ANALGESICS

Algesia (pain): - Is defined unpleasant sensation, usually evoked by external or internal noxious stimuli.

Nonopioid Analgesics and Nonsteroidal

Anti inflammatory Drugs.

These are weaker analgesicsm, also called nonnarcotics or aspirin like or antipyretic analgesics.

These agents do not depress CNS, do not produce physical dependence and have no abuse liability.

M.A: - They act primarily on peripheral pain mechanisma, also in CNS to raise pain threshold

Salicylic acid was obtained by hydntysis of the bitter glysoside obtained from a plant called **Salixalba,** sodium salicylate ws used for fever and pain as far back as 1875 and this lead to the introduction of acety/salhcilic acid (aspirin) in 1899. phenacetin and antipyrine were also produced at that time and the major advancement was the development of phenylbtazone in 1949 and later the introduction of indoinemacin in 1963, and also the addition of the newer non-steroidal anti-inflammatory drugs (NSAIDs).

CLASSIFICATION┐

These drugs are chemically diverse, but most are organic acids. The relative analgesic, antipyretic and anti inflammatory activity of the different members differs considerably.

A. **ANALGESIC AND ANTI-INFLAMMATORY**

1. Salicylates – Aspirim, Salicylamide
2. Purazolone Derivatives – Phenylbutazone, Oxyphenbutozone
3. Indole Derivatives – Indomethacin, Sulindac.
4. Propionic Acid-Derivative – Ibuprofen, Naproxen, Ketoprofen.
5. Anatronilic Acid Derivative – Mephenamic Acid
6. Aryl-Acetic Acid Derivative – Diclofenac
7. Oxicam Derivative – Piroxicam, Tenoxicam
8. Pyrrolo- Pyrrole Derivative – Ketorolac
9. Sulfonanilide Derivative – Nimesulide
10. Alkanones – Nabumetone

B. ANALGESIC BUT POOR ANTIINFLAMMATORY

1. Paraaminophenol Derivative – Paracetamol (Acetominophen)

2. Pyrazoline Derivative – Metamizol (Dipyrone)

3. Benzoxazocine Derivative – Nefopam

NASAIDs and Prostaglandin (PG) Synthesis Inhibition: - In 1971, it as observed by Vane and Co-worker that aspirin and some NSAIDs blocked PG generation. This is now considered to be the major mechanism of action of NSAIDs.

Prostaglandins, prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) are produced from arachidoic acid by the enzyme cyclooxygenase which exist in a constitutive (COX – 1) and an inducible (COX-2) Isoforms; the former serves physiological "house keeping" functions, while the latter, normally present in minute quantities, is induced by cytokines and other signal molecules at the sites of inflammation leading to the generation of PGs locally which mediate many of the inflammatory changes. Most NSAIDs inhibit COX-1 and COX-2 nonselectively, but now some selective COX-2 inhibitors have been produced.

Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme. Other NSAIDs are competitive and reversible inhibitors of COX, return of activity depends on their dissociation from the enzyme which in turn is governed by the pharmacokinetic characteristics of the compound.

Beneficial actions due PG Synthesis Inhibition	Shared toxicities to PG Synthesis Inhibition
1. Analgesia: preventing pain Nerve ending sensitization	1. Gastric mucosal damage
2. Antipyresis	2. Bleeding: Inhibition of Platelet function
3. Anti-inflammatory	3. Limitation of naval blood flow: Na+ and water retention
4. Antithrombotic	4. Delory/prolongation of labor
5. Closure of doctors arteriosus	5. Asthma and anaphylactoid rxns in susceptible individuals

ANALGESIA: PGs induce hyperalagesia by affecting the transducing property of free nerve ending. Stimuli that normally do not elicit pain are able to do so.

VPC 401 NARACOTIC AND NON-NARCOTIC ANALGESIC AND ANTAPONISTS

Algesia: - Is an illdefined, unpleasant sensation usually evoked by an external or interal noxious stimuli, analgesia is abolishion of pains.

Analgesis: - are agents used to abolished algesia.

OPIOD ANALGESIC

OPIOD RECEPTOR AGONIST AND ANTAGONISTS

Opiod receptors can be subdivided into μ=miu, K=kappa, d= delta and S=sigma

The μ receptor types are associated with analgesia, indifference, cough suppression, respiratory and cardiovascular depression. It is also associated with hypothermia and physical dependence.

Kappa receptor types are associated with analgesis, sedation and atoxia.

Deltareecption types are associated with probably anesthesia and indifference.

Signor Receptor types are associated with euphoria hallucinations, excitement and probably analgesia. There are species vanations in opoid receptors distribution.

NARCOTIC ANALGESICS

They selectively depress pain by a depressant action on the CNS – This include morphine-like dugs and other related ones.

OPIOD ALKALOIDS

These are obtained from the milky exudates from unripe seed capsule of *Papaver Sominferum* plant. They are of 2 types.

1. Benzy/Isoquilonine – non analgesic and spasmilytic
2. Penanthrene – are analgesic and nono spasmilytic

Benzy/Isoquilonine group include Papaaverine, Nacotine and Narceine.

