

MODULE-V

COURSE: B.PHARMACY

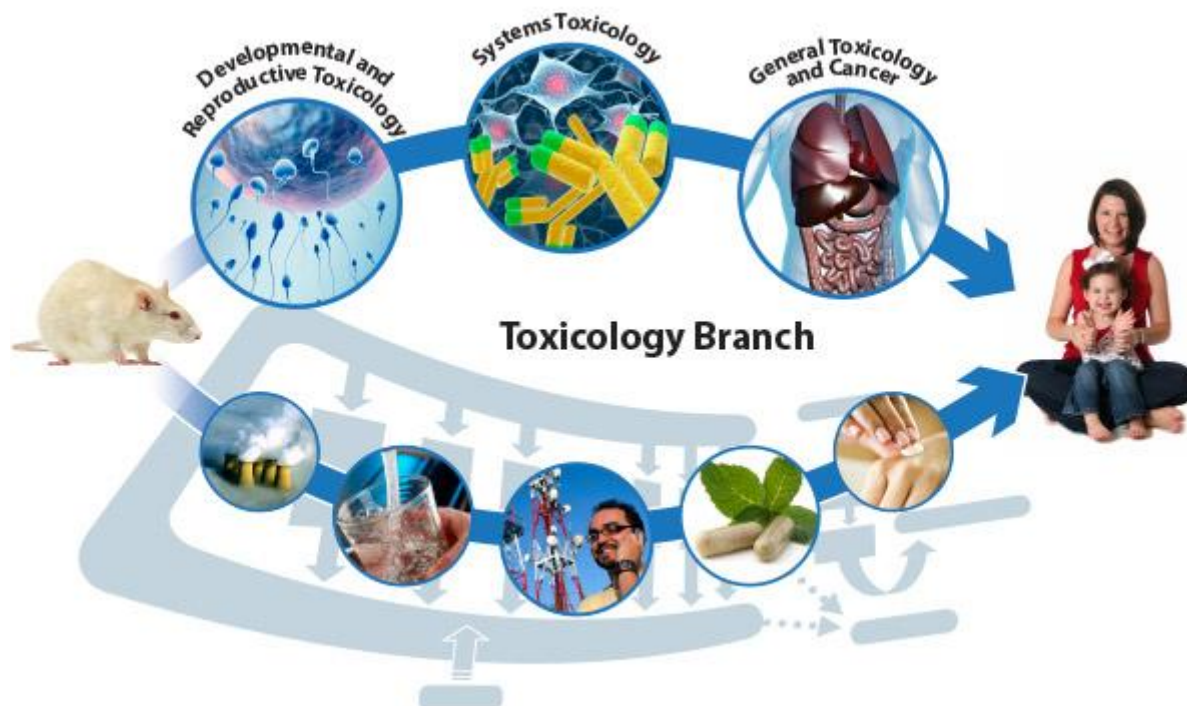
SEMESTER: 6TH

SUBJECT: PHARMACOLOGY-III

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✓ Principles of toxicology

- ✓ **Definition and basic knowledge of acute, subacute and chronic toxicity.**
- ✓ **Definition and basic knowledge of genotoxicity, carcinogenicity, teratogenicity and mutagenicity**



INTRODUCTION

Toxicity testing is paramount in the screening of newly developed drugs before it can be used on humans. Toxicity testing is the determination of potential hazards a test substance may likely produced and the characterization of its action, most of the toxicity testing is carried out on experimental animals. The advantages of using animal models in toxicity testing are enormous. These advantages include the possibility of clearly defined genetic constitution and their amenity to controlled exposure, controlled duration of exposure, and the possibility of detailed examination of all tissues following necropsy.. The information obtained can serves as the basis for hazard classification and labeling of chemicals in commerce[.The essence of toxicity testing is not just to check how safe a test substance is; but to characterize the possible toxic effects it can produce. Toxicity testing was given much attention following early 1960s thalidomide catastrophe; with thousands of children born worldwide with severe birth defects². After this incidence many countries of the world have resolved to go for toxicity testing and teratogenicity in both sexes so as to prevent further tragedies.

Importance of toxicity studies

- ☐ To establish a dose response curve.
- ☐ To ensure safety of new chemicals for use as pesticides, drugs, or food additives before they are registered for general use in industry or doctors clinics.
- ☐ To establish the mode of action or mechanism for a toxic effect that may have been seen in other studies.

- ☐ To produce epidemiological studies to explain observations in the population, for instance, the long investigation into the association of smoking with lung
- ☐ To validate new methods of testing or investigation, particularly those conducted in vitro rather than in animals.

The two basic principles guiding toxicity test in animals

- ☐ To check the effect of the test substances on laboratory animals and its direct toxic effect on human.
- ☐ Exposure of laboratory animals to high doses in order to evaluate its possible hazard on human that are exposed to much lower doses

Toxicity studies are divided into:

Acute toxicity studies

This is a short term assessment and evaluation of potential hazard test substance or consequences of single dose of a test substance. Acute toxicity testing may be used in risk assessments of chemicals for humans and non-target environmental organisms. Acute toxicity study is better described as LD₅₀, which is defined as the dose which kills 50% of animals. LD₅₀ is used for the estimation of the toxicity of the chemical agents. Acute toxicity provides guidelines on the dose to be use in more prolonged studies and it also provides the basis for which other testing program can be design. In acute toxicity studies rodent are mostly used because they are economical and readily available and easy to handle. This test is carried out in each species of animal as the same route as intended to be use in treatment

Importance of acute toxicity testing

- ☐ To identify the target organ of toxicity.
- ☐ To provides safety measures and monitoring guild lines for workers involved in the development and testing of test substances.
- ☐ To provides information needed for the dose selection in prolonged toxicity studies.

- ☐ To generate data containing the adverse effects of a substance on human, animal health and environment.
- ☐ To provides the basis for which other testing program can be design.
- ☐ For academics and regulating purpose; classification, labelling and transportation of chemical agents

Sub-acute toxicity studies

This study is conducted to determine organs affected by different dose levels. This study access the nature of toxic dose under more realistic situation than the acute toxicity studies. Three dose levels are normally used[2].

- ☐ Dose that is high enough to elicit definite signs of toxicity but not to kill many of the animals.
- ☐ Low dose that is expected to induce no toxic effect.
- ☐ Intermediate dose.

Doses are generally selected on the basis of information obtained in acute toxicity studies using both LD50 and the slope of the dose response curve. The duration of sub-acute toxicity studies depend on intended duration of the test substance.

Chronic toxicity studies

This study is basically to determine the organs affected and to check whether the drug is potentially carcinogenic or not. This test extends over a long period of time and it involves large groups of laboratory animals. Chronic toxicity is the development of adverse effects as the result of long term exposure to a toxicant or other stressor. It can manifest as direct lethality but more commonly refers to

sublethal endpoints such as decreased growth, reduced reproduction, or behavioral changes such as impacted swimming performance.

