

CHRONOPHARMACOKINETICS: THE CIRCADIAN RHYTHM OF DRUGS (TIME DEPENDENT PHARMACOKINETICS)



S. Venkateswara Rao, M.Pharm
Assoc. Professor

**VIJAYA INSTITUTE OF PHARMACEUTICAL SCIENCES
FOR WOMEN**

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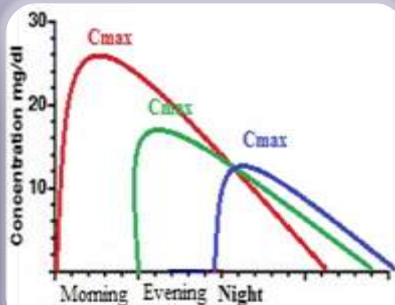
INTRODUCTION



Drug ADME are influenced by different physiological functions of the body which may vary with time of day. The time of day has to be an additional factor influencing the kinetics of a drug, hence many drugs are affected by time of administration and the activity or rest period of the human or animal.



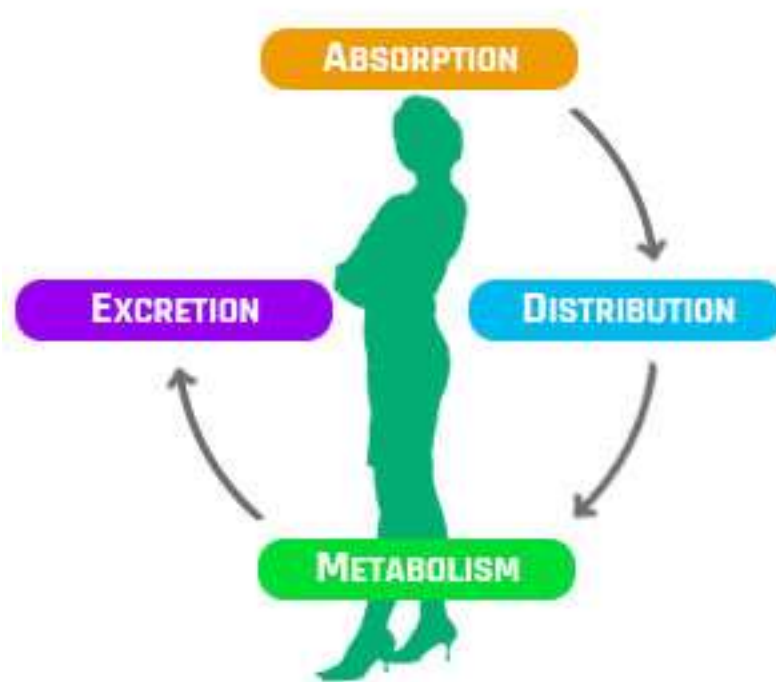
Time dependent pharmacokinetics generally refers to **non cyclic changes** in absorption, distribution, metabolism and elimination over a period of time.



Time dependent pharmacokinetics leads **nonlinear** pharmacokinetics and thus need separate study. The time dependent pharmacokinetics is occurred due to alterations in physiological functions of body and chemically induced factors .

Chronopharmacokinetics

Chronopharmacokinetics deals with the study of the temporal (time) changes in Absorption, Distribution, Metabolism and Elimination and the influence of time of administration on these different steps.



Aim of Chronopharmacokinetics



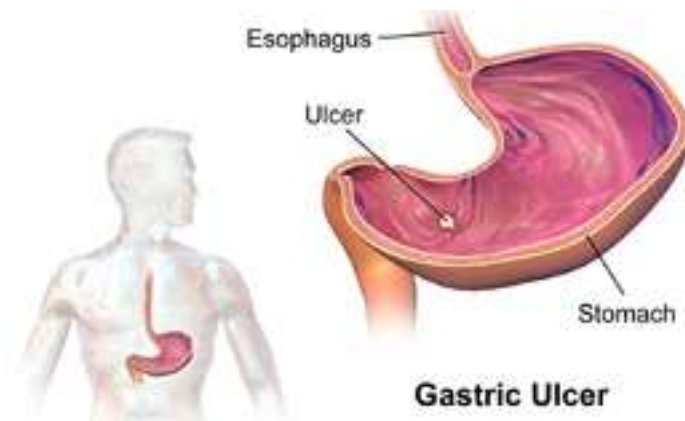
- ✚ To control the time of administration which can be responsible for variations of drug kinetics.
- ✚ To know the time of administration of drug to achieve desired drug plasma concentration.