Phenanthrene group include Morphine, Codeine and Thebaine.

Papaverine is mainly spasmolytic. Nacotine is antitussive (-inhibit cough). Morphine is the most potent analgesic component.

In a decreasing order of analgesic potency but increasing order of spinal stimulation i.e. morphine >Codcine >Thebaine. Synthetic derivatives are now produced. However, the purified extracts of the opium alkaloids contains 50% morphine base.

USES OF MORPHINE AND RELATED DEVIATIVES

1. Cough suppression and anti diarrheic activity
2. Used for pre and post – operative pain, most especially in neuroleptamalgesic and neuroleptanaesthetic techniques. Administration by a subentaneous routes produces pharmacological actions in 5 – 10 minutes with a maximum of effect of 45 – 60 minutes. However, admin by intravenous route produces a peak action in 20 minutes whereas it is 1½ hours after 1 minute route, the analgesic action may last for 4 hours.

PHARMACOLOGICAL ACTION OF MORPHINE – LIKE DRUGS

They produce euphoria in animal, having pain, however in normal patients; there are discomforts, anxiety and apprehension. Morphine also has a sedative calming effect in patients with pain. The method of relieving pain by Morphine – like drugs include:-

1. They raise pain threshold
2. Induce sleep
3. Induce hypercapnia – increase CD_2 in the blood.
4. They cause a reduction in body temperature as a result of reduced muscular activity.
5. They also reduce body temperature by increasing heat loss via vasodilatation and a decrease in body metabolic rate.
6. They have an effect of suppressing dull prolonged pain, they have less action on sharp acute pain
7. They depress the higher functions of brain, they stimulate and depress the medullary activity and stimulate spinal functions.

SPECIES DIFFERENCES AND RESPONSE

In dogs, birds and rabbits, morphine like drugs are depressants, producing sleep and analgesia and in larger doses results in Coma.

CATS: -Produce dehrium and maniacal excitement.

HORSES, CATTLE AND PIGS: - The responses may be unreliable i.e. it could produce narcosis or excitement. There is also individual variation in response to morphine like drugs which is as a result of individual susceptibility and dosage of drugs. Low doses may not produce excitement but high doses may produce it.

CHARACTERISITICS OF MORPHINE – LIKE DRUGS

Morphine-like drugs are also associated with the followings:-

1. The problem of addiction mot especially heroine.

2. They also have parasympathetic activities through the stimulation of the vagal muscles. This results in bradycardia.
3. They also cause depression of vasomotor centre and this tends to decrease sympathetic tone to blood vessels and also cause peripheral vasodilatation.
4. They also produce depression of respiration which results in slow breathing
5. They may also stimulate the chemoreceptor triggerzone within the vomiting centre and this result in emesis.
6. They may also have effect on supraoptic nucleus and the secretion of anti-diuretic hormones which may produce an anti-diuretic effect.
7. The stimulation of vagal nucleus produce increased tone and motility of gastro intestinal tract which may result in defecation.
8. Increase salivary and bronchial secretions

HEROINE

Is a diacety/morphine derivative/diamorphine and it is stimus as potent as morphine in terms of their analgesic action. Heroin is a powerful anti tussine agent.

PETHIDINE: -

Has $^{7}/_{10}$ analgesic potency of morphine and a shorter duration of action. Suitable to be used in pregnant animals as it is less likely to produce narcosis, Vaso depression, and emesis, depression of cough or respiratory centres. Also has atropine –like activity and local anesthetic effect. Used for treatment of smooth muscle pain e.g. spasmodic equine colic.

PROMORPHINE

Its main action is on the chemoreceptor trigger zone which results in emesis. It has less analgesic/narcotic activity.

DEXTROMETHOMORPHINE

Has mainly antitussive properties.

ETORPHINE

Has high lipid solubility and it crosses blood-brain barrier easily. It has high affinity for opiod receptors and therefore has a 1000 to 80,000 times the analgesic potency of morphine. Has a long duration of action. It is therefore used to Immobilize game animals by it. Inclusion in darts (arrow). It is also used in dogs and horses in nemolept analgesic technique.

FENTANY

Has a short duration of action, about 50 – 100 times the potency of morphine. It is used in combination in nemokept analgesic techniques.

BUPRENORPHINE

Has a partial opiod receptor against activity. It is about 30 times more potent than morphine. It has slow onset of action of about 15 minutes after $^{1}/_{v}$ administration and duration of action of 8 hours.

BUTOORPHINE

A partial opiod receptor against and also has a delayed onset of action of about 15 minute with a duration of 4 hours. It is used in horses with higher solution conclusion for $^{1}/_{v}$ relief of pain of the abdominal type resulting from torsion, intussusceptions, impaction or parturition. Also used against spasmodic and tympanic.

COUGH

In dogs, lower solution conclusion of the drug/tablet can be used for anti -tussive effect or on the non-productive cough of tracheitis, bronchitis, tonsillitis and tracheobroncheitis.

NALORPHINE

A competitive antagonist of morphine – like drugs and their action tend to reverse the respiratory depression associated with morphine – like drugs. Other antagonist includes Naloxone, Natrexone.