Common aquatic chronic toxicity tests

Chronic toxicity tests are performed to determine the long term toxicity potential of toxicants or other stressors, commonly to aquatic organisms. Examples of common aquatic chronic toxicity test organisms, durations, and endpoints include:

- Fathead minnow, *Pimephales promelas*, larval survival and growth
- Daphnia, *Daphnia magna*, 21-d survival and reproduction
- Green algae, *Raphidocelis subcapitata*, 72-h growth
- Amphipod, *Hyalella azteca*, 42-d survival, growth, and reproduction

GENOTOXICITY AND MUTAGENICITY- TERATOGENICITY

- – **Genotoxicity** covers a broader spectrum of endpoints than mutagenicity, includes DNA damage assessments. DNA damage are not themselves necessarily transmissible to the next generation of cells, pre-mutagenic
- – **Mutagenicity** refers to the production of transmissible genetic alterations. Somatic cell genotoxicity may lead to cancer. Germ cell genotoxicity may lead to infertility or diseased children
- **TERATOGENICITY** □ Capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. □ Placenta does not consider a strict barrier and any drug can cross it to a greater or lesser extent. □ The embryo is one of the most dynamic biological systems

Genotoxicity • Genotoxicity tests can be defined as in vitro and in vivo tests designed to detect compounds that induce genetic damage by various mechanisms. • These tests enable hazard identification with respect to damage to DNA and its fixation. Genotoxins can be of the following category depending on its effects 1) Carcinogens or cancer causing agents 2) Mutagens or mutation causing agents 3) Teratogens or birth defect causing agents. Agents that can cause direct or indirect damage to the DNA • Reactive oxygen species. • UV and ionizing radiations. • Nucleoside analogues . • Topoisomerase inhibitors . • Protein synthesis inhibitors .

OECD GUIDELINES • Genetic Toxicology : was first published in 1987 .Following a global update of the Genetic Toxicology • Latest revision provides : (1) general background and historical information on the OECD genetic toxicology. (2) a brief overview of the important types of genetic damage evaluated by these tests. (3) a description of the specific tests.

SCHEDULE –Y • Gene mutation in bacteria

- An in-vitro test with cytogenic evaluation of chromosomal damage
- . • An in-vivo test for chromosomal damage using rodent hematopoietic cells (chromosomal aberration , micronucleus • DNA adduct tests , DNA strands break , DNA repair /recombination .

ICH • S2A:Guidance on Specific aspects of Regulatory Tests for Pharmaceuticals .

- S2B: Standard Battery for Testing of Pharmaceuticals • M3:Timing of Pre-Clinical Studies in Relation to Clinical Trials.

Importance • Genotoxicity assays have become an integral component of regulatory requirement.

- Compounds which are positive in these tests, have the potential to be human carcinogens and/or mutagens. so it's used in prediction.

Aim • To identify substances that can cause genetic alterations in somatic and/or germ cells.

- To identify substances that causes genetic alterations and thus use this information in regulatory decisions.

Mechanism of Genotoxicity

- The damage to the genetic material is caused by the interactions of the genotoxic substance with the DNA structure and sequence.
- These genotoxic substance interact at a specific location or base sequence of the DNA structure causing lesions, breakage, fusion, deletion, mis-segregation or non- disjunction leading to damage and mutation .

Standard test battery for genotoxicity •

AMES TEST (Bacterial reverse mutation test) Bacteria : Salmonella typhimurium or strains E.coli.

Ames test was brought forward by Bruce Ames in 1970. • He is professor in university of California , berkely . In department of biochemistry. • He developed this method because previous methods were expensive and time consuming.

Principle • Identifies substances that induce gene mutations by base substitutions or frame-shifts.

- Two species of bacteria Salmonella typhimurium and Escherichia coli with identified mutations in an amino acid i.e. His or Trp as the reporter locus.
- It detects mutations which revert mutations present in the test strains and restore the functional capability of the bacteria to synthesize an essential amino acid

PROCEDURE • 2 methods : 1.Plate incorporation method. 2. pre-incubation method.

STEPS OF AMES TEST: • Prepare the culture of Salmonella histidine auxotroph's (His-). • Mix the bacterial cells and test substance in dilute molten top agar with a small amount of histidine in one set, and control with complete

medium plus large amount of histidine . • Pour the molten mixture on the top of minimal agar plates and incubate at 37°C for 2-3 days. Until histidine is depleted all the His- cells will grow in the presence of test mutagen. • When the histidine is completely exhausted only the revertants will grow on the plate. • High number of colonies represent the greater mutagenicity

INVITRO MAMMALIAN CELL MICRONUCLEUS TEST -2010 •

Micronuclei is the small nucleus that forms whenever a chromosome or its fragment is incorporated with daughter nuclei during cell division.

principle • Micronuclei are the product of fragmented chromosomes or mitotic spindle failure in a cell. Micronuclei are formed by condensation of acentric chromosomes that are not included in the main nuclei following the anaphase. • Micronuclei are formed in the cytoplasm through the following events: • In anaphase, a chromatid and chromosomal fragments lag behind when the centric elements move towards the spindle poles. Micronucleus arises from chromosomal fragments or acentric chromosomes that are not incorporated into daughter nuclei at mitosis because they lack a centromere.

Mammalian Erythrocyte Micronucleus Test • Animals are exposed to the test substance by an appropriate route • If bone marrow > the animals are sacrificed, bone marrow extracted, and preparations made and stained • If peripheral blood > the blood is collected at appropriate times after treatment and smear preparations are made and stained. • Preparations are analysed for the presence of micronuclei
Principle • For the detection of damage induced by the test substance to the chromosomes or the mitotic apparatus of erythroblasts (rodents) • Identifies micronuclei containing lagging chromosome fragments or whole chromosomes. • An increase in the frequency of micronucleated polychromatic erythrocytes in

treated animals is an indication of induced chromosome damage because they lack main nucleus

INVITRO MAMMALIAN CHROMASOMALABBERATION TEST

PRINCIPLE • After exposure of cell cultures , treated with a metaphase-arresting substance colchicine . with and without metabolic activation • harvested, stained and metaphase cells are analysed microscopically for the presence of chromosome aberrations .

Cell lines: CHO, CHL, V79, TK6. • Structural aberrations may be of two types: chromosome or chromatid.

MAMMALIAN BONE MARROW CHROMOSOME ABERRATION TEST

principle • For the detection of structural chromosome aberrations induced by test compounds only in bone marrow cells of animals (rodents). • Animals are exposed to the test substance , metaphase-arresting agent , sacrificed at appropriate times after treatment.