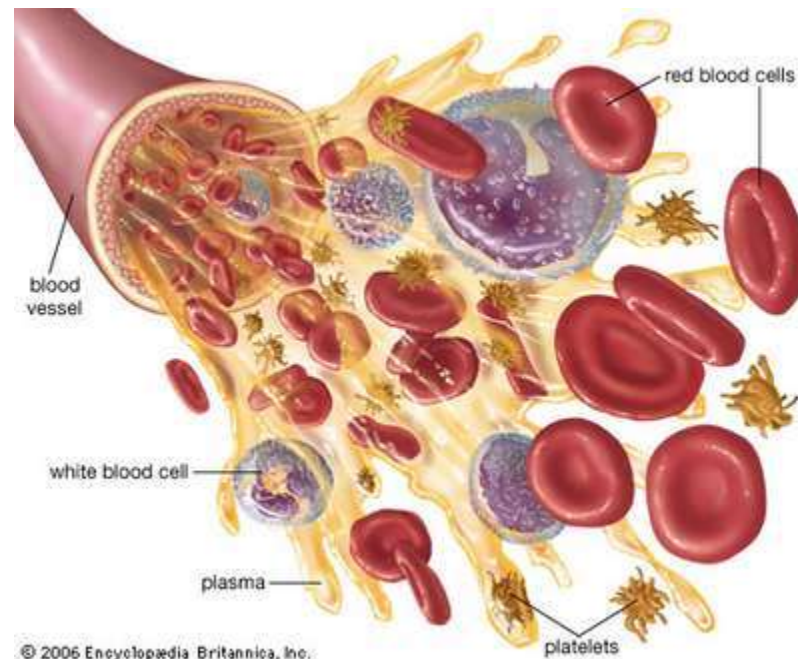
When do we need Chronopharmacokinetics?



- ❖ When possible daily **variation in pharmacokinetics** may be responsible for variations in drug effects. e.g. some antimicrobial agents are more effective at a specific time of day.
- ❖ When drugs have a narrow therapeutic range.
- ❖ When symptoms of a disease are clearly circadian phase-dependant (ex: Nocturnal asthma, Angina pectoris, Ulcer etc.)



- ❖ When drug plasma concentration & therapeutic effect is circadian-phase dependant.
- ❖ When the drug has some serious adverse effects that can be avoided or minimized by time of administration (ex: Amino glycosides -Nephrotoxicity)



REASON FOR CHRONOPHARMACOKINETICS:

The time dependant changes are probably due to **circadian variation in GIT**. It may also be due to variations in levels of various metabolic enzymes such as cytochrome P450 (CYP 3A) plasma concentration.



RELATED TERMS

Chronesthesia

- Changes in the sensitivity of a target system over a period of time.

Chronobiology

- Science that studies biological rhythms.

Chronotherapeutics

- Application of chronobiological principles to the treatment of diseases.

Chronopathology

- It is the study of biological rhythms in disease processes and morbid and mortal events.

BODY RHYTHMS

These are the biological process that show cyclic variation over time.

