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## ANALGESICS

SUNALI MEHTA

Narcotic analgesics have originated from crude extract of opium poppy. Opium contains many different compounds which have effect on the human body. Morphine is the main compound that has analgesic property. Codine is also an analgesic.

There are two compounds of opium noscapine not sold in ausie and nz and the other is papaverine which is used as an antispasmodic.

Morphine and its analogue are called opiates and the ones made synthetically are called opiods. Opiods have no structural resemblance to morphine but have the same effect on the CNS. The synthetic form of opium is pithidine.

These are used to treat moderate to severe pain, but for certain pains like bone pains non – narcotic drugs are preferred. They are also not useful for neuralgic pain.

Pain: is a symptom of many conditions. Narcotics are still not used on a large scale since it is feared that patients may get addicted to the drug. There are two types of pain. Productive pain is the pain caused by tissue damage and the person can react to it e.g. touching a hot plate. The second type of pain is non – productive pain and this is also caused by a tissue damage but the person has no control over it e.g. stomach ulcer. Pain is a protective response to tell the person that something is wrong with the body.

Pain results from the stimulation of the small afferent nerve fibers termed as nociceptive neurons. These nerves are activated only by a strong stimuli. The cell bodies of these fibers lie in the dorsal root ganglia just outside the spinal cord.

Pain may persist even after the removal of the stimulus and this is due to the fact that the transmission of the pain message is induced by chemicals released due to trauma. There are many such chemicals the most active being kinins such as bradykinin and kallidin. These are potentiated by prostaglandin, hence pg inhibitors are used in the control of peripheral pain. As such there is no inhibitor available to inhibit the action of kinins and hence pg synthesis is inhibited or by drugs that act on the central transmission of the pain message.

The stimulation of the afferent fibers or the C fiber is via the release of the substance P and other pain producing neuropeptides.

#### Narcotic Analgesics:

Have an action only on the CNS whereas non – narcotic analgesics have an action on the pain producing lesions, stopping the pain at the source

#### Mechanism of action:

Centrally acting analgesics all stimulate the opioid receptors within the CNS, i.e. they are opioid agonists. The presence of these receptors is due to the fact that we produce certain compounds that help to lessen our response to the painful stimuli, these compounds are called endogenous opioids and these suppress the centrally controlled pain. These are inhibitory neurotransmitters which suppress the pain message to the CNS from the periphery. The general names are endorphins, enkephalins and dynorphins and are polypeptides which are distributed in the CNS and are rarely found outside it.

The euphoric effect of the opioids are due to the presence of receptors in the limbic region of the brain ( part of the brain involved in emotions)

**Adverse effect:**

Many adverse effects and the dilemma of addiction is also present. Stimulates the chemoreceptor trigger zone and can lead to severe nausea. The morphine analogue apomorphine when injected iv can lead to severe vomiting and is useful in the case of poisoning. The gi tract also has some opioid receptors and stimulation of these receptors can cause segmentation type contraction and simultaneously decrease in the peristaltic movement leading to inc water consumption and swelling of the bowels leading to constipation. They cause the contraction of the biliary smooth muscles and hence can lead to spasm. They cause a depression of cough and respiratory centers of the CNS. They reduce the responsiveness of the brain stem centers to the levels of CO<sub>2</sub> and hence respiratory depression is the main cause of death. Tolerance can also be developed with prolonged use. They also cause Miosis ( pupillary constriction). Euphoria, sedation, nausea, analgesia, Miosis, cough suppression, dry mouth, decrease in respiration, itch and constipation.

**Opiates :** Morphine and its derivatives are called opioids.

**Morphine:** has a short half life of about 4 hours and hence frequent dosing is required. An impure opium preparation consists of morphine, codeine, noscapine and papaverine called papaveretum and this helps in the relief of pain involving the smooth muscle spasm.

**Codeine:** much less potent though chemically related to morphine. It is required in very high dose and some of the codeine is converted in the liver to morphine and it can be this that gives it the analgesic property. It is used as an antidiarrhoeal and antitussive but rarely by itself as an analgesic. It potentiates the analgesic activity of both aspirin and paracetamol and hence is given with these.