Bone marrow cells are usually obtained from the femurs or tibias immediately after sacrifice , and stained using established methods. • Blood :tail vein or other appropriate blood vessel , smear preparations are made and then stained • DNA specific stain [e.g acridine orange or Hoechst 33258 plus pyronin-Y]

Prior to sacrifice, animals are injected i.p with an appropriate dose of a metaphase arresting agent , sampled thereafter. Cells are harvested from the bone marrow and analysed from chromosome aberrations. • Chromosome preparation: bone marrow in hypotonic solution , spread on slides and stained

General Principles In Treatment of Poisoning

- ✓ *GENERAL PRINCIPLES OF TREATMENT OF POISONING,*
- ✓ *CLINICAL SYMPTOMS AND MANAGEMENT OF BARBITURATES,*
- ✓ *MORPHINE,*
- ✓ *ORGANOPHOSPHORUS COMPOUND*
- ✓ *LEAD, MERCURY AND ARSENIC POISONING.*



General Principles of Poisoning

Poisoning is contact with a substance that results in toxicity. Symptoms vary, but certain common syndromes may suggest particular classes of poisons. Diagnosis is primarily clinical, but for some poisonings, blood and urine tests can help. Treatment is supportive for most poisonings; specific antidotes are necessary for a few. Prevention includes labeling drug containers clearly and keeping poisons out of the reach of children.

Most poisonings are dose-related. Dose is determined by concentration over time. Toxicity may result from exposure to excess amounts of normally nontoxic

substances. Some poisonings result from exposure to substances that are poisonous at all doses. Poisoning is distinguished from hypersensitivity and idiosyncratic reactions, which are unpredictable and not dose-related, and from intolerance, which is a toxic reaction to a usually nontoxic dose of a substance.

Poisoning is commonly due to ingestion but can result from injection, inhalation, or exposure of body surfaces (eg, skin, eye, mucous membranes). Many commonly ingested nonfood substances are generally nontoxic (see Table: Substances Usually Not Dangerous When Ingested*); however, almost any substance can be toxic if ingested in excessive amounts.

Accidental poisoning is common among young children, who are curious and ingest items indiscriminately despite noxious tastes and odors; usually, only a single substance is involved. Poisoning is also common among older children, adolescents, and adults attempting suicide; multiple drugs, including alcohol, acetaminophen, and other OTC drugs, may be involved. Accidental poisoning may occur in the elderly because of confusion, poor eyesight, mental impairment, or multiple prescriptions of the same drug by different physicians (see also

After exposure or ingestion and absorption, most poisons are metabolized, pass through the GI tract, or are excreted. Occasionally, tablets (eg, aspirin, iron, enteric-coated drugs) form large concretions (bezoars) in the GI tract, where they tend to remain, continuing to be absorbed and causing toxicity.

Symptoms and Signs

Symptoms and signs of poisoning vary depending on the substance (see Table: Symptoms and Treatment of Specific Poisons). Also, different patients poisoned with the same substance may present with very different symptoms. However, 6

clusters of symptoms (toxic syndromes, or toxidromes) occur commonly and may suggest particular classes of substances (see Table: Common Toxic Syndromes (Toxidromes)). Patients who ingest multiple substances are less likely to have symptoms characteristic of a single substance.

Symptoms typically begin soon after contact but, with certain poisons, are delayed. The delay may occur because only a metabolite is toxic rather than the parent substance (eg, methanol, ethylene glycol, hepatotoxins). Ingestion of hepatotoxins (eg, acetaminophen, iron, *Amanita phalloides* mushrooms) may cause acute liver failure that occurs one to a few days later. With metals or hydrocarbon solvents, symptoms typically occur only after chronic exposure to the toxin.

Ingested and absorbed toxins generally cause systemic symptoms. Caustics and corrosive liquids damage mainly the mucous membranes of the GI tract, causing stomatitis, enteritis, or perforation. Some toxins (eg, alcohol, hydrocarbons) cause characteristic breath odors. Skin contact with toxins can cause various acute cutaneous symptoms (eg, rashes, pain, blistering); chronic exposure may cause dermatitis.

Inhaled toxins are likely to cause symptoms of upper airway injury if they are water-soluble (eg, chlorine, ammonia) and symptoms of lower airway injury and noncardiogenic pulmonary edema if they are less water-soluble (eg, phosgene). Inhalation of carbon monoxide, cyanide, or hydrogen sulfide gas can cause organ ischemia or cardiac or respiratory arrest. Eye contact with toxins (solid, liquid, or vapor) may damage the cornea, sclera, and lens, causing eye pain, redness, and loss of vision.

Some substances (eg, cocaine, phencyclidine, amphetamine) can cause severe agitation, which can result in hyperthermia, acidosis, and rhabdomyolysis.

Diagnosis

- Consideration of poisoning in patients with altered consciousness or unexplained symptoms
- History from all available sources
- Selective, directed testing

The first step of diagnosis of poisoning is to assess the overall status of the patient. Severe poisoning may require rapid intervention to treat airway compromise or cardiopulmonary collapse.

Poisoning may be known at presentation. It should be suspected if patients have unexplained symptoms, especially altered consciousness (which can range from agitation to somnolence to coma). If purposeful self-poisoning occurs in adults, multiple substances should be suspected.

History is often the most valuable tool. Because many patients (eg, preverbal children, suicidal or psychotic adults, patients with altered consciousness) cannot provide reliable information, friends, relatives, and rescue personnel should be questioned. Even seemingly reliable patients may incorrectly report the amount or time of ingestion. When possible, the patient's living quarters should be inspected for clues (eg, partially empty pill containers, a suicide note, evidence of recreational drug use). Pharmacy and medical records may provide useful information. In potential workplace poisonings, coworkers and supervisors should be questioned. All industrial chemicals must have a material safety data sheet

(MSDS) readily available at the workplace; the MSDS provides detailed information about toxicity and any specific treatment.

Testing

In most cases, laboratory testing provides limited help. Standard, readily available tests to identify common drugs of abuse (often called toxic screens) are qualitative, not quantitative. These tests may provide false-positive or false-negative results, and they check for only a limited number of substances. Also, the presence of a drug of abuse does not necessarily indicate that the drug caused the patient's symptoms or signs. Urine drug screening is used most often but has limited value and usually detects classes of drugs or metabolites rather than specific drugs. For example, an opioid urine immunoassay test does not detect fentanyl or methadone but does react with very small amounts of morphine or codeine analogues. The test used to identify cocaine detects a metabolite rather than cocaine itself.

For most substances, blood levels cannot be easily determined or do not help guide treatment. For a few substances (eg, acetaminophen, aspirin, carbon monoxide, digoxin, ethylene glycol, iron, lithium, methanol, phenobarbital, phenytoin, theophylline), blood levels may help guide treatment. Many authorities recommend measuring acetaminophen levels in all patients with mixed ingestions because acetaminophen ingestion is common, is often asymptomatic during the early stages, and can cause serious delayed toxicity that can be prevented by an antidote. For some substances, other blood tests (eg, PT for warfarin overdose, methemoglobin levels for certain substances) help guide treatment. For patients who have altered consciousness or abnormal vital signs or who have ingested certain substances, tests should include serum electrolytes, BUN, creatinine,

serum osmolality, glucose, coagulation studies, and ABGs. Other tests (eg, methemoglobin level, carbon monoxide level, brain CT) may be indicated for certain suspected poisons or in certain clinical situations.

For certain poisonings (eg, due to iron, lead, arsenic, other metals, or to packets of cocaine or other illicit drugs ingested by so-called body packers), plain abdominal x-rays may show the presence and location of ingested substances.

For poisonings with drugs that have cardiovascular effects or with an unknown substance, ECG and cardiac monitoring are indicated.

If blood levels of a substance or symptoms of toxicity increase after initially decreasing or persist for an unusually long time, a bezoar, a sustained-release preparation, or reexposure (ie, repeated covert exposure to a recreationally used drug) should be suspected.

Treatment

- Supportive care
- Activated charcoal for serious oral poisonings
- Occasional use of specific antidotes or dialysis
- Only rare use of gastric emptying

Seriously poisoned patients may require assisted ventilation or treatment of cardiovascular collapse. Patients with impaired consciousness may require continuous monitoring or restraints. The discussion of treatment for specific poisonings, below and in see Table: Common Specific Antidotes, see Table: Guidelines for Chelation Therapy, and see Table: Symptoms and Treatment of Specific Poisons, is general and does not include specific complexities and

details. Consultation with a poison control center is recommended for any poisonings except the mildest and most routine.

Initial stabilization

- Maintain airway, breathing, and circulation
- IV naloxone
- IV dextrose and thiamine
- IV fluids, sometimes vasopressors

Airway, breathing, and circulation must be maintained in patients suspected of a systemic poisoning. Patients without a pulse or BP require emergency cardiopulmonary resuscitation.

If patients have apnea or compromised airways (eg, foreign material in the oropharynx, decreased gag reflex), an endotracheal tube should be inserted (see Tracheal Intubation). If patients have respiratory depression or hypoxia, supplemental oxygen or mechanical ventilation should be provided as needed.

IV naloxone (2 mg in adults; 0.1 mg/kg in children; doses as high as 10 mg may be necessary in some cases) should be tried in patients with apnea or severe respiratory depression while maintaining airway support. In opioid addicts, naloxone may precipitate withdrawal, but withdrawal is preferable to severe respiratory depression. If respiratory depression persists despite use of naloxone, endotracheal intubation and continuous mechanical ventilation are required. If naloxone relieves respiratory depression, patients are monitored; if respiratory depression recurs, patients should be treated with another bolus of IV naloxone or endotracheal intubation and mechanical ventilation. Using a low-dose continuous

naloxone infusion to maintain respiratory drive without precipitating withdrawal has been suggested but in reality can be very difficult to accomplish.

IV dextrose (50 mL of a 50% solution for adults; 2 to 4 mL/kg of a 25% solution for children) should be given to patients with altered consciousness or CNS depression, unless hypoglycemia has been ruled out by immediate bedside determination of blood glucose.

Thiamine (100 mg IV) is given with or before glucose to adults with suspected thiamine deficiency (eg, alcoholics, undernourished patients).

IV fluids are given for hypotension. If fluids are ineffective, invasive hemodynamic monitoring may be necessary to guide fluid and vasopressor therapy. The first-choice vasopressor for most poison-induced hypotension is norepinephrine 0.5 to 1 mg/min IV infusion, but treatment should not be delayed if another vasopressor is more immediately available.

Topical decontamination

Any body surface (including the eyes) exposed to a toxin is flushed with large amounts of water or saline. Contaminated clothing, including shoes and socks, and jewelry should be removed. Topical patches and transdermal delivery systems are removed.

Activated charcoal

Charcoal is usually given, particularly when multiple or unknown substances have been ingested. Use of charcoal adds little risk (unless patients are at risk of vomiting and aspiration) but has not been proved to reduce overall morbidity or

mortality. When used, charcoal is given as soon as possible. Activated charcoal adsorbs most toxins because of its molecular configuration and large surface area. Multiple doses of activated charcoal may be effective for substances that undergo enterohepatic recirculation (eg, phenobarbital, theophylline) and for sustained-release preparations. Charcoal may be given at 4- to 6-h intervals for serious poisoning with such substances unless bowel sounds are hypoactive. Charcoal is ineffective for caustics, alcohols, and simple ions (eg, cyanide, iron, other metals, lithium).

The recommended dose is 5 to 10 times that of the suspected toxin ingested. However, because the amount of toxin ingested is usually unknown, the usual dose is 1 to 2 g/kg, which is about 10 to 25 g for children < 5 yr and 50 to 100 g for older children and adults. Charcoal is given as a slurry in water or soft drinks. It may be unpalatable and results in vomiting in 30% of patients. Administration via a gastric tube may be considered, but caution should be used to prevent trauma caused by tube insertion or aspiration of charcoal; potential benefits must outweigh risks. Activated charcoal should probably be used without sorbitol or other cathartics, which have no clear benefit and can cause dehydration and electrolyte abnormalities.

Gastric emptying

Gastric emptying, which used to be well-accepted and seems intuitively beneficial, should not be routinely done. It does not clearly reduce overall morbidity or mortality and has risks. Gastric emptying is considered if it can be done within 1 h of a life-threatening ingestion. However, many poisonings manifest too late, and whether a poisoning is life threatening is not always clear.

Thus, gastric emptying is seldom indicated and, if a caustic substance has been ingested, is contraindicated (see Caustic Ingestion).

If gastric emptying is used, gastric lavage is the preferred method. Gastric lavage may cause complications such as epistaxis, aspiration, or, rarely, oropharyngeal or esophageal injury. Syrup of ipecac has unpredictable effects, often causes prolonged vomiting, and may not remove substantial amounts of poison from the stomach. Syrup of ipecac may be warranted if the ingested agent is highly toxic and transport time to the emergency department is unusually long, but this is uncommon in the US.

For gastric lavage, tap water is instilled and withdrawn from the stomach via a tube. The largest tube possible (usually > 36 French for adults or 24 French for children) is used so that tablet fragments can be retrieved. If patients have altered consciousness or a weak gag reflex, endotracheal intubation should be done before lavage to prevent aspiration. Patients are placed in the left lateral decubitus position to prevent aspiration, and the tube is inserted orally. Because lavage sometimes forces substances farther into the GI tract, stomach contents should be aspirated and a 25-g dose of charcoal should be instilled through the tube immediately after insertion. Then aliquots (about 3 mL/kg) of tap water are instilled, and the gastric contents are withdrawn by gravity or syringe. Lavage continues until the withdrawn fluids appear free of the substance; usually, 500 to 3000 mL of fluid must be instilled. After lavage, a 2nd 25-g dose of charcoal is instilled.

Whole-bowel irrigation

This procedure flushes the GI tract and theoretically decreases GI transit time for pills and tablets. Irrigation has not been proved to reduce morbidity or mortality. Irrigation is indicated for any of the following:

- Some serious poisonings due to sustained-release preparations or substances that are not adsorbed by charcoal (eg, heavy metals)
- Drug packets (eg, latex-coated packets of heroin or cocaine ingested by body packers)
- A suspected bezoar

A commercially prepared solution of polyethylene glycol (which is nonabsorbable) and electrolytes is given at a rate of 1 to 2 L/h for adults or at 25 to 40 mL/kg/h for children until the rectal effluent is clear; this process may require many hours or even days. The solution is usually given via a gastric tube, although some motivated patients can drink these large volumes.

Alkaline diuresis

Alkaline diuresis enhances elimination of weak acids (eg, salicylates, phenobarbital). A solution made by combining 1 L of 5% D/W with 3 50-mEq ampules of NaHCO_3 and 20 to 40 mEq of K can be given at a rate of 250 mL/h in adults and 2 to 3 mL/kg/h in children. Urine pH is kept at > 8 , and K must be replenished. Hyponatremia, alkalemia, and fluid overload may occur but are usually not serious. However, alkaline diuresis is contraindicated in patients with renal insufficiency.

Dialysis

Common toxins that may require dialysis or hemoperfusion include

- Ethylene glycol
- Lithium
- Methanol
- Salicylates
- Theophylline

These therapies are less useful if the poison is a large or charged (polar) molecule, has a large volume of distribution (ie, if it is stored in fatty tissue), or is extensively bound to tissue protein (as with digoxin, phencyclidine, phenothiazines, or tricyclic antidepressants). The need for dialysis is usually determined by both laboratory values and clinical status. Methods of dialysis include hemodialysis, peritoneal dialysis, and lipid dialysis (which removes lipid-soluble substances from the blood), as well as hemoperfusion (which more rapidly and efficiently clears specific poisons—see Overview of Renal Replacement Therapy).

Specific antidotes

For the most commonly used antidotes, see Table: Common Specific Antidotes. Chelating drugs are used for poisoning with heavy metals and occasionally with other drugs (see Table: Guidelines for Chelation Therapy). IV fat emulsions in 10% and 20% concentrations and high-dose insulin therapy have been used to successfully treat several different cardiac toxins (eg, bupivacaine, verapamil).

Antidote therapy N-acetylcysteine (NAC): gives maximum protection against hepatotoxicity when administered within 10 hours of paracetamol overdose, but can be given with (lesser) benefit upto 36 hours Indications 1. Paracetamol ingested is more than 100 mg/kg. 2. Likelihood exists of paracetamol-induced hepatic failure General Principles in Rx of Poisoning & common drug poisoning

Salicylates Acute Poisoning: a. Early : Nausea, vomiting, sweating, tinnitus, vertigo & hyperventilation due to respiratory alkalosis. disorientation, hyperactivity, slurred speech, ataxia, and restlessness may be early findings in patients with severe toxicity b. Late—Deafness, hyperactivity, agitation, delirium, convulsions, hallucinations, hyperpyrexia. Coma is unusual c. Complications—Metabolic acidosis, pulmonary oedema, rhabdomyolysis, cardiac depression, thrombocytopenic purpura General Principles in Rx of Poisoning & common drug poisoning

Chronic Poisoning (Salicylism): — This is characterised by slow onset of confusion, agitation, lethargy, disorientation, slurred speech, hallucinations, convulsions, and coma — Sometimes “salicylism” presents as pseudosepsis syndrome characterised by fever, leukocytosis, hypotension, and multi-organ system failure: ARDS, acute renal failure and coagulopathy (DIC) General Principles in Rx of Poisoning & common drug poisoning Salicylates must not be therapeutically administered to children under 15 years of age, especially if they are suffering from chicken pox or influenza. There is a serious risk of precipitating Reye’s syndrome which can be fatal — Main feature: onset of hepatic failure & encephalopathy General Principles in Rx of Poisoning & common drug poisoning

Treatment • Patients with major signs or symptoms (metabolic acidosis, dehydration, mental status changes, seizures, pulmonary oedema) should be admitted to the Intensive Care Unit regardless of serum salicylate level • Minor symptoms only (i.e. nausea, tinnitus) following acute overdose may be managed in the emergency department with decontamination and alkaline diuresis if the salicylate level is shown to be declining General Principles in Rx of Poisoning & common drug poisoning

Stomach wash may be beneficial upto 12 hours after ingestion, since toxic doses of salicylates often cause pylorospasm and delayed gastric emptying. • Activated charcoal (AC): It is said to be very efficacious in the treatment of salicylate poisoning since each gram of AC can adsorb 550 mg of the drug. A 10:1 ratio of AC to salicylate ingested appears to result in maximum efficiency. The initial dose of AC can be combined with a cathartic to enhance elimination.
General Principles in Rx of Poisoning & common drug poisoning

OP Poisoning 1. Acute Poisoning: a. Cholinergic Excess: • Muscarinic effects: bronchoconstriction with wheezing and dyspnoea, cough, pulmonary oedema, vomiting, diarrhoea, abdominal cramps, increased salivation, lacrimation, sweating, bradycardia, hypotension, miosis, & urinary incontinence • Nicotinic effects: Muscle weakness, fatiguability, and fasciculations are very common. General Principles in Rx of Poisoning & common drug poisoning

CNS Effects—Restlessness, headache, tremor, drowsiness, delirium, slurred speech, ataxia & convulsions. Coma supervenes in the later stages } Death usually results from respiratory failure due to weakness of respiratory muscles, as well as depression of central respiratory drive. θ
Chronic Poisoning: Those who are engaged in pesticide spraying of crops. The following are the main features— a. Polyneuropathy: paraesthesias, muscle cramps, weakness, gait disorders. b. CNS Effects : drowsiness, confusion, irritability, anxiety General Principles in Rx of Poisoning & common drug poisoning

Acute Poisoning: a. Decontamination: — If skin spillage has occurred, it is imperative that the patient should be undressed & washed thoroughly with soap & water — If ocular exposure has occurred, copious eye irrigation should be done with normal saline or Ringer's solution. If these are not immediately available, tap water can be used General Principles in Rx of Poisoning & common drug poisoning Treatment

Antidotes: — Atropine—It is a competitive antagonist of acetylcholine at the muscarinic postsynaptic membrane & in the CNS & blocks the muscarinic manifestations of organophosphate poisoning — Oximes—The commonest is pralidoxime, which is a nucleophilic

oxime that helps to regenerate acetylcholinesterase at muscarinic, nicotinic, & CNS sites General Principles in Rx of Poisoning & common drug poisoning

Supportive Measures: → Administer IV fluids to replace losses → Maintain airway patency and oxygenation. Suction secretions. Endotracheal intubation and mechanical ventilation may be necessary. Monitor pulse oximetry or arterial blood gases to determine need for supplemental oxygen → The following drugs are contraindicated: parasympathomimetics, phenothiazines, antihistamines General Principles in Rx of Poisoning & common drug poisoning

Barbiturates Poisoning is mostly suicidal, rarely accidental θ Characterized by respiratory failure, cardiovascular collapse, coma & renal failure θ Treatment : Gastric lavage, artificial respiration & forced alkaline diuresis with mannitol & sodium bicarbonate General Principles in Rx of Poisoning & common drug poisoning