1. CIRCADIAN RHYTHMS:

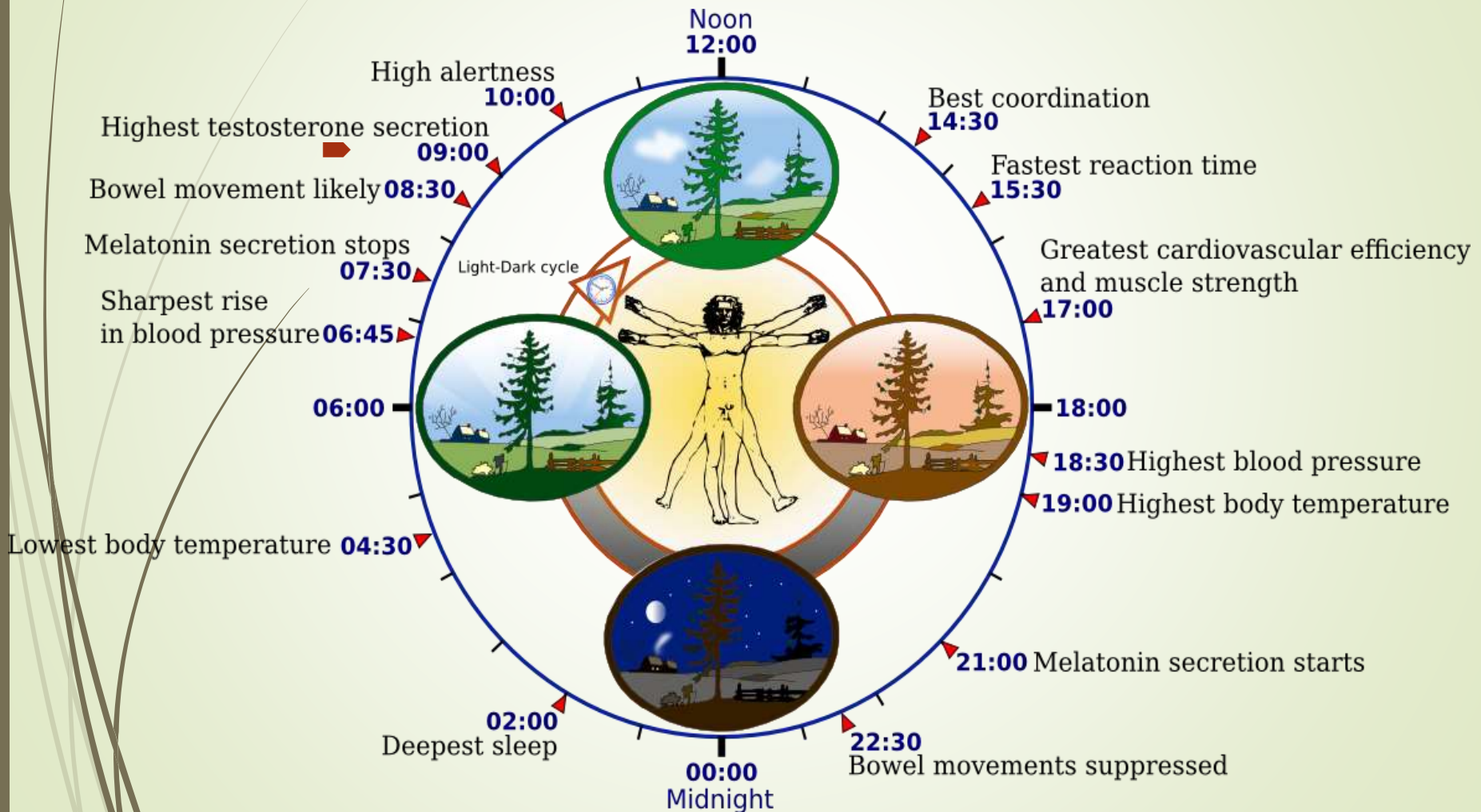
“Circa” means around and “dies” means day. ($20 < \tau < 28\text{h}$).

Humans demonstrate a series of changes which lasts about a day .

