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Chronotherapeutic And Time Controlled Drug Delivery Systems

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ABSTRACT

Cirrcadian rhythm are an adaptive phenomena relating to predictabe changes in environmental factors that regulate many body functions like metabolism, sleep pattern, hormone production and physiology. Synchronizing drug delivery in a consistent manner with body's circadian rhythm is the basic concept for chronotherapeutic drug delivery system. The safety and efficacy of a drug can be improved by conducting the peak plasma concentration with the circadian rhythm of the body. The time controlled or pulsatile drug delivery systems are the best approach for chemotherapy. It offers rapid and transient release of certain molecules within short period which is a time and site specific drug delivery system. These systems delivers the drug at the right time in the right amount for patient suffering from circadian phase dependent disorders like asthma, myocardial infarction, angina pectoris, hypertension, arthritic, epilepsy etc. So various systems like osmotic and coated system are being made.

Keywords: Cirrcadian rhythm, Chronotherapeutic, Pulsatile drug delivery

1. INTRODUCTION

Cirrcadian rhythm

Circadian rhythms are endogenous in nature driven by "Oscillators" or Clocks and persist under free running conditions. The rhythm in human body temperature which is timed by the biological clocks has an about 25 hours period under free running conditions. Thus circadian variations in gastricacid secretion and PH, motility, gastric emptyingtime, gastrointestainal bloodflow, drugprotein binding, liver enzyme activity, hepatic bloodflow, glomerular filtration, renal bloodflow, urinary PH, and tubular reabsorption may play a role in such kinetic variations.

Chronopharmacology

Chronopharmacology is the study of predictability in time differences in the effects and pharmacokinetics of the drug both in experimental animals and human beings. Chronopharmacology of living organisms are composite of rhythms with varying frequency ranging from seconds to seasons. Chronobiological frequency is the circadian rhythm that approximates the earth 24 hr rotation. Chronopharmacology investigates both effects and side effects of the drug on the temporal changes in biological functions. Circadian rhythm in the rate of absorption, hepatic conjugation and urinary excretion contributes towards variation in responsiveness of the drug. Selection of the correct timing for drug administration has been shown to be important in certain clinical situations like asthma, arthritis, hypertension, angina and epilepsy. The drug therapy can be optimized by tailoring the dosing schedule based on chronobiological pattern [1,2].

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Chronopharmacokinetics is defined as the predictable rhythamical changes dependant on the of dosing. Absorption, distribution, metabolism, and elimination are influenced by different physiological functions that may vary with the of dosing.The of administration of a drug or toxic agent may influence the response of the organism. Chronopharmacokinetics studies are needed for better understanding of non-linear behavior of a drug. Circadian rhythm in gastric acid secretion, gastric motility, gastric blood flow and urinary pH play an important role in time

dependent variation of drug plasma concentration. Chrono-pharmacokinetics includes the temporal aspects of absorption, distribution, metabolism and elimination of the drug.

Temporal aspects of drug absorption

Temporal changes in gastric pH, motility, digestive secretions, gastric blood flow, membrane permeability and gastric emptying may be involved. Variation in absorption is due to the presence of food, posture and galvanic form of the drug. Most of the lipophilic drugs seem to be absorbed faster when they are taken early morning. Chronopharmacokinetics studies also have

been reported for menstrual rhythms e.g. Sodium salicylate absorption varies along with the menstrual cycle with maximum in mid of the menstrual cycle.

Drug distribution

It is related to changes in binding with plasma proteins that are involved in drug transport from the site of administration to the receptor site. For acidic and basic drugs, variations in free plasma drug levels exist. The temporal binding protein for acidic drugs varies with the dark phase. Changes are involved in membrane passage and accumulation of the drug e.g. Cisplatin binding is found to be minimum in the afternoon and maximum in the morning.