Atropine • Belladonna poisoning may occur due to drug overdose or consumption of seeds & berries of belladonna/datura plant • Dry mouth, difficulty in swallowing & talking Dilated pupil, photophobia, blurring of near vision, palpitation, psychotic behaviour, ataxia, delirium, visual hallucinations, Hypotension, weak & rapid pulse, cardiovascular collapse with respiratory depression • Convulsions & coma occur only in severe poisoning General Principles in Rx of Poisoning & common drug poisoning

Iron • Has a direct corrosive action on the stomach & proximal small bowel • Once absorbed, produces shock, metabolic acidosis, liver failure & death • Initially, GI symptoms prevail with persistent vomiting, abdominal pain & hemorrhage • A quiescent phase may be observed, followed by shock, coma, metabolic acidosis & liver failure General Principles in Rx of Poisoning & common drug poisoning

Treatment • Management of iron poisoning includes gastric lavage with normal saline • The treatment of choice is the antidote desferrioxamine, which chelates free serum iron in the plasma to form ferrioxamine • Indications : → All critical patients who present with coma, shock, or hemorrhage → All patients with a serum iron level higher than 500 mg/dL → Patients who are

symptomatic with a serum iron > 300 mg/dL General Principles in Rx of Poisoning & common drug poisoning 53

Morphine • It may be accidental, suicidal or seen in drug abusers. The human lethal dose is estimated to be about 250 mg • Stupor or coma, flaccidity, shallow & occasional breathing, cyanosis, pinpoint pupil, fall in BP & shock; convulsions may be seen in few, pulmonary edema occurs at terminal stages, death is due to respiratory failure General Principles in Rx of Poisoning & common drug poisoning 54

Treatment • Consists of respiratory support & maintenance of BP (i.v. fluids, vasoconstrictors) • Gastric lavage should be done with pot. permanganate to remove unabsorbed drug • Specific antidote: Naloxone 0.4–0.8 mg i.v. repeated every 2–3 min till respiration picks up, is the specific antagonist of choice } Due to short duration of action, naloxone should be repeated every 1–4 hours, according to the response.

CHRONOPHARMACOLOGY

INTRODUCTION

Many functions of the human body vary day by day and these types of variations cause the changes in both in disease state and in normal state. Cardiovascular functions such as heart rate and blood pressure show 24 hours variation. The incidence of cardiovascular disease such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation since most of these disorders can induce fatal or severe outcomes. It is important to elucidate the precise mechanism of the onset of these diseases. The dependence of our body functions in the certain diseased state depends on the circadian rhythm. The science dealing with the phenomenon of biological rhythmicity in living organism is called chronobiology.

Circadian rhythm - The phase of circadian rhythm is defined with respect to an easily identifiable reference point of the endogenous circadian oscillation such as through of the body temperature rhythm or the onset of metabolism rhythm. Thus circadian phase shift can be determined by measuring the change in timing of the chosen phase maker from one cycle to the next. During ambulatory conditions, changes in environmental stimuli and behaviour (e.g. - Light/dark, rest/ activity and temperature) often obscure the endogenous component of the underlying circadian oscillation that is being measured. The amplitude of circadian rhythm refers to the half distance from the maximum to the minimum of the observed rhythm.⁴ Circadian clocks regulate a number of key behaviours in a wide variety of organisms. It also helps organism to restrict their activity to species – specific times of the day, which enable them to find food escape predators & avoid undue competition between sympatric species e.g. - in drosophila parasitism activity peaks of different species occurs at different times of the day, which significantly reduces intrinsic competitive disadvantage for the inferior competitor and such temporal portioning is achieved at least partly with the help of circadian clocks.⁵ In the evening, when less light enters in the eyes, the master clock triggers production of a hormone called melatonin which makes feel drowsy and helps stay in asleep. Circadian rhythm and their sensitivity to time may change as the age of the individual person increase.

The Chronopharmacology is useful to solve problems of drugs optimization means to enhance the desired efficiency or to reduce its undesired effects. The chronopharmacologic approach involves a lesser risk of errors or false information than the conventional homeostatic approach.

Many seasonal psychopharmacological drugs are useful in seasonal affective disorders though diazepam has fewer adverse effects and other selected drugs like phenobarbitone and chlorpromazine also have many adverse effects because of which they are leaving the market even though their pharmacological actions are potent. The need of this is to design strategies to ameliorate the side effects which make them more acceptable if the pharmacology and adverse effects of these drugs is circadian time dependant, it can be modulated by altering the time of administration of drugs. Any dependence of these drugs on the circadian time may provide a clue to ameliorate the major drawback of drugs.

Chronotherapeutics: - Chronotherapeutics refers to a treatment method in which drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship

between the peak-to trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs takes into account predictable administration time dependent variation in the pharmacokinetics of drugs as well as the susceptibility due to temporal organization of physiochemical process and function of body as circadian and others rhythms. One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated. Advantages of Chronopharmacotherapy: –

1. It prevents an overdosing of any class of drug.
2. It makes the utilization of the drug more appropriate and thus the value of a drug is increased.
3. It reduces the unnecessary side effects of a drug and helps in carrying out the treatment for only a particular or limited period of time.⁷

Reason for Chronopharmacology

Auto induction:- A repetitive dose of a drug induces or increases enzymes responsible for its elimination, thereby increasing its clearance. This is called as auto induction. It is dependent on dose and concentration of the drug. It has a number of therapeutic consequences. It affects the time to achieve steady state and limits one's ability to use information from a single dose to predict kinetics after repeated dose or continuous administration. Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration that either oral bioavailability decreases or clearance increases with time.

Auto inhibition:- It may occur during the metabolism of certain drugs. The metabolites formed from drug firstly increase in concentration and further inhibit metabolism of the parent drug. This phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition.

Need for Chronopharmacotherapy

It is required to monitor therapy so as to limit the duration of therapy especially in cases where patients are already having compromised renal, cardiac and hepatic or any other function of the body. Any type of accumulation of drugs in these organs causes greater toxicity which may lead to diminished function of the organ. Thus the chronopharmacotherapy becomes a very important part of treatment of several diseases particularly those effecting targeted body parts. According to the 1996 American medical association review, more consideration of chronotherapy in clinical trials is highly welcomed by the whole medical community. The result of the survey

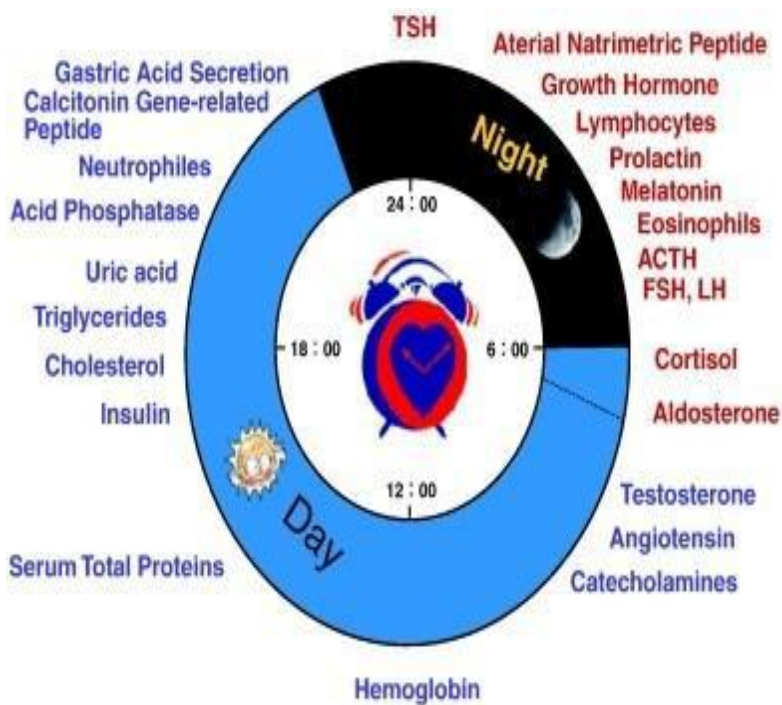
showed that 75 percent of the doctors are in favour of patient's circadian or daily rhythm oriented treatment.

Biological Rhythms and Rhythmic Components

Circadian implies approximately a day, major periodic components of biological rhythms are found around 24 hours (circadian) and 30 days (Circamensual) and one year (Circannual). Circadian rhythms are found in all the organisms, infact the existence of circadian rhythms in living organisms was first established during a detailed study of leaf movement in plants more than 200 year ago. Biological rhythms posses both an internal as well as external components. Rhythmicity has been detected for a numbers of physiological variables like pulse, temperature, blood pressure, hormonal secretion via diurnal variation in effects of insulin on blood glucose.

Human Circadian Time Structure

release should also vary over time. Chronopharmaceutical drug delivery system are gaining importance in the field of pharmaceutical technology as these system deliver right dose at specific time at a specific site. Various technologies such as time- controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for Chronopharmaceutical drug delivery. Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24- hours period). Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy and this brought a new approach to the development of drug delivery systems.



Circadian rhythm in the pathogenesis of diseases- From the various studies, it is formed that the many cardiovascular events including myocardial infarction, stroke and sudden death occur during the initial hours of morning activity between 6 A.M. and 12 noon. And this is much higher during this period than other timing during the day. BP rises rapidly in the early morning hours, the time when most individuals wake and begin their day. This rise in BP corresponds to increased secretion of catecholamine's and increased plasma rennin activity. Thus, vascular tone and total peripheral resistance increase in the morning hours, and rises as a result. At the same time, heart rate increases in the late morning or early afternoon.

Chronotherapy of cardiovascular diseases -

The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented. Chronotherapeutics approach gives more accurate determination of the time when patients are at highest risk and in greatest need of therapy. For example – it has often been found that the blood pressure of hypertensive patient increases rapidly in the morning after awakening, typically peaks in the middle to late time of the day, decreases in the evening and is lowest while the patient sleeps at night. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening. For instance, capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. Blood Pressure is at its lowest during sleeping period and rises steeply during the early morning period. Many anti- hypertensive drugs do not control the early morning blood pressure, when given once daily early in the morning.

VARIOUS CARDIOVASCULAR DISEASES

Blood pressure (B.P) / Hypertension Blood Pressure is well known to exhibit 24 h variation with a peak in the morning. A number of factors influence diurnal variation of blood pressure which is internal factors such as the autonomic nervous system, vasoactive intestinal peptide, plasma cortisol, plasma rennin activity, aldosterone, plasma atrial natriuretic peptide. Both sympathetic activity and the rennin-angiotensin-aldosterone access peak in the early morning hours. In addition, b.p is affected by a variety of external factors including physical activity, emotional state, meal and sleep/wake routine. These extrinsic stimuli also affect the autonomic nervous system thus the 24 h variation in the B.P is representative of both endogenous diurnal rhythms and exogenous factors. Blood pressure is characterized by a circadian rhythm, both in hypertensive and in normotensive subjects; this pattern is associated with lower B.P values during sleeping time and periods of minimal activity and higher B.P levels during wakefulness and mental and physical activity. Various, researchers reported that blood pressure changed depending on whether the subjects was sleeping, resting or working. Blood pressure fluctuates throughout the day and night. The duration of the fluctuations may be short, from seconds to minutes, or long from day to night and season to season. The most easily noted and significant blood pressure variations are the diurnal changes related to the sleep-wake cycle. The pattern of blood pressure values obtained during the sleep-wake cycle from characteristic circadian rhythm. The Continuous monitoring of blood pressure throughout the day and night reveals a pattern with minimum values of systolic & diastolic pressure between midnight & 4 am. The pressure increases during waking hours remaining at a plateau for several hours & then reaching a maximum values early in the morning. This diurnal blood pressure fluctuation is altered in certain disease states, such as preeclampsia & chronic hypertension. **Changing paradigm for targeting blood pressure control** Multiple daily dosing of medication Once daily dosing of long acting medication Evening dosing of long acting chronotherapeutics medication

Acute myocardial infraction (AMI) / pulmonary embolism(PE)-

It is well known that AMI or PE frequently occurs in the early morning. A number of physiological functions exhibit diurnal variation including BP, heart rate, coronary blood flow, platelet function, blood coagulability and fibrnolytic activity. In the early morning, systemic BP & heart rate increases and augment the oxygen demand of the heart. In addition, the vascular tone of the coronary artery rises and coronary blood flow decreases in the morning. This

increases in oxygen demand & decreases in oxygen supply exaggerate a mismatch of oxygen demand and supply in the morning. In addition, platelet function & blood coagulability also increases in the morning. A reduction in fibrinolytic activity resulting in a hypercoagulable state that could elicit the morning onset of thromboembolic events. Accumulating evidences suggests that the autonomic nervous system plays a major role in the circadian variation of the onset of AMI. A morning increase in the frequency of ischemic episodes is absent in diabetic patients with autonomic nervous dysfunction. Patients receiving beta-blocker do not show morning increase in the incidence of angina, AMI & sudden death. Heart rate variability which reflects sympathetic/vagal balance is also associated with the onset of ischemic episode in the chronic stable angina. Platelets are not involved in the variation of AMI or thromboembolic numbers & their aggregation activity possess circadian oscillation. Platelet activation in vivo is induced by catecholamine secreted from the sympathetic nervous system in a circadian fashion. However studies regarding platelet activation do not show clear circadian expression of any surface marker characteristic of platelet activation, therefore it is unclear whether the internal clock system directly affects the circadian functions of platelets.²

Arrhythmia

A number of reports demonstrated the presence of circadian variation of cardiac arrhythmia. Evidences suggest that basic electrophysiological parameters have circadian variations. Atrial & ventricular refractory periods are strongly affected by the autonomic nervous system, in which sympathetic activity shortens it and parasympathetic activity elongates the period. Therefore fluctuations in the activity of autonomic nervous system within a day can be a major trigger of circadian onset of cardiac arrhythmia. Each parameter of ECG was analyzed as to whether it has diurnal variations. ECG, AV nodal function, QT interval, R&T wave voltage & QT interval have been shown to exhibit circadian variations.

BIOLOGICAL RHYTHMS OBSERVED IN VARIOUS BIOLOGICAL SYSTEMS

The basic physiological process governing the drug action the absorption the distribution the metabolism and the excretion are controlled by the following systems of the body. Hence it is important to know the circadian rhythms in these systems and their effect on drug action.

Urinary system- The urinary system which plays a pivotal role in the elimination of a drug has many instances of circadian rhythms altering either the clearance or the urinary flow causing nephrotoxicity. Amino glycosides can produce renal toxicity with chronic administration. Because these antibiotics are primarily eliminated by renal excretion, diminishing renal function with time may cause greater drug accumulation and more toxicity. There is clearly a need to monitor therapy to limit the duration of therapy, especially in patients who already have compromised renal function. Theophylline causes increase in the renal flow by increasing the clearance levels and thereby increase in the urine flow and renal excretion. Carbamazepine shows time dependence in its disposition.

Gastrointestinal system- The gastrointestinal motility, the intraluminal pH, blood flow to stomach and enzymatic action are not the only factors that influence the gastro intestinal absorption of the drug. It even depends on the circadian rhythms and all the above mentioned factors are also influenced by the time of the day. Most of the drugs we generally take are lipophilic and they are found to have more rate of absorption in early mornings rather than any hour of the day.

Hepatic system- The anti-depressant nartryptalline which is injected to significant presystemic hepatic metabolism accumulates in a highly predictable manner on multiple oral dosing. The clearance levels of acetaminophen are decreased due to the effect of circadian rhythms and thus resulting in the hepatotoxicity.

Diseases Showing Dependence on Biological Rhythms Asthma-

Chronic airway inflammation and limitation of airflow in the airways characterize bronchial asthma, and attacks begin with paroxysms of coughing, wheezing, and dyspnoea. Chronopharmacological studies statistically show that the development of asthma symptoms and many types of bronchospastic attacks is clearly more common from midnight to early morning from 2 A.M. and 6am every day. Chronopharmacotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. Several drugs for asthma have been developed based on chronopharmacology. One example is the bronchodilator uniphyl, a long-acting theophylline taken once a day in the evening causes

theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours. Some studies have even proved that a single dose administered in those early hours is equally effective as four doses given in a day. In addition to bronchodilators, the inhaled glucocorticosteroid ciclesonide is now available with once-daily dosing, which also improves patient's compliance. Numerous investigations have demonstrated the usefulness of chronotherapy for asthma, especially for patients with nocturnal asthma.

Diabetes- Biologists have found that a key protein that regulates the biological clocks of mammals also regulates glucose production in the liver and altering the levels of this protein can improve the health of diabetic mice. The additional function of the cytochrome is the regulation of gluconeogenesis according to the diurnal activity and feeding levels. So modulating cytochrome levels can also help decrease the diabetic effect on the patients.

Arthritis- Chronobiological patterns have been observed with arthritis pain. The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting NSAIDs like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes or averts their side effects. People with osteoarthritis, the most common form of the

disease, tend to have less pain in the morning and more at night. For osteoarthritis sufferers, the optimal time for a non-steroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. The overall, back stiffness and pain were a problem throughout the 24 hours, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 and 09:00 than between noon and 15:00.¹⁰

Cancer- The tumour cells and the normal cells differ in their Chronobiological cycles. This fact is the basis for the chronopharmacotherapy of cancer. Based on study which suggested that the DNA synthesis in the normal human bone marrow cells has a peak around noon while the peak of DNA synthesis in lymphoma cells is near midnight, a s-phase active cytotoxic therapy at late nights was administered and it was found that there is a decrease in the tumour cell count with a little effect on normal cells.

Allergy- The allergic reactions both local and systemic are mediated through interactions of immune and inflammatory responses. Such responses during the day are usually coordinated by adrenocortical function and steroid release with high amplitude daily rhythms. Scientists now believe that the symptoms of allergic rhinitis, and even the skin testing results, can vary according to the time of day.

New Techniques of Time Controlled Pulsatile Technology Currently pharmaceutical companies have been focused on developing and commercializing PDDS that fulfil unmet medical needs in the treatment of various diseases. Recently developed technologies are SODAS[®] technology, IPDAS[®] technology, CODAS technology, CONTINR, OROS[®], CEFORMR, DIFFUCAPSR, chronomodulating infusion pumps, TIMERx[®] and physic-chemical modification of API.

Spheroidal Oral Drug Absorption System (SODAS)- This technology is based on the production of controlled release beads and it is characterised by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. SODAS can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give to a fast onset of action, which is maintained for 24 hrs. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day.

Chronotherapeutics Oral Drug Absorption System (CODAS)-

The Chronotherapeutics oral drug absorption system (CODAS) is a multiparticular system which is designed for bedtime drug dosing, incorporating a 4-5 hrs delay in drug delivery. This delay is introduced by the level of non enteric release – controlling polymer applied to drug loaded beads. This technology was designed to release its drug component after a prolonged period of time when administered. A good example is Verelan PM, which was designed to release verapamil approximately four to five hours after ingestion. This delay is introduced by the level of release – controlling polymer applied to the drug –loaded beads. The release controlling polymer is a combination of water-soluble and water –insoluble polymers. When fluid from the gastrointestinal tract contacts the polymer coat beads, the water-soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water- insoluble polymer continues to act as a barrier, maintaining the controlled-release of the drug. controlled onset extended release delivery system enables a maximum Plasma concentration of verapamil in the morning hours, when blood pressure normally is high.

Contintr Technology- In this technology, molecular coordination complexes are formed between a cellulose polymer & a non polar aliphatic alcohol optionally substituted with a aliphatic group by solvating the polymer with a volatile polar solvent & reacting the solvated cellulose polymer directly with the aliphatic alcohol . This constitutes the complex having utility as matrix in controlled release formulations since it has a uniform porosity (Semi permeable matrix).

Chronomodulating Infusion Pumps- Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation , ph, magnetic fields, ultrasound, electronic field, temperature, light, & mechanical stimulation have been developed .

TIMERx Technology- The TIMERx Technology (hydrophilic system) combines primarily Xanthan & Locust bean gums mixed with dextrose .The physical interaction between these components works to form a strong binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the timer x gum matrix which expands to form a gel & subsequently releases the active drug Substances.

CONCLUSION

The major objective of this article is to inform biologists, clinicians, pharmaceutical scientists and other professional about the importance of biological clocks & Chronopharmacology to

human health and disease also motivate the investigator to develop new tools for the treatment of cardiovascular diseases such as cardiac arrhythmia, myocardial infarction etc. this article also provide a new ideas to use of older or already well-established active pharmaceutical ingredients for the treatment of various diseases.

