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TUTOR

ICON

"ANALGESICS / ANTI INFLAMMATORY AGENTS"

1. INTRODUCTION:

You have probably been taking medicines and seeing other people take medicines most of your life. Perhaps you have given medicines to your children, parents, grand parents or others. Have you ever wondered why it's usually okay to give children Tylenol but not aspirin? Why do a lot of middle aged and older people taken an aspirin a day? Why do people with high BP, heart failure or diabetes take ACE inhibitors and what are ACE inhibitors?

You are embarking on an existing journey of discovery as you begin or continue your study of pharmacology. Much of what you learn will apply to your personal and family life as well as your professional life as a nurse. The purpose of this seminar will help you to learn about medications and why, how, when and where they are used in daily life.

2. ANALGESICS:

Analgesics are medications used to relieve pain without reducing the consciousness of the patient. They work by reducing the amount of pain felt and this is generally achieved by interfering with the way the pain message is transmitted by the nerves. Analgesics will not treat the cause of the pain but they will provide temporary relief from pain symptoms.

2.1. Classification:

There are three main categories of analgesics.

The first is the ***opioid analgesics*** which are prescription only medicines that are very potent, being chemically related to morphine.

The second is the ***non-opioid analgesics***. Non-opioid analgesics work by affecting the prostaglandin system, which is the system within the body responsible for producing pain. This category includes non-steroidal anti-inflammatory drugs, or NSAIDs, such as Aspirin, ketoprofen and ibuprofen.

The last category is ***adjuvant analgesics***, which are medicines typically used for purposes other than pain relief. This includes some antidepressants that may also help to relieve pain in specific circumstances.

2.2. Action:

Non-opioid analgesics act peripherally and not centrally like opioids that depress the central nervous system (CNS) and inhibit the brain's ability to feel pain. Non-opioid analgesics target the chemical substances released by the brain in response to injury that facilitate the transmission of the pain stimuli to the brain. The most prevalent of these chemical mediators is prostaglandin. Non-opioid NSAIDs are effective because they serve to block the release of prostaglandin at the peripheral nerve sites.

Prostaglandins serve a variety of regulatory functions within the body. One of these functions is to assist the transmission of pain signals to the brain so that you are readily alerted that damage or dysfunction has occurred within the body. Other prostaglandin actions include the regulating body temperature, inflammation, the elasticity of blood vessels and the contraction of smooth muscle tissue.

When damage occurs to the body, prostaglandins are formed from the unsaturated fatty acids released by damaged cells. Prostaglandins contain an enzyme called cyclo-oxygenase (COX). Prostaglandin synthetase amplifies the amount of pain experienced by serving as a pain activator. They increase the sensitivity of the nerves to pain impulses. By reducing the synthesis of prostaglandin the amount of pain stimuli sent to the brain is correspondingly reduced.

Analgesics like paracetamol and codeine mostly affect the central nervous system (CNS) while NSAIDs like ibuprofen and aspirin are more effective near the actually site of the pain, exerting their analgesic effect in the periphery. Codeine works on the CNS as a

weak opiate agonist that inhibits pain signals so that less pain is felt. Codeine achieves this by binding with receptors at various sites in the CNS to alter the chemical process that stimulates pain signals. Paracetamol is a weak prostaglandin inhibitor that blocks prostaglandin biosynthesis in the CNS.

NSAIDs like Aspirin, ibuprofen, diclofenac, and ketoprofen block the pain impulse at the source of the pain. They work by hindering the body's ability to biosynthesise prostaglandin by adhering to the cyclo-oxygenase (COX) that controls the amount of prostaglandin produced by the immune system. The special nerve endings that transmit the pain message are sensitised to prostaglandin so, by restricting its presence, the pain message is reduced. This weakens the physiological chemical process that results in the sensation of pain.

2.3.Narcotic Analgesics and Related Drugs:

Opioid **analgesics** are the narcotic **analgesics** obtained from the opium plant. More than 20 different alkaloids are obtained from the unripe seed of the opium poppy plant. The **analgesic** properties of opium have been known for hundreds of years. The **narcotics** obtained from raw opium (also called the opiates, opioids, or opiate narcotics) include morphine, codeine, hydrochlorides of opium alkaloids, and camphorated tincture of opium. Morphine, when extracted from raw opium and treated chemically, yields the semisynthetic narcotics hydromorphone, oxymorphone, oxycodone, and heroin.Heroin is an illegal **narcotic** in the United States and is not used in medicine. Synthetic narcotics are those man-made analgesics with properties and actions simi-lar to the natural opioids. Examples of synthetic **narcotic analgesics** are methadone, levorphanol, remifen-tanil, and meperidine.

Actions:

Narcotic analgesics are classified as agonists, partial agonists, and mixed agonists-antagonists. The agonist binds to a receptor and causes a response. A partial agonist binds to a receptor, but the response is limited (ie, is not as great as with the agonist). Antagonists bind to a recep-tor and cause no response. An antagonist can reverse the effects of the agonist. This reversal is possible because the antagonist

competes with the agonist for a receptor site.

USES:

The major use of the **narcotic analgesic** is to relieve or manage moderate to severe acute and chronic pain. The ability of a narcotic analgesic to relieve pain depends on several factors, such as the drug, the dose, the route of administration, the type of pain, the patient, and the length of time the drug has been administered. Morphine is the most widely used opioid and an effective drug for moderately severe to severe pain. Morphine is considered the prototype or "model" narcotic. Morphine's actions, uses, and ability to relieve pain are the standards to which other narcotic analgesics are often compared.Other narcotics, such as meperidine and levorphanol, are effective for the treatment of moderate to severe pain. For mild to moderate pain, the primary health care provider may order a narcotic such as codeine or pentazocine.

In addition to the relief or management of moderate to severe acute and chronic pain, the **narcotic analgesics** may be used for the following reasons:

• To lessen anxiety and sedate the patient before surgery. Patients who are relaxed and sedated when anesthesia is given are easier to anesthetize (requiring a smaller dose of an induction anesthetic), as well as easier to maintain under anesthesia

• Support of anesthesia (ie, as an adjunct during anesthesia)

• Obstetrical analgesia

• Relief of anxiety in patients with dyspnea associated with pulmonary edema

• Intrathecally or epidurally for pain relief for extended periods without apparent loss of motor, sensory, or sympathetic function

• Relief of pain associated with a myocardial infarction (morphine)

• Management of opiate dependence (levomethadyl)

• Detoxification of and temporary maintenance of narcotic addiction (methadone)

• To induce conscious sedation before a diagnostic or therapeutic procedure in the hospital setting

• Treatment of severe diarrhea and intestinal cramping (camphorated tincture of opium)

• Relief of severe, persistent cough (codeine, although the drug's use has declined)

Use in Management of Opioid Dependence

Two opioids are used in the treatment and management of opiate dependence: levomethadyl and methadone. Levomethadyl is given in an opiate dependency clinic to maintain control over the delivery of the drug. Because of its potential for serious and life-threatening proarrhythmic effects, levomethadyl is reserved for use in the treatment of addicted patients who have no response to other treatments. Levomethadyl is not taken daily; the drug is administered three times a week (Monday/Wednesday/Thursday or Tuesday/Thursday/ Saturday). Daily use of the usual dose will cause serious overdose. Methadone, a synthetic narcotic, may be used for the relief of pain, but it also is used in the detoxifi-cation and maintenance treatment of those addicted to narcotics. Detoxification involves withdrawing the patient from the narcotic while preventing withdrawal symptoms.Maintenance therapy is designed to reduce the patient's desire to return to the drug that caused addic-tion, as well as to prevent withdrawal symptoms. The dosages used vary with the patient, the length of time the individual has been addicted, and the average amount of drug used each day. Patients enrolled in an outpatient methadone program for detoxification or maintenance therapy on methadone must continue to receive methadone when hospitalized.

ADVERSE REACTIONS

The adverse reactions differ according to whether the **narcotic analgesic** acts as an agonist or as an antagonist.

Agonists

one of the major hazards of narcotic administration is respiratory depression, with a decrease in the respiratory rate and depth. The most common adverse reactions include light-headedness, dizziness, sedation, and constipation, and anorexia, nausea, vomiting, and sweating.

When these effects occur, the primary health care provider may lower the dose in an effort to eliminate or decrease the intensity of the adverse reaction. Other adverse reactions that may be seen with the **administration of an agonist narcotic analgesic**

include:

• **Central nervous system**—euphoria, weakness,headache, pinpoint pupils, insomnia, agitation,tremor, and impairment of mental and physical tasks

• **Gastrointestinal**—dry mouth and biliary tractspasms

• **Cardiovascular**—flushing of the face, peripheral circulatory collapse, tachycardia, bradycardia, and palpitations

• **Genitourinary**—spasms of the ureters and bladder sphincter, urinary retention or hesitancy

• **Allergic**—pruritus, rash, and urticaria

• **Other**—physical dependence, pain at injection site, and local tissue irritation

Agonist-Antagonists

Administration of a narcotic agonist-antagonist may result in symptoms of narcotic withdrawal in those addicted to narcotics. Other adverse reactions associated with the administration of a narcotic agonist antagonist include sedation, nausea, vomiting, sweating, headache,vertigo, dry mouth, euphoria, and dizziness.

Contraindications

All narcotic analgesics are contraindicated in patients with known hypersensitivity to the drugs. These drugs are contraindicated in patients with acute bronchial asthma, emphysema, or upper airway obstruction and in patients with head injury or increased intracranial pressure. The drugs are also contraindicated in patients with convulsive disorders, severe renal or hepatic dysfunction, acute ulcerative colitis, and increased intracranial pressure. The narcotic analgesics are Pregnancy Category C drugs (oxycodone,Category B) and are not recommended for use during pregnancy or labor (may prolong labor or cause respi-ration depression of the neonate). The use of narcotic analgesics is recommended during pregnancy only if the benefit to the mother outweighs the potential harm to the fetus.

PRECAUTIONS

These drugs are used cautiously in the elderly and in patients with undiagnosed abdominal pain, liver disease, history of addiction to the opioids, hypoxia, supraventricular tachycardia, prostatic hypertrophy, and renal or hepatic impairment. The obese must be monitored closely for respiratory depression while taking the narcotic analgesics. The drug is used cautiously during lactation (wait at least 4 to 6 hours after taking the drug to breastfeed the infant). The narcotics are used cautiously in patients undergoing biliary surgery because the drug may cause spasm of the sphincter of Oddi.

INTERACTIONS

The **narcotic analgesics** potentiate the central nervous system (CNS) depressant properties of other CNS depressants, such as alcohol, antihistamines, antidepressants, sedatives, phenothiazines, and monoamine oxidase inhibitors. Use of the narcotic analgesics within 14 days of the MAO inhibitors may potentiate the effect of either drug. Patients taking the agonist-antagonist narcotic analgesics may experience withdrawal symptoms if the patient has been abusing or using narcotics. The agonist-antagonists drugs can cause opioid withdrawal symptoms in those who are physically dependent on the opioids. There is an increased risk of respiratory depression, hypotension, and sedation when **narcotic analgesics** are administered too soon after barbiturate general anesthesia.

2.4. Synthetic Opioid Analgesics:

An **opioid** is a chemical that works by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract. The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids.

Opioids are among the world's oldest known drugs; the use of the opium poppy for its therapeutic benefits predates recorded history. The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance. The side effects of opioids include sedation, respiratory depression, constipation, and a strong sense of euphoria. Opioids can cause cough

suppression, which can be both an indication for opioid administration or an unintended side effect. Opioid dependence can develop with ongoing administration, leading to a withdrawal syndrome with abrupt discontinuation. Opioids are well known for their ability to produce a feeling of euphoria, motivating some to recreationally use opioids.

Although the term *opiate* is often used as a synonym for *opioid*, the term *opiate* is properly limited to the natural alkaloids found in the resin of the opium poppy *(Papaver somniferum).* In some definitions, the semi-synthetic substances that are directly derived from the opium poppy are considered to be opiates as well, while in other classification systems these substances are simply referred to as semi-synthetic opioids.

Medical uses

Pain

Opioids have long been used to treat acute pain (such as post-operative pain). They have also been found to be invaluable in palliative care to alleviate the severe, chronic, disabling pain of terminal conditions such as cancer, and degenerative conditions such as rheumatoid arthritis. However, opioids should be used cautiously in chronic non-cancer pain (see below). High doses are not necessarily required to control the pain of advanced or end-stage disease. In recent years there has been an increased use of opioids in the management of non-malignant chronic pain. This practice has now lead to a new and growing problem with addiction and misuse of opioids

Clinical indications:

The sole clinical indications for opioids in the United States, according to *Drug Facts and Comparisons,* 2005, are:

- Moderate to severe pain, *i.e.*, to provide analgesia or, in surgery, to induce and maintain anesthesia, as well as allaying patient apprehension right before the procedure. Fentanyl, oxymorphone, hydromorphone, and morphine are most commonly used for this purpose, in conjunction with other drugs such as

scopolamine, short and intermediate-acting barbiturates, and benzodiazepines, especially midazolam which has a rapid onset of action and lasts shorter than diazepam(Valium) or similar drugs. The enhancement of the effects of each drug by the others is useful in troublesome procedures like endoscopies, complicated and difficult deliveries (pethidine and its relatives and piritramide where it is used are favoured by many practitioners with morphine and derivatives as the second line), incision & drainage of severe abcesses, intraspinal injections, and minor and moderate-impact surgical procedures in patients unable to have general anesthesia due to allergy to some of the drugs involved or other concerns.

- Cough (codeine, dihydrocodeine, ethylmorphine (dionine), hydromorphone and hydrocodone, with morphine or methadone as a last resort.)
- Diarrhea (generally loperamide, difenoxin or diphenoxylate; but paregoric, powdered opium or laudanum or morphine may be used in some cases of severe diarrheal diseases, e.g. cholera); also diarrhea secondary to Irritable Bowel Syndrome (Codeine, paregoric, diphenoxylate, difenoxin, loperamide, laudanum)
- Anxiety due to shortness of breath (oxymorphone and dihydrocodeine only)
- Opioid dependence (methadone and buprenorphine only)

Opioids are not typically used for psychological relief (with the narrow exception of anxiety due to shortness of breath).

Opioids are often used in combination with adjuvant analgesics (drugs which have an indirect effect on the pain). In palliative care, opioids are not recommended for sedation or anxiety because experience has found them to be ineffective agents in these roles. Some opioids are relatively contraindicated in renal failure because of the accumulation of the parent drug or their active metabolites (e.g. codeine and oxycodone). Age (young or old) is not a contraindication to strong opioids. Some synthetic opioids such as pethidine have metabolites which are actually neurotoxic and should therefore be used only in acute situations.

Adverse effects

Common adverse reactions in patients taking opioids for pain relief include: nausea and vomiting, drowsiness, itching, dry mouth, miosis, and constipation.

Infrequent adverse reactions in patients taking opioids for pain relief include: dose-related respiratory depression (especially with more potent opioids), confusion, hallucinations, delirium, urticaria, hypothermia, bradycardia/tachycardia, orthostatic hypotension, dizziness, headache, urinary retention, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses), and flushing (due to histamine release, except fentanyl and remifentanil).

Opioid-induced hyperalgesia has been observed in some patients, whereby individuals using opioids to relieve pain may paradoxically experience more pain as a result of their medication. This phenomenon, although uncommon, is seen in some palliative care patients, most often when dose is escalated rapidly. If encountered, rotation between several different opioid analgesics may mitigate the development of hyperalgesia.

Both therapeutic and chronic use of opioids can compromise the function of the immune system. Opioids decrease the proliferation of macrophage progenitor cells and lymphocytes, and affect cell differentiation (Roy & Loh, 1996). Opioids may also inhibit leukocyte migration. However the relevance of this in the context of pain relief is not known.

Men who are taking moderate to high doses of an opioid analgesic long-term are likely to have subnormal testosterone levels, which can lead to osteoporosis and decreased muscle strength if left untreated. Therefore, total and free testosterone levels should be monitored in these patients; if levels are suboptimal, testosterone replacement therapy, preferably with patches or transdermal preparations, should be given. Also, prostate-specific antigen levels should be monitored.

Addiction

Addiction is the process whereby physical and/or psychological dependence develops to a drug - including opioids. The withdrawal symptoms can reinforce the addiction, driving

the user to continue taking the drug. Psychological addiction is more common in people snorting or injecting opioids recreationally rather than taking them orally for medical reasons.

Recreational use

Drug misuse is the use of drugs for reasons other than what the drug was prescribed for. Opioids are primarily misused due to their ability to produce euphoria. Misuse can also include giving drugs to people for whom it was not prescribed or selling the medicaiton, both of which are crimes punishable by jail time in some countries.

Action:

Opioids bind to specific opioid receptors in the nervous system and other tissues. There are three principal classes of opioid receptors, μ, κ, δ (mu, kappa, and delta), although up to seventeen have been reported, and include the ε, ι, λ, and ζ (Epsilon, Iota, Lambda and Zeta) receptors. Conversely, σ (Sigma) receptors are no longer considered to be opioid receptors because: their activation is not reversed by the opioid inverse-agonist naloxone, they do not exhibit high-affinity binding for classical opioids, and they are stereoselective for dextro-rotatory isomers while the other opioid receptors are stereo-selective for laevo-rotatory isomers. In addition, there are three subtypes of μ-receptor: μ_1 and μ_2, and the newly discovered μ_3. Another receptor of clinical importance is the opioid-receptor-like receptor 1 (ORL1), which is involved in pain responses as well as having a major role in the development of tolerance to μ-opioid agonists used as analgesics. These are all G-protein coupled receptors acting on GABAergic neurotransmission.

The pharmacodynamic response to an opioid depends upon the receptor to which it binds, its affinity for that receptor, and whether the opioid is an agonist or an antagonist. For example, the supraspinal analgesic properties of the opioid agonist morphine are mediated by activation of the μ_1 receptor; respiratory depression and physical dependence by the μ_2 receptor; and sedation and spinal analgesia by the κ receptor. Each group of opioid receptors elicits a distinct set of neurological responses, with the receptor subtypes (such as μ_1 and μ_2 for example) providing even more [measurably] specific responses.

Unique to each opioid is its distinct binding affinity to the various classes of opioid receptors (e.g. the μ, κ, and δ opioid receptors are activated at different magnitudes according to the specific receptor binding affinities of the opioid). For example, the opiate alkaloid morphine exhibits high-affinity binding to the μ-opioid receptor, while ketazocine exhibits high affinity to κ receptors. It is this combinatorial mechanism that allows for such a wide class of opioids and molecular designs to exist, each with its own unique effect profile. Their individual molecular structure is also responsible for their different duration of action, whereby metabolic breakdown (such as N-dealkylation) is responsible for opioid metabolism.

Classification

There are a number of broad classes of opioids:

- **Natural** opiates: alkaloids contained in the resin of the opium poppy, primarily morphine, codeine, and thebaine, but not papaverine and noscapine which have a different mechanism of action; The following could be considered natural opiates: The leaves from Mitragyna speciosa (also known as kratom) contain a few naturally-occurring opioids, active via Mu- and Delta receptors. Salvinorin A, found naturally in the Salvia divinorum plant, is a kappa-opioid receptor agonist.
- **Semi-synthetic** opioids: created from the natural opiates, such as heroin, hydromorphone, hydrocodone, oxycodone, oxymorphone, desomorphine, nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine and buprenorphine;
- **Fully synthetic** opioids: such as fentanyl, pethidine, methadone, tramadol and dextropropoxyphene;
- **Endogenous** opioid peptides, produced naturally in the body, such as endorphins, enkephalins, dynorphins, and endomorphins. Sometimes morphine, and some other opioids, which are produced in small amounts in the body, is included in this category.
- There are also drugs such as tramadol and tapentadol that are chemically not of the opioid class, but do have agonist actions at the μ-opioid receptor. Although their

exact mechanism of action is not fully understood, they both have a dual mode of action, the second mode of action appearing to be on the noradrenergic and serotonergic systems. This second mechanism of action was discovered during testing in where the drugs showed signs of analgesia even when naloxone, an opioid antagonist, was administered.