Drug metabolism

Hepatic clearance of a drug is influenced by the rate of blood flow to the liver, enzymatic transformation and variation in the percent of protein binding. Biological factors that modify drug metabolism are enzyme secretion, endocrine function, environmental factors such as lightning schedule and feeding habits that synchronize the endogenous rhythms e.g. the clearance

of a drug having a high extraction ratio such as Lidocaine and Propranolol are found to be high at night than in the day.

Drug elimination

Circadian rhythm affects the glomerular filtration rate. The filter load is maximum at day time and minimum at night. This difference between day and night time depends on life style, posture, activity and meal times. The rate of excretion of a drug which is completely removed during a single passage through the kidney such as paraaminohippuric acid shows variation due to circadian changes in the renal blood flow. The concentration of plasma anti-diuretic hormone (ADH) shows marked difference with diurnal value lower than the nocturnal ones. Drugs which get eliminated during day time in healthy adults are 20 % quicker than nocturnally.

Chronopharmacodynamics

Chronopharmacodynamics deals with rhythmic changes with the drug including effects indicating temporal but not randomly distributed drug susceptibility or sensitivity of organisms or target tissues down to the cellular or sub cellular level [3,4].

2. CHRONOTHERAPY AND CHRONOTHERAPEUTICS

Chronotherapy aims at establishing maximum drug effect or reducing undesirable side effects by determining the best biological time for drug dosing thus helping to increase the therapeutic index of the drug. Matching drug release with the circadian rhythm of the body is used as a basic concept for new drug delivery systems for safety and efficacy of the drug by coordinating the peak plasma concentration of the drug with the circadian rhythm of the body. Chronotherapeutics

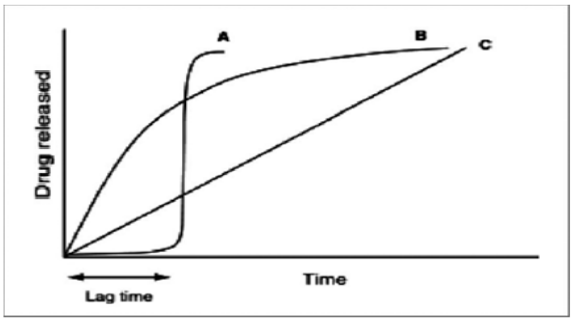
refers to the clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm to produce maximum health benefits and minimum harm. Pulsatile drug delivery systems are time and site-specific drug delivery systems, thus providing special and temporal delivery and increasing patient compliance. Pulsatile release is beneficial when constant drug release or zero order release is not required. Different release patterns are shown in

Fig. 1. It is a time programmed drug release system. The release of the drug as a pulse is designed in such a way that complete and rapid release of the drug follows the lag time [5-7].

Advantages of such drug delivery systems include controlled onset and extended release of the drug. The delivery profile of the drug is designed to complement the circadian pattern of the disease and the rate of the drug release is independent of pH, posture and food. Various systems like capsular systems, osmotic systems etc. based on the use of soluble or erodible coatings, use of rupturable and permeable membranes system have been developed [8].

Fig. 1: Drug release pattern

A: pulsatile release B:Conventional release C: sustained release



Drugs that undergo chronokinetic

(1) Antibiotics- Aminoglycosides, gentamicin, amikacin, ceftrixone, ciprofloxacin
(2) Antihypertensive drugs- Valporic acid, sumatriptane, cyclosporine, methotrexate
(3) NSAID- Ketoprofen, indomethacin

(1) Multiparticulate systems

More reliable gastric emptying pattern is observed for multiparticulate systems and is based on changes in membrane permeability and rupture of the coating. The drug is coated on non-peril sugar seeds followed by coating with swellable polymeric layer. The swelling agents include super disintegrants, effervescent agents and osmotic agents. Upon ingress of water, the swellable layer expands resulting in rupture of the film and rapid drug release. Several delivery systems based on ion exchange principle have been developed. Other used polymers such as Eudragits RS30D. It contains positively charged quaternary ammonium groups in the side chain accompanied by negative hydrocolloid counter ions. The ammonium groups interact with water, change the permeability and allow water to penetrate in to the core layer in a controlled manner [9,10].