**Dihydrocodeine:** it is a moderately potent analgesic.

Heroin: is diacetylmorphine or diamorphine. It easily crosses the blood brain barrier and very rapidly produces an intense euphoria. Since it is more potent than morphine less of the drug has to be given. Half life is slightly shorter than that of morphine. If taken orally it is converted completely into morphine by the hepatic first pass hence it is not given by this route. Heroin is metabolized to monoacetylmorphine which can be detected in the urine and is generally indicative of heroin rather than morphine abuse.

Opioids:

Pethidine: like morphine has a high hepatic first pass and hence the oral dose is more than the parenteral dose. Not as strong as morphine but can be used for moderate to severe pain. Causes less constipation and respiratory depression than morphine. Useful analgesic in labour and in renal and biliary colic but care should be taken in case of labour since the fetus respiratory rate may be affected. Prolonged use of this is not recommended since the concentration of one of its metabolites called norpethidine may rise and this has a half life greater than pethidine and hence its concentration can rise to toxic levels. Norpethidine acts as a CNS stimulant and can lead to convulsions in a person.

Methdone: same effect as a narcotic but has a fewer withdrawal symptom. Has a long half life about 24 hours. It binds strongly to the opiate receptors and hence if heroin is injected there are not empty receptors to bind to hence cannot produce the high.

Tramadol : is unlike other narcotics it does not produce euphoria, tolerance or addiction and has been used since a long time. It has a short half life and hence the drug needs to be given many times in a day.

Naloxone and Naltrexone are narcotic antagonists.

## **Non – Steroidal anti – inflammatory (nsaid), antipyretics and analgesics**

Inflammation of the tissue generally results in pain and is treated with anti inflammatory and or analgesics. If the pain is due to an inflammation then it is better treated with anti – inflammatory which also have analgesic properties. If treated with only analgesic then it may not be of much use.

Drugs that can be used as both anti inflammatory and analgesics are pg inhibitors. These drugs inhibit the enzyme involved in the action of pg biosynthesis. Pg occurs throughout the body and only some drugs can gain excess into the site of action. Different types of pg are found in the body. Some drugs are better at inhibiting the synthesis of one type of pg over the other. The synthesis of pg may involve isoenzymes. Nsaids are normally pg inhibitors and their so called since they have no resemblance to corticosteroids which also have anti – infla property.

Inflammation involves redness swelling heat and pain but the pathological conditions can be varied. These can be minor sprains, extreme agony from acute attack of gout or continued agony from the arthritic pain. The one thing that is common in this case is the presence of pg in excess at the site of inflammation. Infection, injury and an abnormal immune response can all lead to the release of pg from the immunocompetent cells. Pg augment the action of histamine and increase the vasodilation and hence increasing vascular permeability to fluids. Some pg also act directly on pain receptors causing a direct message to be sent to the brain.

There are at least two enzymes involved in the synthesis of pg and these enzymes are cyclo oxygensae COX. It is COX 1 which is a constitutive enzyme and is involved in the synthesis of pg for homeostatic response. It is the inhibition of this enzyme that results in the adverse effect. COX 2 is the enzyme which is inducible and is responsible for the inflammatory response and is also present in some type of carcinoma.

Pg are found in the hypothalamus and are involved in inc the body temp and hence the inhibition of pg can also lead to lowering of the body temp i.e. they act as antipyretics.

These act only to relieve the symptoms caused by inflammation and in no ways do they cure the condition.

Nsaids also have other effects on the immune system apart from the one that it has on pg. it affects the membrane. It acts on the cellular membrane of the immunocompetent cells called neutrophils. They dec the cells adhesiveness to the vascular endothelium , thus reducing the accumulation of the cells at the proinflammatory site and thereby reducing the inflammatory response.

Anti infla drugs are mainly used in the treatment of pain from rheumatoid arthritis and osteoarthritis. Ra is the condition in which the body own immune system starts to destroy the synovial membrane and thereby leads to the complete degeneration of the joint and its associated structure. It is an inflammation of the connective tissue mainly of the joint capsule and is an autoimmune disorder Osteoarthritis results from mechanical damage to the joint and results in degeneration of the articular cartilage.

The adverse effect is their effect on the kidney and stomach. They are irritants to the gastric mucosa. They raise the secretion of the HCl and pepsin in the stomach and hence can lead to ulcer formation. Pg helps in reducing gastric secretion but inhibiting pg can lead to and inc in the gastric secretion.

Pg are involved in the control of renal blood flow and therefore the GFR. Inhibition can lead to a dec in the GFR and thereby there can be an inc in the fluid and sodium retention leading to hypertension and in some cases to renal failure.