Some minor opium alkaloids and various substances with opioid action are also found elsewhere, including molecules present in kratom, *Corydalis*, and *Salvia divinorum* plants and some species of poppy aside from *Papaver somniferum*. There are also strains which produce copious amounts of thebaine, an important raw material for making many semi-synthetic and synthetic opioids. Of all of the more than 120 poppy species, only two produce morphine.

Amongst analgesics are a small number of agents which act on the central nervous system but not on the opioid receptor system and therefore have none of the other (narcotic) qualities of opioids although they may produce euphoria by relieving pain—a euphoria that, because of the way it is produced, does not form the basis of habituation, physical dependence, or addiction. Foremost amongst these are nefopam, orphenadrine, and perhaps phenyltoloxamine and/or some other antihistamines. Tricyclic antidepressants have painkilling effect as well, but they're thought to do so by indirectly activating the endogenous opioid system. Paracetamol is predominantly a centrally acting analgesic (non-narcotic) which mediates its effect by action on descending serotoninergic (5-hydroxy triptaminergic) pathways, to increase 5-HT release (which inhibits release of pain mediators). It also decreases cyclo-oxygenase activity. It has recently been discovered that most or all of the therapeutic efficacy of paracetamol is due to a metabolite (AM404, making paracetamol a prodrug) which enhances the release of serotonin and also interacts as with the cannabinoid receptors by inhibiting the uptake of anandamide.

Other analgesics work peripherally (i.e., not on the brain or spinal cord). Research is starting to show that morphine and related drugs may indeed have peripheral effects as well, such as morphine gel working on burns. Recent investigations discovered opioid

receptors on peripheral sensory neurons. A significant fraction (up to 60 %) of opioid analgesia can be mediated by such peripheral opioid receptors, particularly in inflammatory conditions such as arthritis, traumatic or surgical pain.[51] Inflammatory pain is also blunted by endogenous opioid peptides activating peripheral opioid receptors.

It has been discovered in 1953, that the human body, as well as those of some other animals, naturally produce minute amounts of morphine and codeine and possibly some of their simpler derivatives like heroin and dihydromorphine, in addition to the well known endogenous opioid peptides. Some bacteria are capable of producing some semi-synthetic opioids such as hydromorphone and hydrocodone when living in a solution containing morphine or codeine respectively.

Many of the alkaloids and other derivatives of the opium poppy are not opioids or narcotics; the best example is the smooth-muscle relaxant papaverine. Noscapine is a marginal case as it does have CNS effects but not necessarily similar to morphine, and it is probably in a category all its own.
Dextromethorphan (the stereoisomer of levomethorphan, a semi-synthetic opioid agonist) and its metabolite dextrorphan have no opioid analgesic effect at all despite their structural similarity to other opioids; instead they are potent NMDA antagonists and sigma 1 and 2-receptor agonists and are used in many over-the-counter cough suppressants.
Salvinorin A is a unique selective, powerful κ-opioid receptor agonist. It is not properly considered an opioid nevertheless, because 1) chemically, it is not an alkaloid; and 2) it has no typical opioid properties: absolutely no anxiolytic or cough-suppressant effects. It is instead a powerful hallucinogen.

Endogenous opioids

Opioid-peptides that are produced in the body include:

- Endorphins
- Enkephalins
- Dynorphins

- Endomorphins

β-endorphin is expressed in Pro-opiomelanocortin (POMC) cells in the arcuate nucleus, in the brainstem and in immune cells, and acts through μ-opioid receptors. β-endorphin has many effects, including on sexual behavior and appetite. β-endorphin is also secreted into the circulation from pituitary corticotropes and melanotropes. α-neo-endorphin is also expressed in POMC cells in the arcuate nucleus.

met-enkephalin is widely distributed in the CNS and in immune cells; [met]-enkephalin is a product of the proenkephalin gene, and acts through μ and δ-opioid receptors. leu-enkephalin, also a product of the proenkephalin gene, acts through δ-opioid receptors.

Dynorphin acts through κ-opioid receptors, and is widely distributed in the CNS, including in the spinal cord and hypothalamus, including in particular the arcuate nucleus and in both oxytocin and vasopressin neurons in the supraoptic nucleus.

Endomorphin acts through μ-opioid receptors, and is more potent than other endogenous opioids at these receptors.

Opium alkaloids

Phenanthrenes naturally occurring in (opium):

- Codeine
- Morphine
- Thebaine
- Oripavine

Preparations of mixed opium alkaloids, including papaveretum, are still occasionally used.

Semi-synthetic derivatives

- Heroin (diacetylmorphine)

- Dihydrocodeine
- Hydrocodone
- Hydromorphone
- Nicomorphine
- Oxycodone
- Oxymorphone

Synthetic opioids

Anilidopiperidines

- Fentanyl
- Alphamethylfentanyl
- Alfentanil
- Sufentanil
- Remifentanil
- Carfentanyl
- Ohmefentanyl

Phenylpiperidines

- Pethidine (meperidine)
- Ketobemidone
- MPPP
- Allylprodine
- Prodine
- PEPAP

Diphenylpropylamine derivatives

- Propoxyphene
- Dextropropoxyphene
- Dextromoramide
- Bezitramide

- Piritramide
- Methadone
- Dipipanone
- Levomethadyl Acetate (LAAM)
- Difenoxin
- Diphenoxylate
- Loperamide (used for diarrhoea, does not cross the blood-brain barrier)

Benzomorphan derivatives

- Dezocine - agonist/antagonist
- Pentazocine - agonist/antagonist
- Phenazocine

Oripavine derivatives

- Buprenorphine - partial agonist
- Dihydroetorphine
- Etorphine

Morphinan derivatives

- Butorphanol - agonist/antagonist
- Nalbuphine - agonist/antagonist
- Levorphanol
- Levomethorphan

Others

- Lefetamine
- Meptazinol
- Tilidine
- Tramadol
- Tapentadol

Opioid antagonists

- Nalmefene
- Naloxone
- Naltrexone

2.5. Narcotic Antagonists:

An **opioid antagonist** is a receptor antagonist that acts on opioid receptors.

Naloxone and naltrexone are commonly used opioid antagonist drugs which are competitive antagonists that bind to the opioid receptors with higher affinity than agonists but do not activate the receptors. This effectively blocks the receptor, preventing the body from responding to opiates and endorphins.

Some opioid antagonists are not pure antagonists but in fact do produce some weak opioid partial agonist effects, and can produce analgesic effects when administered in high doses to opioid-naive individuals. Examples of such compounds include nalorphine and levallorphan. However the analgesic effects from these drugs are limited and tend to be accompanied by dysphoria, most likely due to action at the kappa opioid receptor. As they induce opioid withdrawal effects in people who are taking, or have recently used, opioid full agonists, these drugs are considered to be antagonists for practical purposes.

The weak partial agonist effect can be useful for some purposes, and has previously been used for purposes such as long-term maintenance of former opioid addicts using nalorphine, however it can also have disadvantages such as worsening respiratory depression in patients who have overdosed on non-opioid sedatives such as alcohol or barbiturates. Naloxone on the other hand has no partial agonist effects, and is in fact a partial inverse agonist at mu opioid receptors, and so is the preferred antidote drug for treating opioid overdose.

Naltrexone is also a partial inverse agonist, and this property is exploited in treatment of opioid addiction, as a sustained course of low-dose naltrexone can reverse the altered homeostasis which results from long-term abuse of opioid agonist drugs. This is the only treatment available which can reverse the long-term after effects of opioid addiction known as post acute withdrawal syndrome, which otherwise tends to produce symptoms such as depression and anxiety that may lead to eventual relapse. A course of low-dose naltrexone is thus often used as the final step in the treatment of opioid addiction after the patient has been weaned off the substitute agonist such as methadone or buprenorphine, in order to restore homeostasis and minimise the risk of post acute withdrawal syndrome once the maintenance agonist has been withdrawn.

Selective antagonists

All of the opioid antagonists used in medicine are non-selective, either blocking all three opioid receptors, or blocking the mu-opioid receptor but activating the kappa receptor. However for scientific research selective antagonists are needed which can block one of the opioid receptors but without affecting the other two. This has led to the development of antagonists which are highly selective to one of the three receptors;

- Cyprodime is a selective mu opioid receptor antagonist
- Naltrindole is a selective delta opioid receptor antagonist
- Norbinaltorphimine is a selective kappa opioid receptor antagonist

Other selective antagonists are also known, but the three listed above were the first selective antagonists discovered for each respective opioid receptor, and are still the most widely used.

2.6. Non Norcotic Analgesics:

a. Nonnarcotic analgesic/antipyretic drugs are used to relieve pain of mild to moderate intensity and reduce body temperature in selected febrile conditions. Examples are: acetylsalicylic acid (aspirin) and acetaminophen (Tylenol , Datril).

b. Nursing care implications consist of administering aspirin products with food or milk, monitoring the patient for complications from aspirin therapy, observing the patient for allergic reactions to the drugs, and monitoring the patient's temperature.

c. Gastric irritation or bleeding and tinnitus (sensation of ringing in the ears) are complications of aspirin therapy. Gastric side effects may be minimized by giving medication with a full glass of water or with milk, food, or an antacid. An exception is enteric-coated tablets, which may dissolve too quickly if taken with milk. Tinnitus is an indication of salicylate toxicity. The drug is generally discontinued with the onset of tinnitus. Inform the patient that the hearing impairment is reversible.

3. ANTI INFLAMMATORY DRUGS:

Antihistamines, usually as tablets, are the basic treatment of hayfever and some other allergic illnesses. They are also the main treatment for a kind of skin rash called 'urticaria' or 'hives', also called 'nettlerash'.

In hayfever, the big advantage of antihistamines is that they treat the nose, the eyes, and the terrible itching which some sufferers get in the throat or ears. The only other treatments which help so many of the symptoms are steroid tablets or injections, and desensitising injections. Both of these other treatments have disadvantages not shared by antihistamines.

In hayfever the drawback of antihistamines is that they are not so effective for the blockage in the nose which troubles some people.

Asthma is helped only slightly by antihistamines; they are rarely used for asthma in Britain because there are so many better medicines for that.