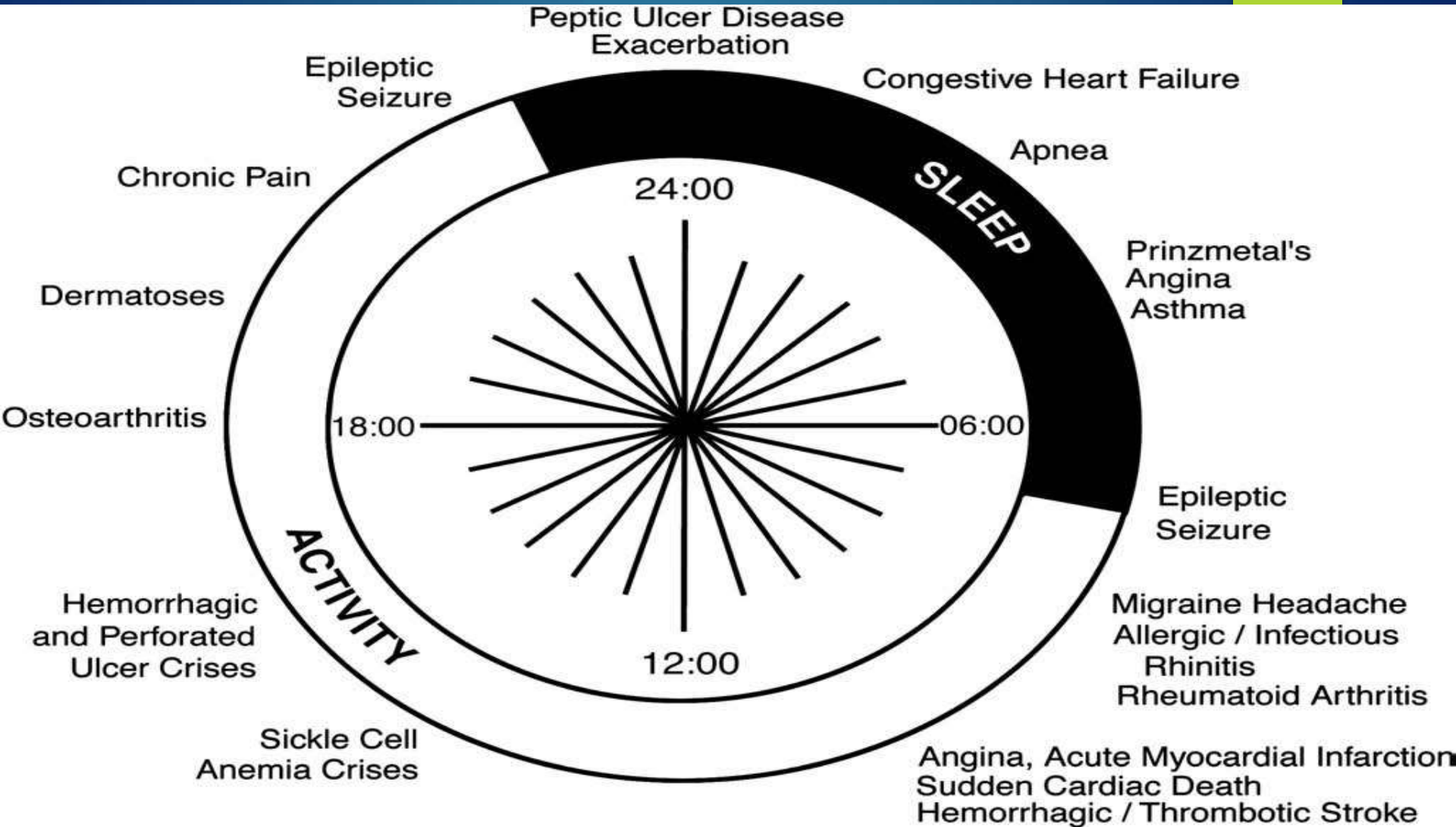
Temperature , Respiration,
Hormone Secretion, Metabolism ,
Sleep/Wake Cycle , Gastric acid secretion

- Disruption of the normal circadian rhythm or incomplete circadian adaptation leads to:
 - ❖ Decreased alertness,
 - ❖ Increased subjective fatigue, and
 - ❖ Decreased physical and mental performance

CIRCADIAN RHYTHMS



Circadian rhythms & Severity of clinical disease

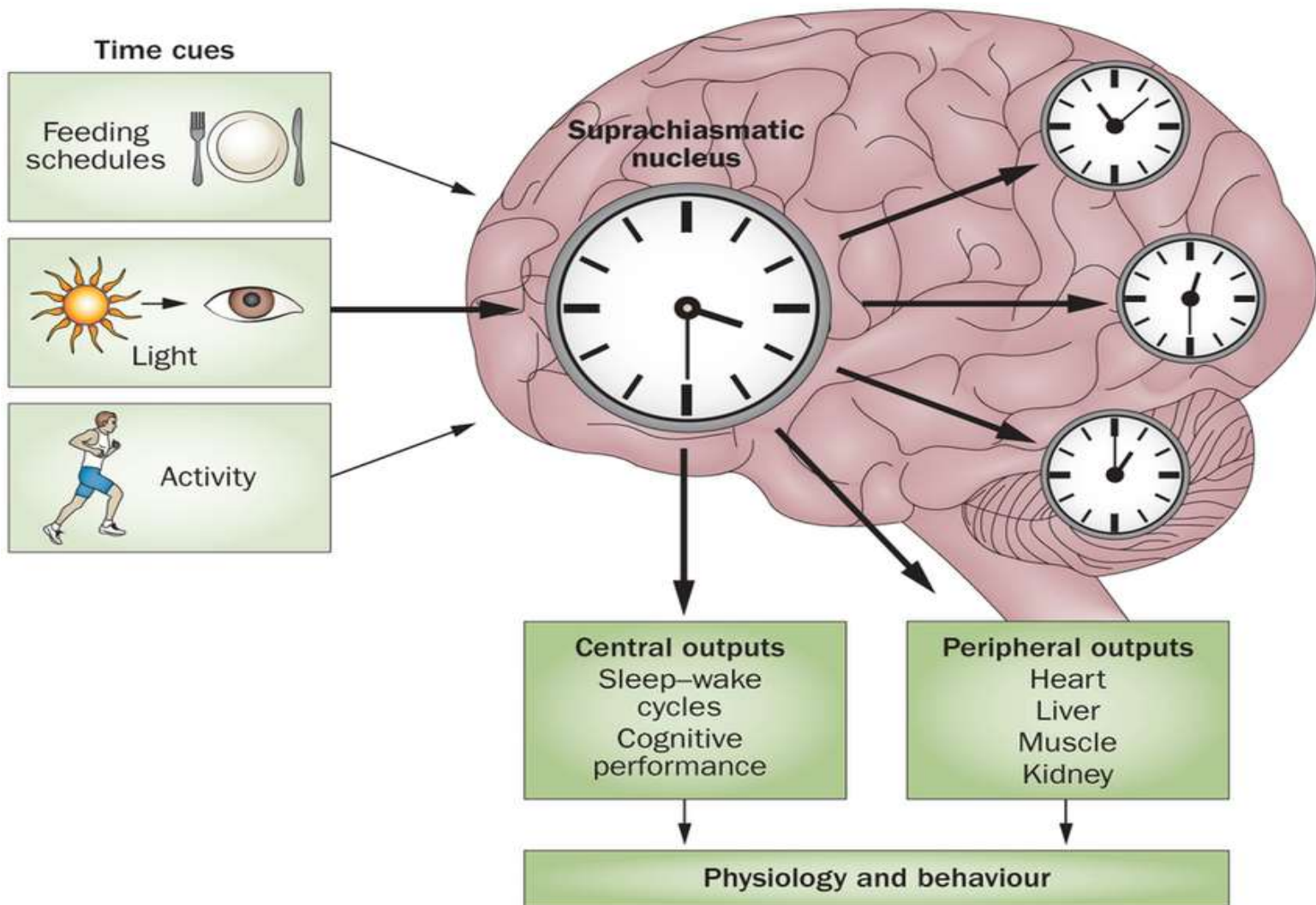


FACTORS AFFECTING CIRCADIAN RHYTHMS:

- Food
- Meal timing
- Gastro-intestinal motility
- Digestive Secretions
- Intestinal blood flow
- Light
- The timing of exposure to light
- The length of exposure
- Intensity & wavelength of light

OTHER FACTORS:

- Physical Activity
- Music
- Temperature
- Sexual Stimuli
- Stress



2. ULTRADIAN RHYTHMS:

Oscillation of shorter duration are termed as Ultradian. (less than one cycle/day).

Ex: Heart beat

3. INFRADIAN RHYTHMS:

Oscillations that are longer than 24h (more than one cycle/day) (≥ 28 h).

Ex: Woman's menstrual cycle which lasts for 28 days.

CLASSIFICATION

Time-dependent phenomena were classified in two categories:

I. PHYSIOLOGICALLY-INDUCED TIME DEPENDENCY

1. Chronopharmacokinetics

II. CHEMICALLY-INDUCED TIME DEPENDENCY

1. Auto Induction

2. Auto Inhibition

CHRONOPHARMACOKINETICS

TIME DEPENDENT CHANGES IN **A D M E**

1. ABSORPTION: Is altered by circadian changes in

Oral Route: -Gastric Motility

-Gastrointestinal blood flow

-Gastric emptying time

-Gastric acid secretion & pH

Parenteral Route: Transdermal permeability, ocular permeability, pulmonary permeability.

Most lipophilic drugs seems to be absorbed faster when the drug is taken in the **morning** compared with the evening.

Eg: 1. For lipophilic drugs (Phenytoin, Valproic acid) – faster absorption in the **morning** than in the evening.

2. NSAIDs – Indomethacin and Ketoprofen better absorption in the **morning**.

3. Paracetamol – extent of absorption is **less at night**

4. Skin penetration of lidocaine and prilocaine is **peaks in evening**.

Cont.....