(2) Ultrasound drug delivery systems

Ultrasound is an enhancer forimprovement of drug penetration through biological barriers such as skin, blood vessels etc. The ultrasound effect enhances degradation of the polymer in which the drug molecules are incorporated. The drug can be released by repeated ultrasound exposure. Pulse delivery is achieved by onoff application of ultrasound [11,12].

(3) Enteric coated systems

It is the traditional method used to prevent the degradation of pH sensitive drugs and localizes the drug in the GIT. Enteric coated polymers such as Eudragits, cellulose acetate phthalate, hydroxypropylmethyl cellulose are used for coating which protects the dosage forms from the acidic environment of the GIT and allows delivery of the drug to the small or large intestine based on solubility, pH and coating thickness of the polymeric layer. Enteric coated systems are used for site specific and time controlled drug delivery[13].

(4) Pulsincap

It is a single unit system comprised of a water insoluble capsule body enclosing the drug reservoir. The capsule body is closed at one end with a swellable hydrogel plug.Various hydrogels such as hydroxypropylmethyl cellulose, hydroxypropyl, polyvinylpyrrolidone are used as plug materials. Enzymatically controlled erodible polymers such as pectin can also be used as plugging material. When the capsule comes in contact with water it absorbs water and swells. After a lag time the plug gets pushed out and the drug gets release rapidly in the form of a pulse. The total length of the plug, its position of the insertion into the capsule and the polymer used for making the plug controls the lag time of the system. Rapid release of the drug can be ensured by the inclusion of effervescent agents, superv disintegratnts and osmotic agents[14,15].

(5) Compression coated systems

It involves direct compression of the core with the coating material avoiding the need for the separate coating procedures and the use of coating solutions. In case of some compression coated systems, the outermost layer provides the rapidly releasing initial dose. The pulsatile system is formed due to the alternate drug free and drug containing layers. Normally used excepients and conventional compression techniques can be utilized for production. The limitation of the system is that central position of the core layer cannot be assured. The system can be two or three component, that is two or three layered tablet. One layer provides the initial dose of the drug while other layers are formulated with the components that are insoluble in gastric media but dissolves in intestine. The tablet can be coated with a semi permeable polymeric coating layer that controls drug release [16-17].

(6) Swelling and erodible systems

In this system the drug reservoir is surrounded by a polymeric barrier layer that swells and gets dissolved when it is in contact of dissolution media and drug is released after the lag time. The coating layer is made up of various hydrophilic polymers. In addition to this enteric coating can be applied outside to overcome the gastric pH effect on the drug. The lag time of the system can be

controlled by thickness of the polymeric coat and the viscosity grade of the polymer used [18-21].

(7) Osmotic systems

In the case of the osmotic system, osmotic pressure acts as a driving force for the pulsatile drug release. The system consists of application of a semi permeable membrane around the core of an osmotically active drug or a drug combined with an osmotic agent. The delivery orifice is drilled in to the system by laser technique or a highspeed mechanical drill. When the system comes in contact with fluid, due to the differences in the osmotic pressure, the drug inside the system is pumped out at controlled rate. A lag time of 1-10 hr can be achieved depending on the thickness, orifice diameter and concentration of an osmotic agent. e.g. Port system. This system consists of a capsule coated with a semi permeable membrane. The capsule acts as a reservoir of the drug and osmotic agent. Water enters into the system through the semi permeable membrane and leads to the development of osmotic pressure and expulsion of the drug after a desired lag Time [22].

3. CONCLUSION

If drug released is designed in a time controlled manner and maximum drug is made available at peak time, optimization of the therapy can be achieved for diseases that follows the circadian rhythm. A significant amount of progress has been made towards developing pulsatile chronotherapeutic drug delivery systems that can effectively treat diseases with non-constant drug release dosing therapies.

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