Action of antihistamines:

In allergic reactions special allergy cells in the body release chemical called histamine. Histamine causes rashes, sneezing, itching and runniness of your nose, and the other features of allergic ailments. It does this by causing blood vessels to widen and leak, nerves to itch, secretions to pour from the lining of your nose or lungs, and in a variety of other ways.

Antihistamines do exactly this. They are chemicals which look enough like histamine to fool the cells of the body, but not enough like histamine to make the cells of the body do the nasty things which cause allergy symptoms. (In technical jargon, they 'block histamine receptors').

In other words, antihistamines stop histamine from working in the body.

But histamine is is not just involved in allergies. In fact it plays a vital role in the brain. What it does in the brain is to keep us attentive, alert, and awake.

So if we stopped all the histamine in the body from working, we would get rid of allergy troubles, but fall asleep, or at least become inattentive. This would make us dangerous drivers, bad students, and generally bad at the entire daily tasks which need alertness.

That is exactly what happens if you take old antihistamines. They should not be used any more, except for special reasons, such as when the doctor wants to make you sleepy.

Fortunately newer antihistamines help allergies with little or no effect on your brain. How do they do this? It's very simple. Some medicines hardly get into the brain from the blood. This is a disadvantage with antibiotics for brain infections. But when research workers made antihistamines which hardly got into the brain it solved the problem of sleepiness and inattentiveness. So the new antihistamines are vastly better.

Side effects:

Older antihistamines do have more side effects. The most serious of these are both sleepiness, and a harmful effect on driving, learning and similar tasks even when they don't seem to make you feel sleepy. They affect your brain in the same way as alcohol.

There is no real doubt in the minds of researchers that older antihistamines can cause road accidents.

They also hinder learning, exam performance and skilled tasks.

Older antihistamines also had some other side effects which might in a few people cause difficulty passing water or increased pressure in the eyes (glaucoma), although this seems to have been rare.

There is now little reason to use the older antihistamines.

How do we know that the new antihistamines are better? There has been lots of research which shows this, but two experiments are specially interesting.

3.1. Non Steroidal anti inflammatory drugs:

NSAIDs are **non-steroidal anti-inflammatory drugs**, also known as **NAIDs**, **non-steroidal anti-inflammatory agents/analgesics** (NSAIAs) or **non-steroidal anti-inflammatory medicines** (NSAIMs). They are medications with analgesic (pain reducing), antipyretic (fever reducing) effects. In higher doses they also have anti-inflammatory effects - they reduce inflammation (swelling). *Non-steroidal* distinguishes NSAIDs from other drugs which contain steroids, which are also anti-inflammatory. NSAIDs are non-narcotic (they do not induce stupor).

The most common NSAIDs are aspirin, ibuprofen and naproxen - probably because they are available over-the-counter (OTC, no prescription required).

NSAIDs can be used for a number of conditions. While some OTC medications, others can only be accessed with a prescription. Typically, NSAIDs are used to treat the following symptoms and conditions:

- **Pain and discomfort** - for example muscle strain/sprain, headaches, migraines, and dysmenorrhea (painful cramps during menstruation).
- **Fever** - NSAIDs are effective at reducing body temperature.

- **Inflammation** - NSAIDs are often used for the treatment of inflammation, as may occur in rheumatoid arthritis.

- **Some other conditions** - sometimes NSAIDs are recommended for the treatment of menorrhagia (heavy menstrual periods).

According to Medilexicon's medical dictionary:

Nonsteroidal antiinflammatory drugs (NSAIDs) are *"a large number of drugs exerting antiinflammatory (and also usually analgesic and antipyretic) actions; examples include aspirin, acetaminophen, diclofenac, indomethacin, ketorolac, ibuprofen, and naproxen. A contrast is made with steroidal compounds (hydrocortisone or prednisone) exerting antiinflammatory activity."*

Types of NSAIDS

NSAIDs are based on their chemical structure:

- **Propionic acid derivatives** - Examples include: Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin
- **Acetic acid derivatives** - Examples include: Indomethacin, Sulindac, Etodolac, Diclofenac (Safety alert by FDA)
- **Enolic acid (Oxicam) derivatives** - Examples include: Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam

- **Fenamic acid derivatives** - Examples include: Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid

- **Selective COX-2 inhibitors (Coxibs)** - Examples include: Celecoxib (FDA alert), Rofecoxib (withdrawn from market), Valdecoxib (withdrawn from market), Parecoxib (FDA withdrawn), Lumiracoxib (TGA cancelled registration), Etoricoxib (FDA withdrawn)

Action of NSAIDs

Enzymes - these are protein-based molecules that either trigger or speed up specific chemical reactions in the body, and convert substrates (specific set of reactants) into specific products. For example, digestive enzymes help the digestive system break up large food particles into smaller ones so that the body can absorb them. Without enzymes life as we know it would not exist.

NSAIDs interfere with cyclo-oxyganase (COX), a type of enzyme. Different types of COX enzymes exist in various parts of the human body - they control the production of prostaglandins, which have different functions. COX-1 enzymes exist in the stomach and control the production of prostaglandins which protects the stomach from acid. COX-2 enzymes exist in white blood cells, which control the prostaglandins involved in pain and inflammation.

Prostaglandins - these are hormone-like substances that participate in a wide range of body functions, one of which causes pain and inflammation. NSAIDs prevent the COX enzymes from releasing the prostaglandin chemicals responsible for inflammation and pain. However, prostaglandins have other vital functions, such as protecting the stomach from indigestion and ulcers, so NSAIDs can have undesirable side effects.

COX-2 inhibitors - these are newer NSAIDs. While the COX-1 enzyme protects the stomach, COX-2 enzymes cause inflammation and pain in the body. Until COX-2 inhibitors arrived, NSAIDs inhibited both COX-1 and COX-2 enzymes - while helping with pain and inflammation; they would also make the stomach more vulnerable to damage.

Specific COX-2 inhibitor - NSAID medications were created that inhibited the COX-2 enzyme, but not the COX-1 ones. The aim was to relieve pain and inflammation without causing side effects for the stomach. However, COX-2 inhibitors, while not damaging the stomach, do cause more side effects for the heart compared to the old NSAIDs. So specific Cox-2 inhibitor NSAID medications are suitable for patients who are more likely

to develop intestinal and/or stomach problems, but unsuitable for those with circulation or heart problems.

Factors to consider

Some patients may be more at risk of developing side effects after taking NSAIDs than others. In fact, there are possible side effects for anybody who takes them.

Stomach and intestinal side-effects (gastrointestinal side effects) - NSAIDs can cause such gastrointestinal problems as stomach ulcers or indigestion. The following groups of people may be at higher risk of developing gastrointestinal problems when taking NSAIDs:

- Elderly individuals (aged over 65 years)
- Heavy smokers
- Patients who are taking other medications at the same time
- Patients who have a history of gastrointestinal problems
- Patients who take NSAIDs in high doses
- Patients who take NSAIDs long-term
- Patients with some other conditions, such as hypertension, cardiovascular disease, or diabetes

Cardiovascular and kidney side effects - in some cases, NSAIDs may raise the risk of problems for the kidneys, heart or blood vessels. The following groups of people have a higher risk of these types of side effects when taking NSAIDs:

- Elderly patients (aged over 65 years)
- Patients with hypertension (high blood pressure)
- People with faulty/damaged hearts or kidneys
- People with kidney or heart failure

Pregnancy - women who are pregnant, and those planning to become pregnant should avoid NSAIDs. There is a health risk to both the mother and the baby. During the first

and second trimesters of pregnancy, taking NSAIDs poses a very small risk for the baby's health; during the third trimester there is a risk the baby may develop pulmonary hypertension (arteries in the lungs become narrowed, causing hypertension and some other problems).

Fertility - some people may find it harder to conceive when taking NSAIDs. Experts advise such people to use other painkillers, such as acetimophen (Tylenol, paracetamol) if they are trying to have a baby.

Giving birth - a mother who takes NSAIDs shortly before giving birth may find the labor process takes longer.

Breastfeeding - breastfeeding mothers should avoid NSAIDs while breastfeeding, even though the risk to the child is very small, says the National Health Service (NHS), UK. The NHS adds that if an NSAID is prescribed to a nursing mother, it is usually a very low dose.

Asthma - there is a risk symptoms may worsen if asthma patients take NSAIDs. It is recommended that asthma patients try to avoid them. In some cases, doctors may prescribe an NSAID for asthma patients if they are deemed to be beneficial; in such cases it will be a short course of medication.

Post-surgery bleeding - there is a risk of excessive bleeding after surgery or a traumatic injury if the patient takes NSAIDs.

Long-term NSAIDs - patients on long-term NSAID therapy should be monitored carefully.

NSAID interactions with other medications or alcohol

In some cases, a combination of an NSAID with certain medications or alcohol may cause undesirable side effects.

NSAID interactions with certain medications - if a patient is taking an NSAID together with any of the medications below, they should be monitored closely in case an undesirable side effects develop (some in the list below should never be taken alongside NSAIDs):

- **Ciclosporin** - an immunosuppressant medication taken by organ transplant recipients so that their bodies do not reject the new organ.
- **Clozapine** - an antipsychotic drug used in the treatment of schizophrenia.
- **Lithium** - a mood stabilizer for the treatment of bipolar disorder.
- **Methotrexate** - used to treat diseases associated with abnormally rapid cell growth such as certain tumors and psoriasis. Also used for the treatments of rheumatoid arthritis.
- **Phenytoin** - an anticonvulsant used in the treatment of epilepsy.
- **Quinolones** - synthetic antibiotics that inhibit the replication of bacterial DNA.
- **Some diuretics** - products that promote the formation of urine by the kidney; they increase the amount of water the body gets rid of.
- **SSRIs** (selective serotonin reuptake inhibitors) - medications commonly prescribed for the treatment of depression.
- **Sulphonylurea** - medication that raises the secretion of insulin by the pancreas. Prescribed for patients with Type 2 Diabetes to lower blood glucose levels.
- **Warfarin** - a blood thinner used to prevent blood clots.

NSAID interactions with alcohol - in most cases a man can consume 3 to 4 units of alcohol per day, and a woman 2 to 3 units per day, while taking ibuprofen or aspirin. If alcohol is consumed in higher amounts, while taking aspirin or ibuprofen there is a risk of irritation to the stomach lining.

