.

Central nervous system. Methylxanthines stimulate the CNS, increasing alertness. They can cause tremor

and nervousness, and can interfere with sleep and have a stimulant action on respiration. This may be

useful in patients with COPD and reduced respiration evidenced by a tendency to retain CO2 (see below).

Cardiovascular. Methylxanthines stimulate the heart having positive chronotropic and inotropic

actions, while relaxing vascular smooth muscle. They cause generalised vasodilatation but constrict

cerebral blood vessels.

Kidney. Methylxanthines are weak diuretics, although this effect is not therapeutically useful.

Mechanisms of action

The relaxant effect on smooth muscle has been attributed to inhibition of the phosphodiesterase (PDE)

isoenzymes, with resultant increase in cAMP and/or cGMP . However, the concentrations necessary to

inhibit the isolated enzymes exceed the therapeutic range of plasma concentrations.

Competitive antagonism of adenosine at adenosine A1 and A2 receptors may contribute, but the PDE inhibitor

enprofylline, which is a potent bronchodilator, is not an adenosine antagonist.

Type IV PDE is implicated in inflammatory cells and non-specific methylxanthines may have some antiinflammatory

effect. (Roflumilast, a type IV PDE inhibitor.

Clinical use of theophylline

 As a second-line drug, in addition to steroids, in patients whose asthma

does not respond adequately to β2-adrenoceptor agonists.

 Intravenously (as aminophylline ,

a combination of theophylline

with ethylenediamine to increase its solubility in water) in acute

severe asthma.

Muscarinic receptor antagonists

The main compound used as a bronchodilator is ipratropium, is a quaternary derivative of N-isopropylatropine.

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Cysteinyl leukotriene receptor antagonists

All the cysteinyl leukotrienes (LTC4, LTD4 and LTE4) act on the same high-affinity cysteinyl leukotriene

receptor termed CysLT1. Two receptors have been cloned, CysLT1 and CysLT2, and both are expressed in

respiratory mucosa and infiltrating inflammatory cells, but the functional significance of each is unclear.

The 'lukast' drugs (montelukast and zafirlukast ) antagonise only CysLT1.

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Used for some patients with chronic obstructive pulmonary disease, especially long-acting drugs (e.g.

tiotropium). ANTI-INFLAMMATORY AGENTS

The main drugs used for their anti-inflammatory action in asthma are the

glucocorticoids. Glucocorticoids

Systemic : Prednisolone, Hydrocortisone

Inhalational: Triamcinolone, Beclomethasone

They are not bronchodilators but prevent the progression of chronic asthma and are effective in acute severe asthma.

Actions and mechanism

The basis of the anti-inflammatory action of glucocorticoids . An important action, of relevance for asthma,

is that they decrease formation of cytokines), in particular the Th2 cytokines that recruit and activate

eosinophils and are responsible for promoting the production of IgE and the expression of IgE receptors .

Glucocorticoids also inhibit the generation of the vasodilators PGE2 and PGI2, by inhibiting

phospholipase A2. By inducing annexin 1, they could inhibit production of leukotrienes and plateletactivating

factor, although there is currently no direct evidence that the release of this protein is involved

in the antiasthma effects of glucocorticoids. The main compounds used are beclometasone, budesonide ,

fluticasone, mometasone and ciclesonide.

Cromoglicate and nedocromil ('mast cell stabiliser')

These drugs are now hardly used for the treatment of asthma. Cromoglicate is a 'mast cell stabiliser',

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preventing hista release from mast cells.

Anti-IgE treatment

Omalizumab is a humanised monoclonal anti-IgE antibody. It is effective in patients with allergic as allergic rhinitis.

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COUGH

Cough is a protective reflex that removes foreign material and secretions from the bronchi and

bronchioles. It is a very common adverse effect of angiotensin-converting enzyme inhibitors.

Drugs for cough

Codeine (methylmorphine) is a weak opioid. Dextromethorphan and pholcodine are believed to

have fewer adverse effects.

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NSAIDS

They provide symptomatic relief from pain and swelling in chronic joint disease such as occurs in osteoand

rheumatoid arthritis, and in more acute inflammatory conditions such as sports injuries, fractures,

sprains and other soft tissue injuries. They also provide relief from postoperative, dental and menstrual

pain, and from the pain of headaches and migraine.