2. DISTRIBUTION: Is altered by circadian changes in

- » Body size & composition
 - » Blood flow to various organs
 - » Drug protein binding
- Peak plasma concentration of plasma proteins like albumin occurs in the **afternoon**, while troughs are found during the night.

Eg: Antineoplastic like Cisplatin is found maximum plasma proteins binding in **afternoon** & minimum in the morning.

Eg: Diazepam, Phenytoin, Valproic acid, is found maximum in **afternoon** and minimum in morning

Cont.....

3. METABOLISM: Is altered by circadian changes in

- » Liver enzyme activity
- » Hepatic blood flow

- Drugs with low extraction ratio - metabolism depends on liver enzyme activity.
- Drugs with high extraction ratio – metabolism depends on hepatic blood flow.
- Hepatic blood flow high in **morning**
- Metabolism reduces in night

Limitations :

- Enzyme induction - Carbamazepine - \uparrow hepatic clearance
- Decreased hepatic blood flow - Propranolol – \downarrow hepatic clearance

Cont.....

4. **EXCRETION:** Is altered by circadian changes in

- Renal blood flow
- Glomerular filtration
- Tubular reabsorption
- Urinary pH

➤ All above changes **lower during the resting period** than in activity period.

Eg: Acidic drugs like sodium salicylate and Sulfasymazine excreted quickly in morning than night time administration.

➤ Systemic clearance decreases at night and increases during day time.

Ex: Ethosuximide, valproic acid, carbamazepine and clonazepam

Limitations:

Active **re-absorption**, increases the renal clearance of **ascorbic acid**.

Increase in urine **blood flow** increases the renal clearance of **theophylline**.

Change in urine **p^H** decreases the renal clearance of **salicylic acid**.

CHEMICALLY INDUCED TIME DEPENDENCY

- ❖ **Auto-Induction:** Some drugs increasing own metabolising ability is called as auto induction or own induction.

Ex: Carbamazepine, Cyclophosphamide, Rifampicin etc.

- The metabolizing ability of enzyme can be increased by increasing synthesis of enzyme or decrease in degradation of enzyme.
- Decreasing in pharmacological activity due to formation of inactive metabolites.

Some times increasing in pharmacological activity due to the formation of active metabolites.

- ❖ **Auto-Inhibition:** The metabolites formed increase in concentration and further inhibit metabolism of the parent drug.
- The metabolizing ability of enzyme can be decreased by drugs interact with active site of enzyme or saturation of active sites.
- Inhibition of drug metabolism causes prolonged pharmacological action.

Ex: Verapamil, Xanthine oxidase inhibitor - Allopurinol

Cont

advantage

- Reduction in dose and dosage frequency.
- Reduce side effects
- Prevent first pass metabolism
- Lower daily cost ,due to fewer dosage units
- Improved patient compliance
- Extended day time or night time activity



CONT.....



- Very complex anticancer drug development.
- Experimental difference between species – rodents and humans.
- Harmful to rodents/experimental animal.
- Large number of animals.
- Technical skills are required
- Not suitable for patient working in shifts
- Time consuming is required



Cont.....

DRUGS THAT UNDERGO CHRONOKINETICS

CLASS OF DRUG	EXAMPLE
Antibiotics	Amino glycosides Amikacin
General anesthetics	Benzodiazepines Halothane
NSAIDs	Indomethacin Ketoprofen
Anti Cancer Drugs	5-Fluoro Uracil Cisplatin

All this advantages made India a preferable location for conducting R & D activities

APPLICATIONS

Not only increase the efficacy of the drug may also decrease toxicity of certain drugs at different time of day.

1. Antibiotics: Renal toxicity of aminoglycosides can be reduced by giving the drug as a single daily injection **when patients are active** (at day time or in other words in the activity period)

Eg: Gentamycin, Tobramycin, Amikacin



2. Antihypertensive drugs:

Blood pressure, Cardiac output, Blood flow are **higher in morning** and decrease later in the day.

Atenolol (hydrophilic drug) is not absorbed **rapidly** after **morning** administration.



3. Anti-inflammatory drugs :

They have greater rates and **extents of bioavailability** when administered in the **morning** than evening.

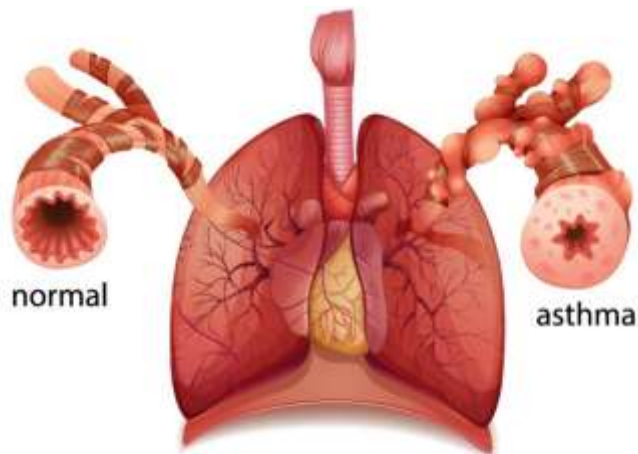
Eg. Indomethacin, Ketoprofen

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4. Anti-Asthmatic drugs:

Asthma is attacked more frequently in **night** hours.

Theophylline must be given in higher doses during the **night time** than day time.



6. Local anesthetics:

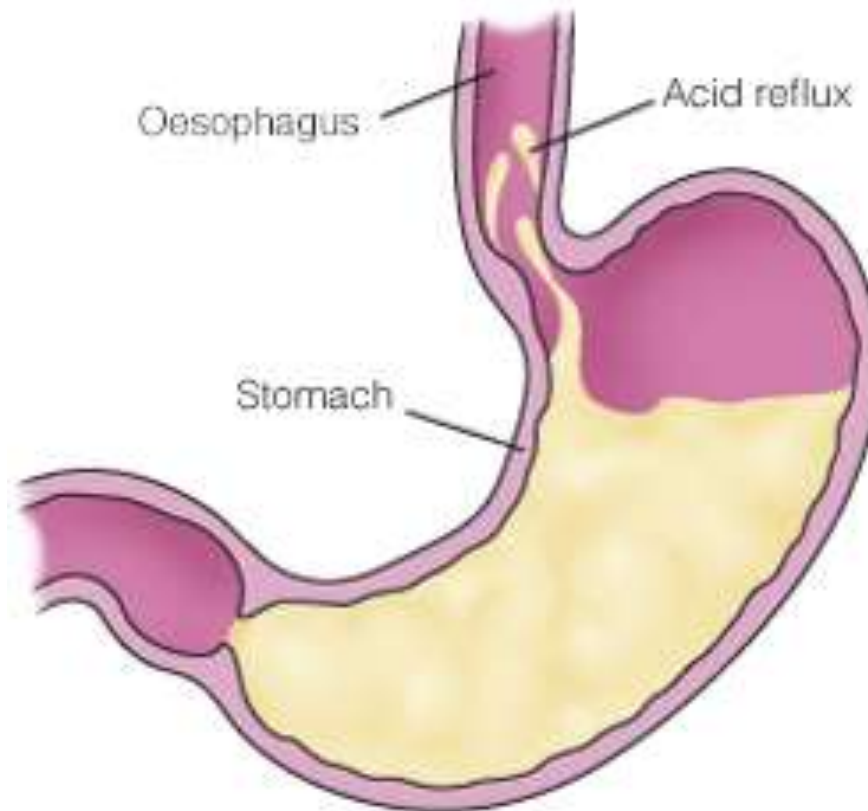
Area under the lidocaine plasma concentration curves (AUC) was largest in the **afternoon**.

The plasma levels of lidocaine were significantly **higher in the evening than** at any other time of day.

5. Antiulcer drugs:

Gastric acid **secretion** is highest at **early night or late afternoon**.

H₂ blockers like Ranitidine, Cimetidine, Famotidine should be taken once a day in the **late afternoon or early night** when acid secretion is more.



DRUG DELIVERY SYSTEMS

1. ENTERIC COATING SYSTEM:

- Which is film coated with two polymers, first with HPMC and then with a gastro resistant polymer (Eudragit ® L30D).
- Duration of absorption can be controlled by the thickness of the HPMC layer.