Inhibition of pg can also lead to prolonged bleeding time and delayed parturition. Pg play a role in causing dysmenorrhea and hence the use of nsaids in labour help to slow down or stop premature labor.

## Salicylates:

Aspirin: chemical name acetylsalicylic acid. Has good anti – infla, antipyretic, antiplatelet and analgesic properties. Antiplatelet property is it acts as a non – competitive inhibitor for the platelet prostaglandins. It can be considered to be a prodrug as it undergoes a high hepatic first pass metabolism to produce salicylic acid. it is weakly acidic. When taken by mouth it enters the stomach in a lipophilic state and is absorbed thru the walls of the stomach for systemic effects. If taken on a full stomach then it is dispersed among the food and acts fairly fast but if taken on an empty stomach it causes gastric erosions. In the enteric coated form aspirin has a lipophobic property but since the surface area of the ileum is large there is no problem with the absorption. It is a pg inhibitor.

Adverse effects: can lead to Reyes syndrome when young children are treated with aspirin in the cases of chicken pox and influenza. Can lead to ulcers and bleeding. When combined with caffeine its analgesic effect is increased. They can promote allergic reactions. They can dec the renal excretion of uric acid and hence should be avoided when the person is suffering from gout.

Can lead to papillary necrosis over the years and irreversible renal failure. This is termed as analgesic nephropathy.

Chronic aspirin poisoning can occur in patients consuming several grams of aspirin per day to treat RA. Ear problems such as tinnitus and deafness are indications of an over dose. Other symptoms include epigastric discomfort, sweating, hyperventilation and mental confusion. If still continued can lead to mania, convulsions and eventually coma.

Propionic Acid derivatives are also a type of Nsaid. Generic names normally have the suffix profen. E.g. ibuprofen, ketoprofen and tiaprofenic acid.

Adverse effect: GI upset can cause ulceration, tinnitus, dizziness oedema, headache rash and nervousness. These drugs are better tolerated. They are all metabolized in the liver.

Indoleacetic acid: includes indomethacin and sulindac. Sulindac is an example of a prodrug which by itself is inactive but is converted to its active form after metabolism. Another one ketorolac trometamol unusual anti – inflammatory and when injected IM can be as strong as morphine or pethidine and has an added advantage of longer duration and does not induce physical dependence. Most effective pg inhibitors. Higher incidence of adverse effects.

Fenamates : two common ones mefenamic acid and diclofenac. Diclofenac is used for pain associated with the connective tissue and muscular injuries such as RA and osteoarthritis. Mefenamic acid is used to treat painful conditions emanating from the uterus such as dysmenorrhoea. Gastric problems are rare. Mefenamic acid has a tendency to produce diarrhoea as against constipation produced by other drugs. Long term use of mefenamic acid is not considered since it causes a fall in the hemoglobin levels in blood and there is a high incidence of diarrhea. Diclofenac causes gi upset.

It is advisable for treatment of people suffering from a GI condition and ulceration since it does not have this as its major adverse effect.

COX 2 Inhibitors is another class of nsaid which are becoming very popular. The nsaid inhibit the enzyme cox. The isoform found in the stomach, intestine and platelet are cox1 and the one found in joints and tissue is cox2. function of both the enzyme is similar but their active centers are different. Hence cox 2 inhibitors inhibit cox 2 enzyme and have no effect on cox 1 hence the chances of peptic ulcer is dec. e.g. rofecoxib, celecoxib, etoricoxib, parecoxib and meloxicam. These help to relieve musculoskeletal pain

Adverse effect: effects some of the cytochrome P450 enzymes. Useful in the treatment of patients with coexisting cardiovascular problems. Celecoxib is mainly recommended since they do not aggravate platelet aggregation and may also inc the prothrombotic activity.

Paracetamol : analgesic and antipyretic has no anti – inflammatory and antiplatelet activity. Hence useful in the treatment of febrile disease such as influenza and chicken pox. As an analgesic it is better taken on an empty stomach for better absorption rates. Mechanism of action is little understood and may act as a pg inhibitor centrally rather than peripherally . has a narrow therapeutic index and hence care should be taken. Alcohol drinkers are more prone to para poisoning since ethanol induce enzyme that inc the rate of conversion of para to its toxic metabolite. Can lead to liver damage.

Notes: