PHARMACOLOGY-III

UNIT 5 NOTES

TOXICOLOGY

- DEFINITION
- GENOTOXICITY & CARCINOGENECITY
- TREATMENT OF POISONING
- CLINICAL SYMPTOMS

CHRONOPHARMACOLOGY

- DEFINITION OF RYTHMS
- BIOLOGICAL CLOCK

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Principles Of Toxicology

Toxicology

- Toxicology word derived from the latin and Greek word toxicum meaning poison.
- Toxicology is the study of harmful or Adverse effects that chemicals, substances or agents can have on living things including humans, animals and plants.
- Paracelsus (1493 - 1541) and Mathieu Joseph Bonaventure Orfila (1787-1853) both are considered as to be fathers of mordern Toxicology.
- Toxicology help us to understand how these substances can make us sick or cause damage to our health and it plays an important role in keeping us safe from poisons and harmful chemicals.

Principles Of Toxicology

- Dose - response relationship.
- How toxins enters into body.
- The potential of a substance to cause damage.
- Toxins can work together to cause greater harm.

Toxicity

- Toxicity is the ability of a substance of cause harm or damage to living things, like humans, animals or plants.
- It depends on how much of the substance is present, how long someone is exposed to it, and how sensitivity they are to it.

- A substance can be toxic if it causes sickness, injury or even death when it enters in the body in certain amounts or over time.
- For examples - Chemicals, certain foods or medicines can be toxic if used incorrectly or in large amounts.

Types Of Toxicity

① Acute Toxicity

- Acute toxicity refers to the harmful or Adverse effects that happen shortly after exposure to a toxic substance, usually within 24 hrs to days.
- It's kind of toxicity that causes immediate or sudden damage to the body.

Causes

- It happens when someone is take or contact with harmful substances in a large amount, like breathing in toxic chemicals.

Symptoms

- They can include symptoms like nausea, dizziness, troubling in breathing, vomitting or even loss of conciousness or death etc.

Examples

- Mercury poisoning, Overdose of medicine or drugs etc.

Treatment

- It requires immediately medical attention to remove the harmful substances from body or treat the symptoms quickly.

② Sub - Acute Toxicity

- Sub acute toxicity refers to harmful effects or Adverse effects that occurs from a toxic substance within 30 days or more.
- It develops more slowly but still causes damage to body over time.

Cause

- It happens when you are exposed to a harmful substance more than once, but not for a long - time.

Symptoms

- Its symptoms may not appear immediately but over time they are noticeable.
- These effects can include symptoms like headache, fatigue, skin irritation, nausea or stomach problems.

Treatment

- Medical treatment may include helping the body recovery or removing the toxins.

③ Chronic Toxicity

- Chronic toxicity refers to adverse effects from long - term contact with toxic substances, usually within more than 90 days to years.
- It develops slowly - slowly and can lead to lasting health problems.

Causes

- It occurs when a person is repeateadly contact with harmful substances over a long term (1 year).
- It could be from breathing in polluted air, working with dangerous chemicals or taking harmful substances for long - time.

Symptoms

- It's symptoms can take a long while to show. Thes symptoms can range from mild to severe and includes :
- Fatigue
- Headache
- Breathing problems
- Cancer
- Nerve damage etc.

Examples

- Smoking, Long - term contact with chemicals like **asbestos**, Heavy metals like **lead** or **mercury** can harm the brain or kidneys over time.

Treatment

- Chronic toxicity is harder to treat because the damage has already occured over time.
- Treatment focused on managing symptoms, stopping contact to harmful substances and helping the body heal as much as possible.

GENOTOXICITY

- Genotoxicity is the ability of a substance to damage the genetic material (DNA) in living cells.
- If this material gets damage, it can lead to changes or mutations in DNA.

MECHANISM OF GENOTOXICITY

Genotoxic agents enters into body
(like radiation, chemicals or viruses)

↓

They can directly damaged the DNA by:

- Breaking the DNA stands
- Changing the DNA bases
- Creating cross-links b/w DNA stands

↓

Cell are failed to repair DNA damage.

↓

Causing mutations (Permanent changes in DNA)

↓

Cell may die, cell become cancerous or damage may pass to the next generation

↓

Genotoxicity caused

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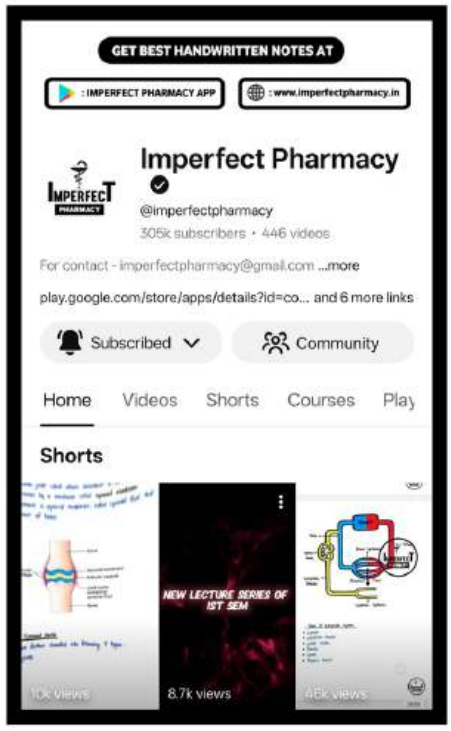

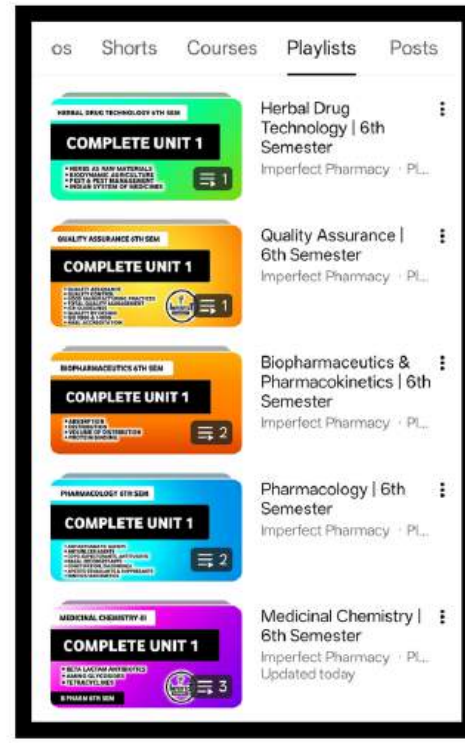

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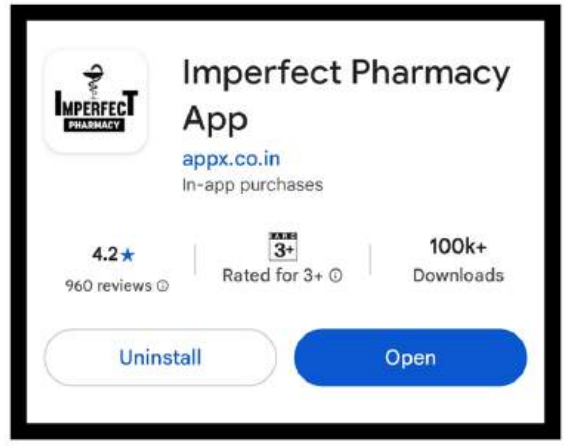

TREATMENT

- **antioxidants** - Vitamin C , Vitamin E , N- acetylcystiene , Selenium- help reduce oxidative stress and DNA damage.
- **Cytoprotective agents**- Amifostine (used during chemotherapy or radiation).
- **DNA repair enhancers**- Experimental use of agents promoting DNA repair (e.g. Resveratol, Polyphenols)
- **Lifestyle modification**-
  - Diet with rich antioxidants fruits & vegetables.
  - Avoid smoking , Alcohols or toxins.
  - Maintain a healthy weight and regular physical activity.

RISK FACTORS

- Chemicals
- Radiation
- Genetics
- Age
- Smoking
- Alcohol
- Immune deficiency etc.

CARCINOGENICITY

- Carcinogenicity is the ability of a substance or exposure to cause cancer in living cells.
- Cancer happens when cells in the body grow out of control.
- A carcinogen is anything that can increase the risk of getting cancer.

MECHANISM OF CARCINOGENICITY

Exposure to carcinogen (cancer causing agents)
(like tobbacoo, smoke, chemicals, radiations)

↓

They damage the cell (DNA) and cause mutations.

↓

Mutation changes affects Oncogens & Tumor suppress genes, and cell may dividing too much.

↓

Uncontrolled cell growth forming tumor

↓

Cancerous cells avoid immune system, don't die and keep growing

↓

Spread of cancer and travel to other body parts (Metastasis)

↓

Cancer occurs

Risk Factors

- Immunosuppression
- Genetics
- Smoking
- Alcohol
- Pollution
- Asbestos etc.

Management Of Carcinogenicity

- Use antineoplastic agents to treat or manage the cancer.
- Avoid smoking, Alcohol etc.
- Balanced diet rich in antioxidants.
- Vaccination like HPV vaccine (cervical vaccine) and Hepatitis B vaccine (liver cancer).
- Surgery, Radiotherapy, chemotherapy, Target therapy, Immunotherapy.

TERATOGENICITY

- A teratogen is that can disturb the normal growth and development of a baby while the baby still in the womb.
- If a pregnant woman is contacted with teratogen - especially in early stages of pregnancy, it can affect the baby's organ, limbs, brain or body parts develop.
- Teratogenicity is the ability of a substance to cause birth defects or problems in the development of baby during pregnancy.

MECHANISM

Teratogen enters into pregnant woman

↓

Reaching and crossing the Placenta barrier

↓

Interfare in development of baby in womb

↓

Cause birth defects

- Brain or Neoves defects
- Growth delays or miscarriage
- Physical defects etc.

RISK FACTORS

- Alcohol
- Hyperthermia
- Hypoxia
- Obesity
- Smoking
- Radiations etc.

TREATMENT

- Folic Acid - Prevent neural tube defects.
- Levothyroxine - Prevent fetal brain damage.
- Iodine - Prevent mental retardation.
- Dexamethasone - Used to treat fetal adrenal hyperlapsia (CAH)
- Antioxidants
- Antivirals etc.

MUTAGENICITY

- Mutagenicity is the ability of a substance to cause mutations in the DNA of living cells.
- DNA is like the instruction manual for how your body works.
- Mutations can affects cell growth, division or functions or they can cause serious problems.
- Mutagenicity is like genotoxicity.

MECHANISM

Mutagens enters into person's body

↓

Mutagens reaches to cells and interact with DNA

↓

DNA repair or copying system fails & damage DNA incorrectly

↓

Cause Mutation (Mutagenicity)

RISK FACTORS

- Radiation
- Smoking
- Pollutions
- Toxins
- Pesticides
- UV & X-Rays
- Alcohol etc.

MANAGEMENT / TREATMENT

- Use antioxidants, DNA repair enhancers, Cytoprotective agents, folate & B12, supplements as pharmacological management.
- Avoid smoking, alcohol and processed foods.
- High antioxidant diets like fouits, vegetables, whole grains.
- Regular exercise to reduce oxidation stress and improves DNA repair mechanisms.

General Principle Of Treatment Of Poisoning

Poison

- Poison is any substance that can cause harm, injury, illness or death to a living organism when introduced into the body in relatively small quantities by chemical action.
- Poisons can affects normal body functions by interfaring with biological processes at the molecular, cellular or organ level.
- Poison can be in various forms, including solids, liquids or gases and they may have a variety of chemical compositions and mechanism of action.

Classification Of Poison

Categories	Types	Examples
Corossives	i) Strong Acids ii) Strong Alkalis	i) H_2SO_4, HNO_3, HCl ii) Caustic Soda, Caustic Potash
Irritants	i) Inorganic a) Non-metallic b) Metal ii) Organic a) Herbal b) Animal iii) Mechanical	i) Inorganic a) P, Cl, Br, I b) Heavy metals (As, Sb, Pb etc.) ii) Organic a) Castor seeds, Croton oil etc. b) Snake venoms, cathartics etc. iii) Diamond dust, Glass powder

Categories	Types	Examples
Neurotics	i) Cerebral a) Sleep causing (Narcotics) opium & its derivatives b) Intoxicants c) Anaesthetics d) Deliriant ii) Acting on spinal cord iii) Acting on cardiac system iv) Poisons acting peripherally	i) Cerebral a) Morphine b) Alcohol c) Ether, $CHCl_3$ d) Dhatura, Belladona ii) Nux vomica iii) Digitals, Aconite Tobbacco iv) CO_2, CO, Coal gas

MECHANISM OF POISONING

- Poisoning happens when a harmful substances enters the body & interfare with normal body functions.

Poisons enters in the body
(through orally, inhalation, skin contact, injection)

↓

Poison absorbed & spread by blood and travels to different parts of body

↓

They interfare with body systems :
- Block enzymes
- Damage organs
- Distrupt nervous system etc.

↓

Symptoms occurs mild to severe headache, siezures, coma or death

↓

Body response to excrete out poison by vomiting, sweating, detoxifying in the liver and after sometimes it needs medical help to remove poison.

TREATMENT OF POISONING

① Identify the poison -
- Try to find out what caused the poisoning (medicine, chemical, gas, spoiled food etc.).
- Note the name, amount and how it was taken (swallowed, inhaled, skin contact etc.).

② Remove the poison -
- From the mouth - wipe it or rinse it safe.
- From skin - wash with plenty of water.
- From eyes - Rinse eyes gently with clean water for 15-20 minutes.
- From air - Move the person away from toxic fumes or gases.

③ Proper Ventilation -
- If the poison was inhaled, take the person to fresh air immediately.
- Open windows and doors for airflow.

④ Suppression of convulsion (siezures) -
- If siezures happen, keep the person safe and lying on their side.
- Don't put anything in their mouth.
- Medical help may be needed to give anti-siezures medicine.

⑤ Fluid & Electrolyte therapy -
- If the person is dehydrated or imbalanced body salts due to vomitting or diarrhea, fluids may be given through IV drip in hospital.

⑥ Prevention of further absorption of poison -
- Activated charcoal may be given to absorb poison in the stomach.
- In some cases, the stomach may be washed (gastric lavage).

⑦ Supportive and Symptomatic Care -
- Breathing support (oxygen or ventilator if needed).
- Treat symptoms like low blood pressure, heart problems, or confusion.

Specific Antidotes, Indication, Mechanism Of Action

Antidote	Indication (Poison)	Mechanism Of Action
N-acetycytiene	Acetamenophen overdose	Replenishes gluthiaone stores.
Naloxone	Opioid overdose	Competitive opioid receptor antagonists (mu-receptor)
Atropine	Organophasphate or Carbamate poisoning	Block Muscuranic receptors
Pralidoxime (2-PAM)	Organophasphate poisoning (with atropine)	Reactivates acetycholinesterase by cleaving phosphate-enzyme bond
Flumazenil	Benzodiazepene overdose	Competitive GABA-A receptor antagonists
Ethanol/ Fomepizole	Methanol or ethylene glycol poisoning	Inhibits alcohol dehydrogyrase to prevent formation of toxic metabolites
Deferoxamine	Iron overdose	Chelates free iron to form a complex excreted in urine
Dimercaprol (BAL)	Arsenic, Mercury, Gold poisoning	Chelating agents that binds heavy metals, forming stable, excretable complexes
Succimer (DMSA)	Lead, Arsenic, Mercury poisoning (esp. in children)	Oral chelator that binds heavy metal for renal excretion
Sodium thiosul-fate	Cyanid poisoning (adjunct)	Convert cyanide to thiocyanate, which is renally excreted.

Clinical Symptoms And Management Of:

Barbiturates Poisoning

- Barbiturates poisoning occurs when a person consumes a toxic doses or high doses of barbiturates, which are CNS depressants.
- Taking too much dose of barbiturates can slow down the brain and body, which can be very dangerous, it can cause addiction and leads to coma or death.

Mechanism Of Action

Consume high dose of barbiturates

↓

They effect on GABA receptors and calms the brain but overdose can over-slow the brain

↓

Depression of body systems:

- Slow or stop breathing
- Heart Rate ↓
- Body Temperature ↓
- Reflexes weaken

↓

Loss of conciousness or fall into coma

↓

Without treatment it leads to death.

Clinical Symptoms

- Nervous system - Feeling very sleepy and drowsy
  Confusion or unconciousness
  weak or no reflexes
  Poor - coordination (Ataxia)
  Slurred speech etc.
- Cardiovascular - Hypotension
  Bradycardia
  Shock in severe cases etc.
- Skin - Blisters, Hypothalmia etc.
- Respiratory - Respiratory depression → Apnea etc.
- Other symptoms - Prolonged sedation, Hypothermia, Hypoflexia etc.

Management

- ABCs - Ensure airway, Breathing, Circulation are stable.
- Activated Charcoal - Give, if within 1-2 hours of igenstion and airway protected.
- Urinary Alkalinization - Enhance renal elimination by making urine more alkaline (use Na_2CO_3).
- Hemodialysis - In severe cases or when dry levels are high.
- Supportive care - IV fluids for hypotension, mechanical ventilation if needed.

Morphine Poisoning

- Morphine poisoning happens when someone takes too much morphine, a strong painkiller.
- Morphine is an opioid and too much dose can slow down the brain, breathing and heart, which can be more dangerous and even deadly.

Mechanism of Action

- High dose taken ⟶ Attached with opioid receptors, cause brain to slow down too much when taking high dose ⟶ Leading to slow, shallow or stopped breathing ⟶ Person becomes very sleepy and can fall into coma ⟶ Low Heart Rate and Low Blood pressure ⟶ Person can die due to lack of O_2 into body.

Clinical Symptoms

- CNS - Drowsiness, Coma, Pinpoint pupils, Siezures etc.
- Respiratory - Respiratory depression (slow-shallow breathing), apnea etc.
- Cardiovascular - Bradycardia, Hypotension, shock (in severe case).
- GIT - Nausea, vomiting, constipation etc.
- Skin - Flushing, Pruritis, Cyanosis (in severe case) etc.

MANAGEMENT

- ABCs - Proper airway, support breathing, stable circulation
- BP maintainence- Can be achieved by providing IV fluids and vasoconstrictions.
- Gastric lavage- Unabsorbed drug can removed by pottassium permaganate.
- Specific antidote- Naloxone – opioid antagonist → Reverses CNS and respiratory depression.

Organophosphorous Compound

- Organophosphorous poisoning happens when someone is contacted with organophosphate chemicals, a group of insectisides or pesticides and nerve agents that inhibit the enzyme acetycholinestearase (AChE).
- These chemicals and agents affects the nerves and cause overstimulation of nerves, which can be dangerous.

Mechanism Of Action

- Exposure to organophosphates ⟶ They block enzyme AChE ⟶ Too much acetycholine build up and cause nerves to keep firing again and again ⟶ Overstimulation of muscles and glands: Muscle twitching, cramps, weakness, tears, runny nose etc. ⟶ Siezures unconciousness and death (respiratory failure).

Clinical Symptoms

- Nervous System- Confusion, anxiety, siezures, Headache, dizziness, can lead to coma etc.
- SLUDGE Symptoms-
  - S Salivation
  - L Lacrimation (watery eyes)
  - U Urination
  - D Diarrhea
  - G GIT upset (Cramps, Nausea etc.)
  - E Emesis (vomiting)
- Other symptoms- Too sweating, Small pupils, Low Heart Rate, Breathing trouble, Muscle twitching etc.

MANAGEMENT

- **Decontamination** - Remove contaminated clothing
  Wash skin with soap and water
  Use gloves, masks etc.
- **Antidotes** - Atropine - block effects of excess acetylcholine and help in breathing and dries up body fluids.
  Pralidoxime (2-PAM) - help to restore normal nerve function.
  Diazepam - To control seizures effects/ CNS symptoms.
- **Supportive Care** - IV Fluids for hypotension.
  Mechanical ventilation if needed.
  Monitor ECG, electrolytes and respiratory status etc.

Lead Poisoning

- Lead poisoning happens when lead, a harmful metal build up the body over time or eating junk food or contaminated water.
- Lead is very dangerous especially for young children, because it can damage the brain, nerves and other organs.
- It usually comes from paint, dust, soil, water or old pipes etc.

Mechanism Of Action

- Lead enters in the body → Spread through blood and stored in bones, brain, liver and kidneys → Distrupts cells functions and cause anemia, harm brain, kidney damage, nerve damage → It leads to organ damage, coma, siezures and even death.

Clinical Symptoms

- Brain & Nerves - Headache
  Tiredness or weakness
  Irritability or Behaviour problems
  Trouble concentrating
  Coma or siezures (in severe cases)
- Body & Blood - Anemia, can cause pale skin
  Stomach pain, nausea, vomitting, constipation
  Loss of appetite and weight loss
- Other signs - Blue or dark line on the gums (in serious cases)
  Joint or muscle pain
  Delayed growth in children.

MANAGEMENT

- **Remove the source -** Identify and remove lead exposure.
- **Antidotes -** Dimercaprol (BAL) - severe poisoning.
  EDTA - moderate to severe poisoning.
  Succimer (DMSA) - Poisoning treating in children (orally chelation).
  Penicillamine - oral chelating
- **Supportive care -** Treat anemia
  Nutrition support
  Monitor neurological and development status.

Mercury Poisoning

- Mercury poisoning happens when a person is exposed too much mercury, a toxic metal.
- Mercury can be found in thermometers, old batteries, some fishes (like tuna) and certain factories or mining area.
- It can harm the brain, kidneys and other organs.
- It is highly toxic to nervous systems, kidneys and GI Tract and can cause the placenta, harmful fetal development.

Mechanism Of Action

- Mercury enters into the body ⟶ enter into blood and travels to organs like brain, nervous system and kidneys ⟶ Damage cell and enzymes and causing kidney damage, memory loss, tremors ⟶ Produce oxidative stress (free redicals that causes cell & tissue damge) ⟶ Cause long-term health problems.

Clinical Symptoms

① Acute mercury poisoning – usually from inhalation of mercury vapour or inorganic salts.

- Lungs: Cough, shortness of breath, pneumonitis
- GIT: Metallic taste, abdominal pain, vomiting, bloody diarrhea
- Kidneys: Acute renal failure
- CNS: Headache, tremors, irritability etc.

② Chronic Mercury Poisoning – Most often from organic mercury or vapour inhalation.

- CNS: Memory loss, tremors, insomnia, emotional stability
- PNS: Peretheasis, weakness
- Oral: Excessive salivation, gingivitis, stomatitis
- Skin: Rashes, peeling, discoloration
- Fetal exposure: Mental retardation, cerebral palsy, development delay (during pregnancy)

Management

- Remove the source: Stops exposure to mercury (leave the area, avoid contaminated fish or product)
- Medication: Doctors may given chelation therapy (Dimercaprol and succimmer), these help the body remove mercury through urine.
  - Penicillamine – Oral chelator (less commonly used due to side effects)
- Supportive care: Hydration to support renal exposure.
  - Dialysis in severe renal failure.
  - Monitor for neurological damage and long-term development effects.

Arsenic Poisoning

- Arsenic poisoning happens when a person swallows, breathes in or come into contact with too much arsenic.
- A naturally occuring heavy metal found in groundwater, pesticides, industrial processes and some traditional medicines.

Mechanism Of Action

Arsenic enters into body ⟶ It moves through bloodstream and reaches to cells all over body (especially skin, liver, lungs & kidneys) ⟶ Stops the function of enzymes and leads to organ failure, can't make enough energy ⟶ produce oxidative stress ⟶ It leads to nerve problems, stomach issues ⟶ Cancer or long-term exposure.

Clinical Symptoms

① Acute arsenic poisoning -

- GI: Severe abdominal pain, vomiting, nausea, dehydration
- CVS: Hypotension, Shock, Tachycardia
- CNS: Headache, Confusion, Siezures
- Renal: Acute kidney injury
- Hematologic: Hemolysis, Pancytopenia, Risk of arrythmias

② Chronic Arsenic Poisoning -

- Skin: Hyperpigmentation, hyperkeratosis
- Nervous system: Peripheral neurotherapy numbness, tingling, weakness
- Hematologic: Anemia, Leukopenia, Thrombocytopenia
- Cancer: Increased risk of lung, skin, bladder cancer
- Liver: Hepatomegaly, cirrhosis in long-term exposure.

MANAGEMENT

- **Remove the source :** Avoid source of arsenic (like contaminated water & food).
- **Medication (chelation therapy):** Dimercaprol - For acute to severe poisoning.
  Succimer - Oral chelator for acute to, chronic or mild poisoning.
  Chelation is most effective early in poisoning, especially within the first few days.
- **Supportive Care :** IV fluids for dehydration.
  Treat vomiting, diarrhea or shock.
  Monitor kidney & liver function.

CHRONOPHARMACOLOGY

- In 1960s, Chronopharmacology was first introduced by Halberg.
- Chronopharmacology is the study of how the effects of drugs changes according to the biological time or body rythms, especially the circadian rythm.
- Circadian Rythm is body's natural 24 hour cycle that controls many activities like:
  - Sleeping & waking up
  - Body Temperature
  - Hormone Levels
  - Heart Rate
  - Digestion

Aim / Objectives Of Chronopharmacology

- To study how biological rythms affect drug action.
- To determine best time to give a drug.
- To reduce side effects.
- To improve patient outcomes.
- To match drug action with body's natural clock.

Biological Rythms & Cycles

- Biological Rythms are natural, repeating patterns of activity in the body that occur at regular time intervals.
  These rythms help maintain body functions like sleep, hormone release, digestion & temperature regulation.
- Biological Cycles refer to the time period or duration over which these rythms repeat.

Types of Biological Rythms

① Circadian Rythm

- Duration : ~ 24 hours
- Controlled By : Suprachiasmatic nucleus (SCN) in the brain
- Examples :
  - Sleep - wake cycle.
  - Body temperature changes.
  - Hormone secretion (cortisol in morning, melatonin in night)
  - Blood pressure variation.

② Ultradian Rythm

- Duration : Less than 24 hours.
- Examples :
  - Heartbeat
  - Breathing rate
  - Digestion

③ Infradian Rythm

- Duration : More than 24 hours
- Examples :
  - Menstrual Cycle (28 days)
  - Seasonal Mood changes.

CLINICAL SIGNIFICANCE

Disruption of biological rythms can cause :

- Sleep Disorders
- Depression or Mood Changes
- Poor response to medicines

CHRONOTHERAPY

- Chronetherapy is the science of giving medications at specific times of the day to match the body's biological rythms. in order to increase effectiveness & reduce side effects.
- In simple words " It is the science of giving medicine at the right time according to the body's natural clock so it works better and causes fewer problems.

EXAMPLE

- Asthama Inhalers : Given at night (because asthama worsens at night).
- BP Medicines : Given in the morning (When BP usually rises)
- Statins (Cholesterol Drugs) : Given at night (When cholesterol is made more).
- Antiinflammatory Drugs : : Given Early Morning (Inflammation peaks in the morning)

IMPORTANCE OF CHRONOTHERAPY

- Our body does not work the same at all times of the day.
- Hormones, body temperature, enzyme levels, and blood pressure changes in a daily cycle.
- So, a medicine might work better at one time & worse at another.
- Chronetherapy uses this idea to give the right drug at right time.

THANK YOU

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