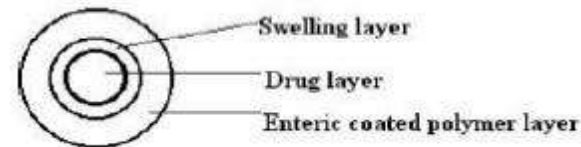
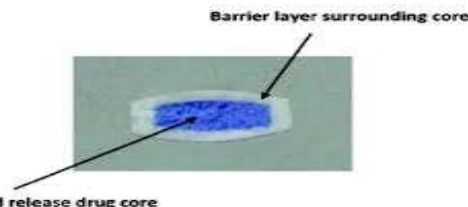


Figure 2: Schematic representation of enteric coated system

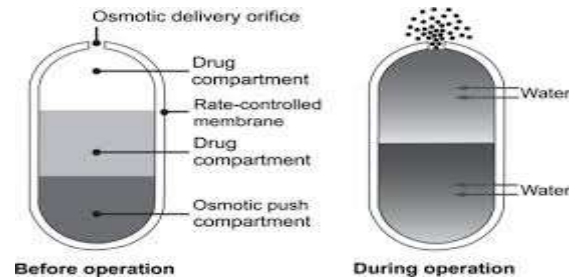
- ## 2. TIME EXPLOSION SYSTEM (TES):
- The core contains the drug, an inert **osmotic agent** and suitable disintegrants. Individual units can be coated with a protective layer and then with a semi-permeable layer, which is the rate controlling membrane for the influx of water into the osmotic core.



CONT.....

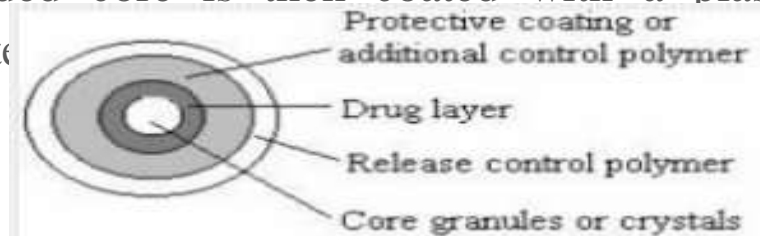
3. SIGMOIDAL RELEASE SYSTEM (SRS):

SRS containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times.



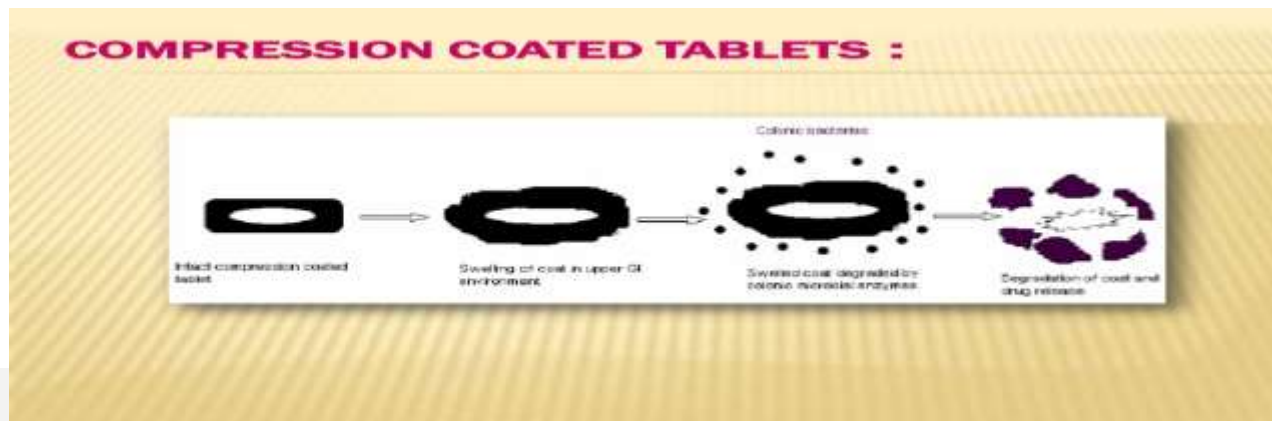
4. DIFFUCAPS:

- Inert particle such as sugar spheres, crystals or granules.
- Inert binder is used to bind the drug particles to the inert core
- The drug-loaded core is then coated with a plasticized enteric coating and thereafter coated with enteric polymers
- Size < 1 mm



5. PRESS COAT SYSTEM:

- Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, avoiding the need for a separate coating process and the use of coating solutions.
- Large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process.



CONCLUSION

- ❖ The concept of drug treatment was earlier *“right drug for the right person”* is now changed to *“right dose for the right person at right time”* .
- ❖ Time dependant pharmacokinetics can be designed to maximize the plasma drug availability at peak hours with minimum side effects and toxicity.

ACKNOWLEDGEMENT

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**Thank
You**