Heavy drinkers who take ibuprofen or aspirin have a higher risk of bleeding in the stomach.

Some more powerful prescription NSAIDs should not be taken with alcohol.

3.2. Cortico steroids:

Definition:

Corticosteroids are a group of related drugs used in cancer treatment to reduce the growth of tumors, stimulate the appetite, and treat skin rashes, nausea and vomiting, allergic reactions, inflammation, accumulation of fluid in the brain, and autoimmune disease.

Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of physiologic systems such as stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

- **Glucocorticoids** such as cortisol control carbohydrate, fat and protein metabolism and are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms.
- **Mineralocorticoids** such as aldosterone control electrolyte and water levels, mainly by promoting sodium retention in the kidney.

Some common natural hormones are *corticosterone* ($C_{21}H_{30}O_4$), *cortisone* ($C_{21}H_{28}O_5$, 17-hydroxy-11-dehydrocorticosterone) and *aldosterone*.

Classification

By route of administration

Topical steroids

For use topically on the skin, eye, and mucous membranes.

Topical corticosteroids are divided in potency classes I to IV, with the additional complication that in Europe class IV is the most potent, while in the US this is called Class I.

Inhaled steroids

for use to treat the nasal mucosa, sinuses, bronchii, and lungs. This group includes:

- Flunisolide
- Fluticasone propionate
- Triamcinolone acetonide
- Beclomethasone dipropionate
- Budesonide

There is also a combination preparation (trade name Advair), containing fluticasone propionate and salmeterol xinafoate (a long-acting bronchodilator). It is approved for children over 12 years old.

Oral forms

Such as prednisone and prednisolone.

Systemic forms

Available in injectables for intravenous and parenteral routes.

Purpose

Corticosteroids have broad use in cancer treatment. Some are used to treat adult leukemias, adult lymphomas, acute childhood leukemia, multiple myeloma, and advanced prostate cancer. Others are used in creams to treat skin rashes from radiation

therapy. Corticosteroids are also used to reduce swelling, especially in the brain and spinal column, reduce nausea and vomiting, and improve appetite.

Description

Corticosteroids occur naturally in the body. They are produced by the cortex of the adrenal glands, a small, pea-sized pair of glands that are located in the lower back, just above the kidney. Some corticosteroids regulate fluid balance in the body. Others influence fat and sugar (glucose) usage. Corticosteroids are chemically related to the sex hormones estrogen and testosterone.

Many different corticosteroids are produced artificially to use as drugs. They are administered as creams, tablets, liquids, or intravenously (or injection directly into a vein). Many people are already familiar with hydrocortisone, a corticosteroid found in low doses in over-the-counter creams.

The most common corticosteroids used in cancer treatment are:

- dexamethasone (Decadron)
- hydrocortisone
- methylprednisolone (Medrol)
- prednisone
- cortisone
- betamethasone
- prednisolone There are many trade names for drugs containing these corticosteroids.

Recommended Dosage

Corticosteroids come in tablets, liquids, intravenous solutions, and creams. Because of their wide variety of uses and forms, there is no standard recommended dose. Dosage is individualized, and depends on the type of cancer, the patient's body weight and general

health, the goal of the treatment, the other drugs being given, and the way a patient's cancer responds to the drug. Corticosteroids should be stored away from heat.

Precautions

People taking corticosteroids may want to go on a low-salt, high-potassium diet in order to reduce water retention. They may also want to watch their calorie intake unless corticosteroids are being given to improve appetite. Patients taking large doses of corticosteroids are more susceptible to infection and should try to avoid contact with crowds or any individuals that may have an infection. Patients should seek immediate medical advice if they are exposed to chicken pox or measles.

Side Effects

Corticosteroids have several side effects. Not every side effect is seen in every patient. The most serious, although rare, side effect is an allergic reaction to corticosteroids when given intravenously (IV). Other side effects can include:

- salt and water retention
- excessive potassium loss
- high blood pressure
- other fluid and electrolyte imbalances
- loss of muscle tissue
- loss of bone strength (osteoporosis)
- easily fractured bones
- heartburn and ulcers
- thin, fragile skin
- slow wound healing
- skin rashes
- masking of infection
- convulsions
- headache
- dizziness

- reproductive irregularities
- strong mood changes
- changes in the functioning of the adrenal gland
- increased pressure in the eye
- glaucoma, cataracts, and blindness (rare)
- nausea
- fatigue
- increased appetite
- weight gain
- increased urination

Interactions

Many drugs interact with nonprescription (over-thecounter) drugs and herbal remedies. Patients should always tell their health care providers about these remedies, as well as any prescription drugs they are taking. Patients should also notify their physician if they are on a special diet.

Corticosteroids can also interact with anticoagulants (blood thinners such as Coumadin), cyclosporine, phenobarbitol, and antidepressants.

—Tish Davidson, A.M.

3.3. Leukotriene receptor antagonists:

Definition

Leukotriene inhibitors are prescription medications that treat asthma and some allergies by blocking the formation or activity of leukotrienes—small mediator chemicals produced by cells in the body.

Purpose

More than 50 million Americans suffer from asthma and allergies. Asthma is one of the most prevalent chronic diseases in the United States, affecting 9 million (12.7%) of

children. Seasonal allergies affect 20-40 million (20%) of Americans, about 40% of them children. It is estimated that 60-70% of those with asthma also suffer from allergic rhinitis, allergies affecting the mucous membranes of the nose.

Asthma, an inflammation of the bronchial airways, and seasonal allergies and allergic rhinitis involve several chemical mediators including histamine and leukotrienes. Leukotrienes are a class of unsaturated fatty-acid chains containing 20 carbon atoms.

During an asthma attack or within minutes of exposure to an allergen such as dust or pollen, leukotrienes are released by a type of blood cell in the lungs, causing the following responses:

- contraction of the bronchial airway muscles
- inflammation of the airway linings
- swelling and narrowing of the airways
- production of mucus and fluid
- wheezing and shortness of breath
- nasal congestion

Leukotriene inhibitors may decrease the symptoms of mild to moderate allergen-induced asthma, improve nighttime symptoms, and reduce the number of acute asthma attacks. Taken daily on a long-term basis they may help to prevent or control the symptoms of persistent asthma—asthma with symptoms that last at least two days per week or two nights per month. They also are prescribed for children with frequent or more severe asthma attacks and for those who dislike or have difficulty using asthma inhalers. Although leukotriene inhibitors may decrease the need for inhaled beta-agonists or corticosteroids, they are not used to treat asthma attacks. Leukotriene inhibitors also may be used to treat symptoms of allergic rhinitis or short-term seasonal allergies, including sneezing, runny nose, itching, and wheezing.

Description

Leukotriene inhibitors are often called leukotriene:

- blockers

- modifiers
- antagonists
- pathway modifiers

When they were first introduced in 1996, leukotriene inhibitors represented the first new class of asthma medication in two decades. Classified as anti-inflammatories, they were originally developed to improve lung function in asthmatics by relaxing the smooth muscles around the bronchial airways and by reducing lung inflammation.

Types of leukotriene inhibitors

The available leukotriene inhibitors are: montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo).

Montelukast and zafirlukast are leukotriene-receptor antagonists that prevent leukotriene from binding to cell receptors and initiating the chain of events leading to symptoms of allergy and asthma. Montelukast works rapidly. It is the only leukotriene inhibitor that has been approved by the U.S. Food and Drug Administration (FDA) for use in children as young as two, as well as for the treatment of seasonal allergies.

Zafirlukast is a synthetic peptide that inhibits the receptor binding of three leukotreines (LTC4, LTD4, and LTE4) that cause smooth muscle constriction. It is used for mild to moderate persistent asthma, exercise-induced asthma, and the management of allergic rhinitis in those aged seven and older.

Zileuton is a 5-lipooxygenase pathway inhibitor that interferes with the synthesis of LTA4, LTC4, LTD4, and LTE4. It is used to treat chronic asthma in adolescents and adults.

Effectiveness

Leukotriene inhibitors may be prescribed along with inhaled corticosteroids for control of mild to moderate, persistent asthma. Used alone they are less effective than low-dose inhaled corticosteroids. However, they enable some people to reduce their doses of inhaled corticosteroids. Leukotriene inhibitors may be an option for people with mild asthma who want to avoid corticosteroids, which can cause serious side effects with long-

term use. When used in conjunction with beta-agonists, leukotriene inhibitors reduce symptoms and may lower the beta-agonist usage.

Leukotriene inhibitors appear to decrease the symptoms of seasonal allergic rhinitis. Although they may relieve nasal congestion better than antihistamines, they are less effective than corticosteroid nasal sprays. A leukotriene inhibitor combined with an anti-histamine may be more effective than either drug alone.

Leukotriene inhibitors have helped some children who suffer from nocturnal asthma, exercise- and aspirin-induced asthma, allergic rhinitis, and seasonal allergies.

Other uses

Leukotriene inhibitors have been used successfully to treat inflammations of the esophagus (esophagitis) or stomach and intestines (gastroenteritis) that are caused by white blood cells called eosinophils that are involved in allergic reactions. Montelukast has been used to successfully treat symptoms of interstitial cystitis, a chronic inflammation of the bladder.

Recommended dosage

Montelukast is taken once per day in the evening so as to relieve morning allergy symptoms. Although dosing may vary, average daily doses of montelukast for asthma and seasonal allergies are: children aged 1-5: one 4-mg chewable tablet or 4-mg oral granules (one packet), swallowed whole or mixed in a spoonful of soft food; children aged 6-14: one 5-mg chewable tablet; children over 14 and adults: one 10-mg tablet.

The average doses of zafirlukast for children aged 7-11 are 10-mg tablets twice a day. Children aged 12 and older and adults usually take 20-mg tablets twice a day. Zafirlukast is taken one hour before or two hours after a meal, since food reduces its bioavailability by about 49%.

The average dose of zileuton is a 600-mg tablet four times per day for children aged 12 and older and adults.

Leukotriene inhibitors are expensive. Missed doses should be taken as soon as possible unless it is almost time for the next dose, in which case the dose should be skipped.