COX-1 is a constitutive enzyme expressed in most tissues, including blood platelets. It has a

'housekeeping' role in the body, being involved in tissue homeostasis, and is responsible for the

production of prostaglandins involved in, for example, gastric cytoprotection platelet aggregation renal

blood flow auto regulation and the initiation of parturition.

In contrast, COX-2 is induced in inflammatory cells when they are activated, and the primary

inflammatory cytokines-interleukin (IL)-1 and tumour necrosis factor (TNF)-α are important in this

regard. Thus the COX-2 isoform is responsible for the production of the prostanoid mediators of

inflammation although there are some significant exceptions. For example, there is a considerable pool of

'constitutive' COX-2 present in the central nervous system (CNS) and some other tissues, although its

function is not yet completely clear.

Most 'traditional' NSAIDs are inhibitors of both isoenzymes of COX by inhibiting dioxygenation step.

although they vary in the degree to which they inhibit each isoform. It is believed that the antiinflammatory

action (and probably most analgesic actions) of the NSAIDs is related to their inhibition of

COX-2, while their unwanted effects-particularly those affecting the gastrointestinal tract-are

largely a result of their inhibition of COX-1. Compounds with a selective inhibitory action on COX-2

are now in clinical use, but expectations that these inhibitors would transform the treatment of

inflammatory conditions have received a setback because of an increase in cardiovascular risk

(Rolecoxib)

Normal body temperature is regulated by a centre in the hypothalamus that controls the balance between

heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat',

which leads to the set point of body temperature being raised. NSAIDs 'reset' this thermostat. The

NSAIDs exert their antipyretic action largely through inhibition of prostaglandin production in the

hypothalamus. During an inflammatory reaction, bacterial endotoxins cause the release from

macrophages of a pyrogen-IL-1 which stimulates the generation, in the hypothalamus, of E-type

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prostaglandins that elevate the temperature set point. COX-2 may have a role here, because it is

induced by IL-1 in vascular endothelium in the hypothalamus.

So NASIDS have following actions:

 Anti-inflammatory action: the decrease in prostaglandin E2 and prostacyclin

reduces vasodilatation and, indirectly, oedema. Accumulation of inflammatory cells is

not reduced.

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 An analgesic effect: decreased prostaglandin generation means less sensitisation of

nociceptive nerve endings to inflammatory mediators such as bradykinin and 5-

hydroxytryptamine. Relief of headache is probably a result of decreased prostaglandinmediated

vasodilatation.

 An antipyretic effect: interleukin-1 releases prostaglandins in the central nervous

system, where they elevate the hypothalamic set point for temperature control, thus

causing fever. NSAIDs prevent this.

Classification

A. Nonselective COX inhibitors

1. Salicylates: Aspirin, Diflunisal

2. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone

3. Anthranilic acid derivatives: Mephenamic acid

4. Aryl acetic acid derivatives: Diclofenac

5. Indole derivatives: Indomethacin, Sulindac

6. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flubiprofen

7. Oxicam derivatives: Piroxicam, Tenoxicam

8. Pyrrolo-pyrrole derivatives: Ketorolac

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

C. Selective COX-2 inhibitors: Celecoxib, Rofecoxib, Valdecoxib, Parecoxib (Prodrug of valdecoxib)

D. Analgesic-antipyretic with poor anti-inflammatory: Paracetamol

1. Pyrozolone derivatives: Metamizole (Dipyrone), Propiphenazone

2. Benzoxazocine derivatives: Nefopam

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Some important points:

1. NSAIDS which are prodrugs: Sulindac, Fenoprofen, Nabumetone

2. NSAIDS which reduce chemotaxis of leukocytes and useful in acute gout:

Indomethacin, Naproxen, Piroxicam

3. Drugs for post-operative pain: Ketorolac, Nefopam, Etodolac

4. Gastric intolerance to conventional NASIDS uses Rofecoxib or selective COX-2 inhibitors.

5. Patients with history of asthma or anaphylaxis:

Nimesulide Some adverse effects of NASIDS:

 Aspirin cause local damage to the gastric mucosa directly or some gastric bleeding.

Oral administration of prostaglandin analogues such as misoprostol (PGE1 analogue) can

diminish the gastric damage produced by these agents.

 Severe rashes or idiosyncratic reaction are common with Mefenamic acid and Sulindac.

 Analgesic nephropathy characterised by chronic nephritis and renal papillary necrosis

is caused by chronic NSAID consumption i.e. Phenacetin (Prodrug of Paracetamol)

one of its metabolite but paracetamol is safe.

 Paracetamol over dose can cause liver toxicity. This occurs when the liver enzymes

catalysing the normal conjugation reactions are saturated, causing the drug to be

metabolised instead by mixed function oxidases. The resulting toxic metabolite, Nacetyl-

p-benzoquinone imine, is inactivated by conjugation with glutathione, but when

glutathione is depleted the toxic intermediate accumulates and reacts with nucleophilic

constituents in the cell. This causes necrosis in the liver and also in the kidney tubules.

The liver damage can be prevented by giving agents that increase glutathione

formation in the liver (N-acetylcysteine intravenously, or methionine orally).

 Rolecoxib severe cardiovascular toxicity and hence banned.

 Phenylbutazone severe agranulocytosis and fluid retention.

Aspirin

Aspirin is rapidly hydrolysed by esterases in the plasma and the tissues-particularly the liver-yielding

salicylate. Salicylate is oxidized, some is conjugated to give the glucuronide or sulfate before excretion.

Aspirin cause Salicylism and Reye's syndrome (a rare disorder of children that is characterised by

hepatic encephalopathy following an acute viral illness).

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Salicylate poisoning is a result of disturbances of the acid-base and the electrolyte balance that may be

seen in patients treated with high doses of salicylate-containing drugs and in attempted suicides. These

drugs can uncouple oxidative phosphorylation (mainly in skeletal muscle), leading to increased oxygen

consumption and thus increased production of carbon dioxide. This stimulates respiration, which is also

stimulated by a direct action of the

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drugs on the respiratory centre. The resulting hyperventilation causes a respiratory alkalosis that is

normally compensated by renal mechanisms involving increased bicarbonate excretion. Larger doses can

cause a depression of the respiratory centre, which leads eventually to retention of carbon dioxide and

thus an increase in plasma carbon dioxide. Because this is superimposed on a reduction in plasma

bicarbonate, an uncompensated respiratory acidosis will occur. This may be complicated by a metabolic

acidosis, which results from the accumulation of metabolites of pyruvic, lactic and acetoacetic acids (an

indirect consequence of interference with carbohydrate metabolism)

 Aspirin causes a potentially hazardous increase in the effect of warfarin, partly by

displacing it from plasma proteins so increase the risk of bleeding.

 Aspirin being a weak acid also interferes with the effect of uricosuric agents such as

probenecid and sulfinpyrazone , and because low doses of aspirin may, on their own,

reduce urate excretion, so aspirin

should not be used in gout.

 Aspirin potentiates the hypoglycemic effect of oral hypoglycemic drugs like Tolbutamide,

Glibenclamide

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Meloxicam: The drug is popular in Europe and many other countries for most rheumatic diseases and has

recently been approved for treatment of osteoarthritis in the USA. Meloxicam is known to inhibit

synthesis of thromboxane A2; it appears that even at supratherapeutic doses its blockade of thromboxane

A2 does not reach levels that result in decreased in vivo platelet function.

Valdecoxib has no effect on platelet aggregation or bleeding time. Valdecoxib was withdrawn from the

market in the USA in early 2005 in response to FDA concerns about cardiovascular risks and Stevens-

Johnson syndrome, but the drug is still available in other countries.

Diflunisal is derived from salicylic acid, it is not metabolized to salicylic acid or salicylate. It undergoes

an enterohepatic cycle with reabsorption of its glucuronide metabolite followed by cleavage of the

glucuronide to again release the active moiety.

Etodolac provides good postoperative pain relief after coronary artery bypass operations, although

transient impairment of renal function has been reported.

Ketorolac drug is an effective analgesic and has been used successfully to replace morphine in some

situations involving mild to moderate postsurgical pain. It is most often given intramuscularly or

intravenously.

Nefopam is a nonopioid analgesic which does not inhibit PG synthesis. It also has anticholinergic activity. It

provides good postoperative pain relief

Indomethacin is an indole derivative. It is a potent nonselective COX inhibitor and may also inhibit

phospholipase A and C, reduce neutrophil migration, and decrease T cell and B cell proliferation.

Indomethacin is more effective in relieving inflammation than is aspirin or any of the other

NSAIDs. Indomethacin is indicated for use in rheumatic conditions and is particularly popular for gout

and ankylosing spondylitis. In addition, it has been used to treat patent ductus arteriosus. Indomethacin

can cause CNS effects are dizziness, vertigo, light-headedness, and mental confusion and hence avoided

during the driving of vehicles.

Piroxicam an oxicam is a nonselective COX inhibitor that at high concentrations also inhibits

polymorphonuclear leukocyte migration or chemotaxis of leukocytes, decreases oxygen radical

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production, and inhibits lymphocyte function. Its long half-life permits once-daily dosing.

Naproxen is potent particularly inhibiting leukocyte migration and hence suitable for acute

gout. Ketoprofen is a propionic acid derivative that inhibits both COX (nonselectively) and

lipoxygenase.

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Nabumetone is prodrug and the only nonacid NSAID in current use; it is converted to the active acetic

acid derivative in the body. It is given as a ketone prodrug that resembles naproxen in structure.

Sulindac is a sulfoxide prodrug. It is reversibly metabolized to the active sulfide metabolite, which is

excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of

action. In addition to its rheumatic disease indications, sulindac suppresses familial intestinal polyposis; it

may inhibit the development of colon, breast, and prostate cancer in humans.

Phenylbutazone has powerful anti-inflammatory effects but weak analgesic and antipyretic activities.

Phenylbutazone is prescribed chiefly in short term therapy of acute gout and in acute rheumatoid arthritis

when other NSAID agents have failed. Phenylbutazone is extensively bound to plasma proteins. This

property causes displacement of warfarin, oral hypoglycemics and sulfonamides from binding sites on

plasma proteins, causing transient elevations in the free fraction of these drugs. The most serious adverse

effects are agranulocytosis and aplastic anemia. Other side effects include fluid and electrolyte (sodium

and chloride) retention, with resulting edema and decreased urine volume. Phenylbutazone reduces the

uptake of iodine by the thyroid gland, sometimes resulting in goiter and myxedema.

Diclofenac is approved for long-term use in the treatment of rheumatoid arthritis, osteoarthritis and

ankylosing spondylitis. It is more potent than indomethacin or naproxen. Diclofenac accumulates in

synovial fluid.

Acetaminophen or Paracetamol and Phenacetin act by inhibiting prostaglandin synthesis in the

CNS. This explains their antipyretic and analgesic properties. They have less effect on cyclooxygenase in

peripheral tissues, which accounts for their weak anti-inflammatory activity. Acetaminophen and

phenacetin do not affect platelet function or increase blood clotting time, and they lack many of the sideeffects

of aspirin. Phenacetin can no longer be prescribed in the United States because of its

potential for renal toxicity. Acetaminophen is the analgesic-antipyretic of choice for children with viral

infections or chicken pox (aspirin increases the risk of Reye's syndrome). Acetaminophen does not

antagonize the uricosuric agent probenecid and therefore may be used in patients with gout taking that

drug. Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin in those

patients with gastric complaints and in those for whom prolongation of bleeding time would be a

disadvantage or who do not require the anti- inflammatory action of aspirin.

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Under normal circumstances, acetaminophen is conjugated in the liver to form inactive glucuronidated or

sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl-benzoquinoneimine--

a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups. At normal doses

of acetaminophen, the N- acetyl-benzoquinoneimine reacts with the sulfhydryl group of glutathione,

forming a nontoxic substance. Acetaminophen and its metabolites are excreted in the urine. With large

doses of acetaminophen, the available glutathione in the liver becomes depleted and N-acetylbenzoquinoneimine

reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds.