Precautions

Although leukotriene inhibitors are considered safe, they can raise the levels of liver enzymes. The FDA recommends liver function tests monthly for the first three months on medication, followed by quarterly monitoring for the next year, and continued interim testing. Zileuton is contraindicated for those with elevated liver enzymes, active alcoholism, or liver disease. Increased levels of liver enzymes may be detectable in the blood within two months of starting zileuton. Zileuton can affect liver function and, one rare occasions, can damage the liver.

It is unclear whether leukotriene inhibitors should be taken during pregnancy. Zafirlukast and zileuton should not be used by a woman who is breastfeeding. Both medications have been found to increase the risk of mild to moderate respiratory tract infections in patients aged 55 and older.

Medical conditions that may interfere with the use of montelukast include: allergies to aspirin or nonsteroidal anti-inflammatories (NSAIDs); liver disease, which can increase the blood levels of the drug; and phenylketonuria because chewable tablets may contain aspartame.

A healthcare provider should be contacted if an increased number of short-acting bronchodilator inhalations are needed to relieve an acute asthma attack or if more than the maximum number of daily inhalations are required while using zileuton.

To be effective montelukast and zafirlukast must be taken at the same time every day. Zileuton must be taken at regularly spaced intervals every day, even if asthma symptoms appear to improve. Montelukast should be continued through an acute asthma attack in addition to rescue medication.

Side effects

Although leukotriene inhibitors generally have few side effects and those may subside as the body adjusts to the drug, headaches are common with these medications. Headaches occur in 18-19% of those taking montelukast and in 25% of those taking zileutin. Among 7 to 11 year olds on zanfirlukast, 4.5% suffer from headaches, as do 12.9% of those aged 12 and over.

Other less common side effects of leukotriene inhibitors include:

- rash
- fatigue
- dizziness
- abdominal pain
- nausea and vomiting
- diarrhea

Montelukast appears to cause fewer side effects than other leukotriene inhibitors and is less likely to affect the liver. Side effects occurring in less than 4.2% of patients include:

- heartburn
- weakness
- fever
- nasal congestion
- cough
- dental pain
- rarely, pus in the urine

Rare side effects of zileuton include:

- itching
- flu-like symptoms
- upper right abdominal pain
- yellow eyes or skin (jaundice)

Interactions

Drugs that may interact with montelukast include:

- aspirin
- NSAIDs
- phenobarbital
- rifampin

Zafirlukast and zileuton can raise the blood levels of the asthma medication theophylline (Theo Dur and others) and the blood thinner warfarin (Coumarin). Theophylline levels and blood-clotting times should be monitored frequently.
Medications that may interact with zafirlukast include:

- aspirin
- blood pressure medications
- some seizure medications

Medications that may interact with zileuton include:

- the beta-blocker propanolol
- beta-agonists
- terfenadine (Seldane and others)

ANALGESICS, ANTIPYRETICS & ANTI INFLAMMATORY DRUGS:

ANALGESICS, ANTIPYRETICS & ANTI INFLAMMATORY DRUGS		
ASPIRIN		
General Information		
Drug Code	**Preparation**	**Strength**
1	Tab. Aspirin.	300 mg
Description of the Drug		
Aspirin is a weak organic acid – acetyl salicylic acid. It has antipyretic, anti-inflammatory and analgesic effects. It also has antiplatelet activity.		
Mode of Action		
The antipyretic and anti-inflammatory effects of the salicylates are primarily due to the blockage of prostaglandin synthesis (by inhibiting cyclo-oxygenase enzyme		

irreversibly) at the thermoregulating centers in the hypothalamus and at peripheral target sites. They also prevent the sensitization of pain receptors to both mechanical and chemical stimuli. It has a uricosuric effect in large doses (5-6 gm/day). But in doses generally used, it decreases urate excretion (1-2 gm/day). Salicylates also cause hyperventilation by stimulation of respiratory center.

Pharmacokinetics

After oral adminstration, aspirin is well absorbed from the GIT and hydrolysed to salicylate and acetic acid in the tissues, where saliylate exerts its effects. Onset of action is 15-30 min after ingestion ad lasts for 4-8 hours. Salicylate crosses both the blood brain barrier and the placenta. It undergoes hepatic metabolism and is excreted in the urine.

Clinical Information

Indications

Analgesic effect: Short term adminstration for pain relief in myalgia, headache, arthritis, dysmenorrhoe, dental pain, postpartum pain etc.,

Antipyretic effect: common cold, cough and fever due to any cause.

Anti-inflammatory effect: For relief of pain and inflammation in high doses (more than 3mg/day) and for prolonged periods in musculo skeletal disorders like osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, SLE, ankylosing spondylitis etc.

Antiplatelet effect:

Used in low doses for prolonged periods of time.

Preventionof recurrent myocardial infarction - reduces mortality by 20% in acute

myocardial infarction.

- For stroke or cerebro vascular disorders – prevention of recurrent episodes.
- For transient ischemic attacks – prevention of progression to stroke.
- Prevention of pregnancy induced hypertension and eclampsia.
- Following arterial bypass to prevent restenosis.
- In arterial and venous disorders, such as TAO to reduce inflammation and to increase blood flow to the supplied area.

For analgesic and antipyretic **Indications** : 300-900 mg 6th hourly, upto a maximum of

60 mg/kg/day for children.

For antiplatelet effect : 75-150 mg o.d

Routes of Administration Oral

Contraindications

- Active petic ulcer disease.
- Haemophilia and other haemorrhagic disorders, anticoagulant treatment.
- Apart from low dose aspirin regimes, it should not be used in pregnancy.
- Should not be used in lactating mothers and children under one year of age.
- In treatment of viral haemorrhagic fevers such as dengue.
- Hypersensitive patients, in whom history of bronchial asthma, angioedema or

urticaria have been precipitated by aspirin or other NSAIDS.

Precautions / Practice points

- Alcohol increases the GI adverse effects and hence instruct patients to abstain from alcohol.
- Use with caution in patients with hepatic or renal dysfunction and in elderly – increased risk of side effects.
- Use with caution in children below 12 years except for the treatment of juvenile rheumctoid arthritis. Aspirin should not be used for any other minor illnesses.
- Look out for tinnitus as an early indicator of toxic symptoms and withdraw the drug immediately.
- It is not advisable to take one more NSAID if the patient is already on aspirin – such combinations are more at risk for developing analgesic nephropathy.
- Stop aspirin 7 days before any planned surgery.
- While on long term therapy monitor renal, hepatic parameters and for signs of gastro-intestinal bleeding.
- Aspirin may give false negative results in testing for urine sugar by glucose oxidase strips.
- Administration Instructions:

    - Administer along with food to reduce gastro-intestinal side effects.

    - Instruct patients to report immediately if ringing in ears or any bleeding tendencies like bleeding from gums or persistent abdominal pain occurs. Withdraw the drug

immediately.

- Open package immediately before use.

- Do not administer aspirin exposed to water or air for a long time

Drug Interactions

Potentially fatal:

- With anti coagulants such as warfarin – major bleeding episode may occur due to inhibition of platelet aggregation.

- Increases methotrexate levels and may precipitate toxicity.

Non fatal

- Enhaunces effects of phenytoin, valproate.

- Increases risk of gastro-intestinal bleeds with steroids.

- May antagonize diuretic effects of spirinolactone.

- Metaclopramide increases absorption and hence, effects of aspirin.

Adverse Effects

Usually occurs at doses of more than 1 gm/day.

Common effects:

- GIT - stomach pain, heart burn, nausea, vomiting, epigastric discomfort, ulceration.

- Effects on hearing – tinnitus (very common), vertigo, mild hearing loss.

Rare effects:

- Hypersensitivity – angioedema, skin eruptions, paroxysmal bronchospasm.
- Haematological – iron deficiency anaemia, prolongation of bleeding time, may cause haemolytic anaemia in G6PD deficiency patients.
- Liver – hepatotoxicity (usually reversible).
- Kidney – Analgesic nephropathy – especially if combinations of NSAIDS are used.
- Reye's syndroe – acute encephalopathy and hepatic injury in children, when used for antipyretic effects in viral infections such as flu or chicken pok.

Drug Toxicity (SALICYLISM)

Toxic doses - 150-175 mg/kg.

Symptoms – headache, dizziness, tinnitus, vertigo, mental confusion, restlessness, marked alteration in acid base balance, acidosis, sweating, dehydration, hyperpyrexia, nausea, vomiting, hyperventilation, coma followed by cardiovascular collapse and respiratory arrest due to its CNS depressant activity.

Treatment of Toxicity

- Gastric lavage, activated charcoal or emesis to remove unabsorbed poison.
- Ice packs and external cooling measures to reverse hyperthermia.
- Maintain urinary output, fluid and electrolyte imbalance with adequate I.V. fluids.
- Alkalinization of urine can be done to increase the excretion, by giving IV sodium bicarbonate.
- Cardiovascular and respiratory support.
- Vitamin K, fresh blood – if bleeding is prominent.

Haemodialysis – if severe poisoning and serum levels are above 700 mg/litre.

Storage

Store in airtight containers, in a cool place.

Shelf Life 18 months.

PARACETAMOL

General Information

Drug Code	Preparation	Strength
2	Tab. Paracetamol	500 mg
3	Syr. Paracetamol	60 ml (125 mg/5ml)
249	Paracetamol Oral solution	15 ml (150 mg/ml)
351	Inj. Paracetamol	2 ml / Amp (150 mg/ml)

Description of the Drug

Paracetamol is a non-narcotic nonsalicylate analgesic. Unlike other NSAIDS, it has little or no anti-inflammatory activity.

Mode of Action

It acts by inhibiting prostaglandin synthesis in the CNS (hence acting as antipyretic and analgesic). It has weak anti inflammatory activity in the peripheral tissues and does not inhibit platelet aggregation.

Pharmacokinetics

It is readily absorbed from the upper GIT. Onset of action is 30 minutes after ingestion. Duration of effects is 2-5 hours. It is metabolized predominantly in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates.

Clinical Information

Indications

Pain relief:

- Minor aches and pains, associated with colds and other infections.
- Postpartum pain.
- Headache.
- Dental pain.
- Myalgia.
- Dysmenorrhoea.

Pyrexia:

- For reducing fever of any cause – infective etc.,

Dosage

Adults

0.5-1 gm, every 4-6 hours upto a maximum of 4 gms.