Hepatic necrosis, a very serious and potentially life-threatening

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condition, can result. Administration of N-acetylcysteine, which contains sulfhydryl groups to which the toxic

metabolite can bind, can be life-saving if administered within 10 hours of the overdose.

Ibuprofen is safest NASIDS among the conventional NASIDS. Flurbiprofen is mostly used as ocular

anti- inflammatory.

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ANTI-GOUT DRUGS

Gout is a metabolic disease in which plasma uriate concentration is raised because of overproduction

(sometimes linked to indulgence in alcoholic beverages, especially beer, or purine-rich foods such as

offal, or increased cell turnover as in haematological malignancies, particularly when treated with

cytotoxic drugs) or impaired excretion of uric acid. It is characterised by very painful intermittent attacks

of acute arthritis produced by the deposition of crystals of sodium urate (a product of purine

metabolism) in the synovial tissue of joints and elsewhere.

When an inflammatory response is evoked, involving activation of the kinin, complement and plasmin

systems, generation of lipoxygenase products such as leukotriene B4 and local accumulation of

neutrophil granulocytes. These engulf the crystals by phagocytosis, releasing tissue-damaging toxic

oxygen metabolites and subsequently causing lysis of the cells with release of proteolytic enzymes.

Urate crystals also induce the production of IL-1 and possibly other cytokines too.

Drugs used to treat gout may act in the following ways:

 By inhibiting uric acid synthesis: Allopurinol (Main prophylactic drug)

 By increasing uric acid excretion (uricosuric agents: Probenecid , Sulfinpyrazone both are also used

as prophylactic drug)

 By inhibiting leucocyte migration into the joint (Colchicine for acute attack)

 By a general anti-inflammatory and analgesic effect (NSAIDs).

Allopurinol is an analogue of hypoxanthine and reduces the synthesis of uric acid by competitive

inhibition of xanthine oxidase. Some inhibition of de novo purine synthesis also occurs.

Allopurinol is converted

to alloxanthine by xanthine oxidase, and this metabolite, which remains in the tissue for a considerable

time, is an effective non-competitive inhibitor of the enzyme. The pharmacological action of allopurinol

is largely due to alloxanthine. Allopurinol reduces the concentration of the relatively insoluble urates

and uric acid in tissues, plasma and urine, while increasing the concentration of their more soluble

precursors, the xanthines and hypoxanthines. The deposition of urate crystals in tissues (tophi) is reversed,

and the formation of renal stones is inhibited. Allopurinol is the drug of choice in the long-term

treatment of gout, but it is ineffective in the treatment of an acute attack and may even exacerbate the

inflammation.

Allopurinol can cause potentially fatal skin diseases (Stevens-Johnson

syndrome and toxic epidermal necrolysis-a horrible disorder where skin peels

away in sheets as if scalded) are rare but devastating.

 Allopurinol increases the effect of mercaptopurine , an

antimetabolite used in cancer chemotherapy and also that of

azathioprine (an immunosuppressant used to prevent transplant

rejection which is metabolised to mercaptopurine) . Allopurinol

also enhances the effect of another anticancer drug,

cyclophosphamide

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Colchicine:

Colchicine is drug choice for acute attack. Colchicine an alkaloid extracted from

the autumn crocus. It has a specific effect in gouty arthritis and can be used both to

prevent and to relieve acute attacks.

It prevents migration of neutrophils into the joint, apparently by binding to

tubulin, resulting in the depolymerisation of the microtubules and reduced cell

motility.

Colchicine-treated neutrophils develop a 'drunken walk'. Colchicine may also

prevent the production of a putative inflammatory glycoprotein by

neutrophils that have phagocytosed urate crystals, and other mechanisms may also

be important in bringing about its effects.

References:

1. Conceptual Review of Pharmacology for NBE, Ranjan Kumar Patel, Fourth Edition,CBS

Publication

2. KD Tripathi,Essentials of Medical pharmacology,8th Edition.

3. Lippincott Illustrated Reviews Pharmacology, Karen Whalen,6th Edition.

4.Pharmacology for Medical graduates,Tara V Shanbhag,3rd Edition.

5.Medical Pharmacology,Padmaja Udayakumar,5th Edition.

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