Children

10 mg/kg, every 4-6 hours.

Routes of Administration Oral, Parenteral (I.M.). Never I.V.

Contraindications

Patients who are hypersensitive to paracetamol.

Precautions / Practice points

- Use with great caution in patients with hepatic dysfunction and in alcoholics.
- It is preferable to aspirin in the following patient groups:

  Patients with acid peptic disease.

  Patients with bleeding disorders and haemophiliacs.

  Children with viral infections.

  Patients in whom bronchospasm is precipitated by aspirin.

  Infants less than 6 months of age..
- Safe in pregnancy and lactation.
- Administration instructions:

Administration with food.

Do not give intravenously.

Instruct patients not to drink alcohol.

Drug Interactions

No fatal interactions have been reported.

- Rifampicin may reduce the efficancy of paracetamol.
- Paracetamol increases the serum levels of chloramphenicol when administered together.
- Paracetamol may potentiate the toxicity of zidovudine and warfarin sodium.

Adverse Effects:

Rare in usual doses. There may be:

- Hypersensitivity to the drug – urticaria, dyspnoea, hypotension, angioedema, fixed drug eruptions.
- Elevation of liver enzymes and hepatic dysfunction in large doses (more than 5 to 8 gms, over several weeks).
- Interstitial nephritis, papillary necrosis when used in combination with other analgesics.
- Haemolytic anemia, methaemoglobinemia, thrombocytopenia, leucopenia may occur.

Drug Toxicity

- Toxic doses for adults : More than 10-15 gm or more than 20 tablets.
- For children more than 150 mg/kg.
- Initially causes dizziness, disorientation, abdominal pain, nausea, vomiting, diaphoresis, general malaise. Later, fatal hepatic necrosis, renal tubular necrosis and coma may occur.

Treatment of Toxicity

- Gastric lavage.
- Emetics to induce vomiting to decrease absorption.
- Antidote:
- N-acetylcysteine (when overdose of paracetamol is more than 150 mg/kg).

  Initial bolus dose of 150 mg/kg in 5% dextrose given over 15-60 min.

  Maintenance dose is 50 mg/kg every 4 hours.

  Monitor serum levels of enzymes of liver function - SGOT, SGPT, etc.

Storage

- Store in airtight container.
- Protect from light.
- Cool dry place.

Shelf Life 2 years.

IBUPROFEN

General Information

Drug Code	Preparation	Strength
114	Tab. Ibuprofen	200 mg-100 Tabs.
255	Tab. Ibuprofen	400 mg

Description of the Drug

Ibuprofen is a non-steriodal anti-inflamatory agent of the propionic acid group,

possessing anti-inflammatory, analgesic and antipyretic activity.

Mode of Action

It is a reversible inhibitor of the cyclo-oxygenase enzyme. Thus, it inhibits the synthesis of prostaglandins, and not that of leukotrienes.

Pharmacokinetics

It is readily absorbed from the GIT. It is extensively bound to plasma proteins and is excreted in the urine mainly as metabolites and their conjugates. Onset of analgesia is 30-60 min after ingestion. Duration of action is 6-8 hours.

Clinical Information

Indications

- Short term analgesia in minor aches and pain due to colds, flu, sore throat, headache, dental pain, dysmenorrhoea etc.
- For relief of pain and inflammation, osteo arthritis and other chronic inflammatory disorders.

Dosage

For short term analgesic effects:

Adults - 400 mg 4-6 hours.

Children - 10mg/kg – 8 hourly – 6-12 years.

For chronic inflammatory disorders:

Adult - 1.2 – 1.8 gm in 4 divided doses upto a maximum of 2.4 gm/day.

Children - 20-40 mg/kg in 3, 4 divided doses.

Individualization of dose is necessary, starting from lower most dose possible, gradually increasing till clinical response is satisfactory.

Routes of Administration Oral, Parenteral (I.M.). Never I.V.

Contraindications

- Contraindicated in pregnancy and children less than 6 months.
- Do not administer in case of active gastro-duodenal ulcer disease or liver failure.
- Individuals in whom angioedenia and bronchospasm have been precipated by NSAIDS like aspirin.

Precautions / Practice points

- Use with caution in elderly. Avoid in children less than 7 kg, in bleeding disorders and patients on oral anticoagulants.
- Use with caution in hepatic dysfunction and congestive cardiac failure.
- In renal impairment, ibuprofen can reduce renal blood flow (by inhibition of prostaglandin mediated renal vaso dilation) and can precipitate renal failure.
- On long term therapy, monitor hepatic and renal parameters and signs of gastro-intestinal bleeding.

Drug Interactions

Potentially fatal:

- Increases the effects of oral anticoagulants and risk of bleeding episodes.
- Increases the toxicity of methotrexate, lithium and digoxin by reducing their

excretion.

Non fatal:

- Antagonises hypotensive action of ACE inhibitors and increases risk of renal damage when used together.
- Increases renal toxicity of cyclosporin.

Adverse Effects

Common effects:

- GIT – abdominal discomfort, nausea, vomiting, abdominal pain or activation of peptic ulcer.

Rare effects:

- Dizziness, headache, tinnitus, depression.
- Hypersensitivity reactions – fever and rashes, Steven-Johnson's syndrome, toxic epidermonecrolysis may occur.
- Fluid retention and hepatotoxicity.
- Haematological – agranulocytosis, aplastic anaemia, haemolytic anaemia,reversible, inhibition of platelet aggregation.

Drug Toxicity

Toxic doses - more than 200 mg/kg. Abdominal pain, nausea, vomiting, drowsiness, CVS toxicity like hypotension, arrhythmias and bradycardia. May progress to metabolic acidosis, apnoea and acute renal failure and coma.

Treatment of Toxicity

- Gastric lavage and emesis, if ingested within half an hour, administration of activated charcoal for prevention, of absorption.

- symptomatic and supportive line of management – treat GI bleed, hypotension and metabolic acidosis if present.

Storage

Store in cool dry place.

Shelf Life 3 years.

PETHIDINE

General Information

Drug Code	Preparation	Strength
156	Inj.Pethidine HCI	50 mg/ml.

Description of the Drug

Pethidine is a opioid analgesic with some antimuscarinic effects.

Mode of Action

Similar to morphine, pethidine acts on the opioid receptors to cause analgesia and sedation. Besides, it also acts as an antagonist at the cholinergic rocepton to produce atropine like effects.

Pharmacokinetics

After IM adminstration, onset of action is within 10-15 min; given intravenously, onset of action is within 5 minutes. Duration of effects is 3-4 hours. Metabolized in the liver to active metabolites and excreted in urine. It crosses the placenta and

appears in breastmilk.

Clinical Information

Indications

- Used in pre operative medication as an adjuvant to anaesthesia – for sedative and anxiolytic effects.
- Relief of moderate to severe pain of any cause.
- Obstetrical analgesia.

Dosage

- As an analgesic : 25 –100 mg, 4th hourly, dose to be adjusted according to requirements
- For preoperative medication: 50-100 mg, 30-90 minutes before surgery.
- Obstetric analgesia: 50-100 mg, as soon as pain starts, repeated at 1-3 hourly intervals, upto a maximum of 400 mg/day.

Routes of Administration - IM, IV, SC.

Contraindications

- In patients receiving MAO inhibiton presently or within the past 2 weeks.
- In acute alcoholism, head injuries, states of preexisting CNS depression and conditions in which increased intracranial tension occurs.
- Hypersensitivity.
- Severe renal failure.

Precautions / Practice points

- Should be given cautiously to patients with supraventricular tachycardia or with history of convulsive disorders.
- Being an opioid, the drug has an abuse potential and can be addictive.
- Use with caution in conditions like bronchial asthma, COPD, states with reduced respiratory reserve, because it is a respiratory depressant.
- Instruct patients not to drive or operate machinery as it cause sedation and drowsiness.
- Can cause respiratory depression in newborn. Judicious use is necessary in obstetrical analgesia.
- Not suitable for chronic use as, cumulative toxicity with its active metabolite (non pethidine) could result.
- Adminstration Instruction:

Incompatible with aminophylline, barbiturates, heparin, phenytoin and sodium bicarbonate and should not be mixed or given in the same syringes.

IM adminstration is preferred. If given intravenously, a solution of concentration 10 mg/ml should be used and given very slowly. Rapid IV adminstration may result in hypotension, apnoea and collapse.

Drug Interactions

Potentially fatal:

- Very severe reactions including coma, severe respiratory depression, cyanosis and hypotension similar to narcotic overdose have occurred in patients receiving MAO inhibitors and pethidine concomitantly. Hence, patients should not be given this drug

when they are receivig MAO inhibitors or within 14 days of discontinuation of the drug.

Non fatal:

- Concurrent administration of pethidine with phenothiaziness and tricyclic antidepressants potentiates the effect of pethidine and dose is to be reduced by 50-25%.
- Barbiturates, sedative hypnotics, opioids, alcohols, tricyclic antidepressants given along with pethidine may cause excessive CNS depression.
- Hepatic metabolism of pethidine is enhanced by phenytoin which therefore reduces analgesic effects of pethidine.

Adverse Effects

Common effects:

- Local pain at injection site.
- Sedation, nausea, lightheadedness, vomitting.

Rare effects:

- CNS effects - euphoria, mood changes, agitation, tremor, muscle twitching, disorientation, hallucination.
- Dependency and drug abuse.
- CVS – tachycardia, hypertension.
- Constipation.

Drug Toxicity

Respiratory depression, apnoea, mydriasis (unlike other opoids), extreme somnolence, muscle flaccidity, cold extremities, cold clammy skin, hypotension, cardiovascular depression like bradycardia, stupor, coma and death.

Treatment of Toxicity

- Maintenance of airway, supportive ventilation, oxygen, IV fluids and vasopressors for maintenance of blood pressure.
- Antidote : Nalozone can be given.

Storage

Protect from light.

Shelf Life 2 years.

PENTAZOCINE LACTATE

General Information

Drug Code	Preparation	Strength
157	Inj.Pentazocine lactate	30 mg/ml.

Description of the Drug

Pentazocine is a benzomorphane derivative. It is an opioid analgesic.

Mode of Action

The drug has mixed activity. I.e. both agonist and antagonist actions. Agonist activity is thought to be predominantly at kappa receptors. It acts as a weak antagonist or partial agonist at Mu receptors in the CNS, acting as a CNS depressant.

Pharmacokinetics

When administered IM or SC, onset of analgesic action is 15 minutes after adminstration. After IV injection, onset of action is 2-3 min. Duration of action is 2-3 hours. Pentazocine undergoes metabolism in the liver, to glucoronide conjugates and is excreted in the bile. Small amounts are excreted in the urine.

Clinical Information

Indications

Relief of moderate to severe pain, in postoperative period in bony metastates in cancer patients etc.,

Dosage

Adults:

30-60 mg every 4-6 hours.

Children:

500 mcg/kg upto 1 mg/kg/dose.

Routes of Administration IM, IV, SC.

Contraindications

- In the post myocardial infarction period as it increases cardiac work load.
- In acute alcoholism, head injuries and conditions in which increased intra cranial pressure occurs. (Pentazocine causes respiratory depression and carbondioxide retention, increasing CSF pressure).
- Patients hypersensitive to pentazocine.

Precautions / Practice points

- Use with caution in bronchial asthma, chronic lung diseases, where respiratory reserve is decreased because of its respiratory depressant effects.
- Avoid antihupertensives and cardiac disorders, in patients with heart failure as it causes rise in B.P. and causes tachycardia.
- For dose adjustments in liver and kidney failure see appendix.
- Use with caution after biliary surgery, since opioids increase biliary tract pressure by constriction of sphincter of oddi.
- Warn chronic users not to drive or operate machinery.
- Administration Instructions:

Pentazocine is incompatible with aminophylline, barbiturates and heparin and should not be mixed or given in the same heparin and should not be mixed or given in the same syringe.

Drug Interactions

Non fatal:

- Weakly antagonizes the effects of other opiod analgesics.
- Therefore, addicts and patients on other opioid analgesics may have withdrawal symptoms.
- Produces incomplete reversal of CVS and respiratory system depression induced by morphine.
- Alcohol and other CNS depressants may cause excessive CNS depression.

Adverse Effects

Common effects:

- Drowsiness, light headedness or euphoria.
- Nausea, vomiting.

Rare effects:

- Visual hallucinations, dizziness, disorientation, confusion, headache, visual blurring, nightmares.
- Palpitations, hypotension.
- Drug abuse.

Drug Toxicity

Drowsiness, sedation, respiratory depression and coma.

Treatment of Toxicity

- Monitoring of CVS, respiratory status, supportive ventilation. Naloxone hydrochloride is given as specific antidote in the dose of 0.4-2 mg by IV. Repeated at the intervals of 2-3 minutes, upto a total of 10 mg.

Storage

Protect from sunlight.

Shelf Life 4 years.

DICLOFENAC SODIUM

General Information

Drug Code	Preparation	Strength
251	Tab. Diclofenac Sodium	SR 100 mg/ml.
252	Tab. Diclofenac Sodium	50 mg/ml.
495	Inj. Diclofenac Sodium	25 mg/ml – 3 ml Amp.

Description of the Drug

Diclofenac is a non-steroidal anti-inflammatory agent with anti-inflammatory, antipyretic activities used for a variety of painful and inflammatory conditions.

Mode of Action

It is a cyclo-oxygenase inhibitor. Its anti-inflammatory property is due to decreased prostaglandin synthesis in the tissues.

Pharmacokinetics

On oral administration, completely absorbed in a fasting state. It is subject to first-pass metabolism and only 50% is bioavailable. Onset of action is 10 minutes. Duration is 8 hours. It penetrates the synovial fluid and is detected in breast milk. Excreted in the form of glucoronide and sulphate conjugates, mainly in the urine but also in the bile.

Clinical Information

Indications

Acute or short term analgesia :

Postoperative analgesia.

Abdominal and renal colic.

Dental extraction.

Dysmenorrhoea, abdominal and renal colic.

In localized soft-tissue inflammatory lesions following trauma to tendons, ligaments, muscles and joints, acute attacks of gout.

Long term use in musculo skeletal disorders like rheumatoid arthritis, juvenile rheumatoid arthritis, osteo arthritis, ankylosing spondylitis.

Dosage

Adults: usual : 50 mg 2-3 times a day.

For dysmenorrhoea : 100 mg initially followed by 50 mg after 8 hours if required.

For chronic inflammatory disorders : 150-200 mg in 2,3 divided doses or 100 mg/day of SR **Preparation**.

Children:

Orally : 1-3 mg/kg body WEIGHT/day in divided doses.

Parenteral

I.M. : 75 mg once or twice daily depending on requirements.

Routes of Administration IM, IV, SC.

Contraindications

- Active peptic ulcer.
- Bleeding disorders and patients on anticoagulant, therapy.
- History of hypersensitivity reactions to other NSAIDS.
- Porphyria.

Precautions / Practice points

- Warn chronic users about symptoms of liver toxicity like nausea, fatigue, lethargy, pruritis, right hypochondrial pain, flu like symptoms.
- Use with caution in patients with compromised renal, hepatic orcardiacfailure; renal failure can be precipitated Due to reduction of renal blood flow.
- Monitor blood counts, hepatic and renal parameters periodically in patients on long term therapy.
- Administration Instructions:

Take with food to reduce GI effects.

Drug Interactions

Potentially fatal:

- Oral anticoagulants, corticosteriods, other NSAID's like aspirin increases the risk of peptic ulcer bleeding.
- Lithium, digoxin and methotrexate blood levels will be raised when given with diclofenac. Therefore, diclofenac increases risk of toxicity due to these drugs.
- Increases nephrotoxicity of cyclosporin. If used together, halve the dose of

diclofenac.

Non fatal:

- May decrease effects of thiazide and furosemide.

Adverse Effects

Common effects:

- Epigastric pain, bleeding from ulcers and perforation. Old debilitated patients, smokers, alcoholic patients are especially at risk for GI side effects.

Rare effects:

- Hepatic enzymes like SGOT, SGPT may be elevated, especially in chronic users, rarely acute fulminant hepatitis can occur. Therefore, periodic monitoring of liver function tests to be done in chronic users.
- Fluid retention and edema.
- Precipitation of asthmatic attacks in susceptible individuals.
- Haematological – anaemia due to either gastro-intestinal bleeding or fluid retention, inhibition of platelet aggregation, increase in bleeding time.
- Rashes, pruritis, bullous dermatitis and erythema multiforme.

Drug Toxicity

Drowsiness, CNS depression and acute renal failure.

Treatment of Toxicity

- Reduce absorption by vomiting, lavage, activated charcoal.

- Forced diuresis.

- Symptomatic treatment – monitor electrolyte and fluid balance.

Storage

Store in a cool, dry, dark place.

Shelf Life 3 years.

INDOMETHACIN

General Information

Drug Code	**Preparation**	**Strength**
254	Cap. Indomethacin	25 mg.

Description of the Drug

Indomethacin is an NSAID with anti-inflammatory, antipyretic, analgesic properties.

Mode of Action

It is a highly potent inhibitor of prostaglandin synthesis in peripheral tissues. Apart from its anti-inflammatory **Indications**, it may be used in medical closure of P.D.A.(as an I.V. Preparation).

Pharmacokinetics

Well absorbed orally. Onset of action is 30 min after ingestion. Duration of effects is for 4-6 hrs. Metabolized in the liver and excreted in the urine as gluconoride conjugates.

Clinical Information

Indications

Short term use:

- Acute gouty arthritis.
- Musculoskeletal injuries, bursitis etc.,

Long term use:

- Anti-inflammatory agent in musculoskeletal disorders like rheumatoid arthritis, ankylosing spondylitis and osteo arthritis.

Dosage

Adult

- For musculoskeletal disorders: 25-30 mg two or three times daily,upto 150-200 mg daily.
- In acute gouty arthritis: 50 mg thrice daily.

Children

- Not recommended.

Routes of Administration IM, IV, SC.

Contraindications

- Patients hypersensitive to other NSAIDS and asthmatics, in whom bronchospasm may be precipitated.
- Patients with acid peptic disease – either active disease or with previous history.

- Third trimester of pregnancy – may cause premature closure of PDA.
- Impaired renal function.
- Bleeding disorders and patients on anticoagulants.

Precautions / Practice points

- Avoid in children – risk of side effects such as hepatotoxicity are higher; if used, liver function tests must be monitored frequently.
- May cause fluid retention, hence, use with caution in congestive cardiac failure.
- Use with caution in elderly – a reduction of dose is advised.
- Administration Instructions:
  - Take with food.

Drug Interactions

Potentially fatal:

- May cause major bleeding episodes if given with anticoagulants.
- Increases the serum levels of the drugs like lithium, methotrexate, digoxin and

  May precipitate their toxic side effects.

Non fatal:

- Concurrent administration of other NSAIDS increases GI and renal toxicity.
- It blunts the diuretic action of furosemide and thiazides.
- It decreases the antihypertensive effects of thiazides, furosemide, beta blockers and

ACE inhibitors.

- Increases nephrotoxicity of cyclosporin.

Adverse Effects

Common effects:

- Gastro intestinal disturbance – initially dyspepsia, nausea, etc, may progress to marked gastric irritation, gastric bleeding and diarrhoea, ulcers, perforation of ulcers may occur.

Rare effects:

- Headache, dizziness, vertigo, somnolence, depression, psychiatric disturbances.
- Hypersensitivity reactions – bronchospasm, urticaria, skin eruptions, Steven Johnson's syndrome.
- Fluid retention and edema.
- Ocular – retinal, macular and corneal deposits, with blurring of vision.
- Thrombocytopenia.

Drug Toxicity

Nausea, vomiting, intense heachache, confusion, tinnitus, disorientation, renal failure, GI bleeding, rarely paraesthesia and convulsions.

Treatment of Toxicity

- Gastric lavage and emesis, activated charcoal.
- Symptomatic treatment – under close medical supervision.

Diazepam to manage convulsions.

Storage

Store in airtight containers. Protect from light.

Shelf Life 3 years.

4. CONCLUSION:

Thus, I conclude that we all know the pharmacological treatment aspects used in various systems in our body. From this seminar we have learnt about medications and why, how, when and where they are used in daily life.

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