Review Article

CHRONOTHERAPEUTICS: A NEW VISTA IN NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Chronopharmacokinetics deals with the study of the temporal changes in absorption, distribution, metabolism and elimination and thus takes into account the influence of time of administration on these different steps. Circadian rhythms in disease pathophysiology give rise to day-night patterns in onset and symptoms exacerbation of most diseases like allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke, peptic ulcer disease etc. Circadian time dependent differences are also seen in pharmacokinetics of many classes of medications like cardiovascular active drugs, NSAID's, antidepressants, antihypertensives, local anesthetics, H_1 and H_2 antagonists etc. The role of circadian rhythms in the mechanisms of disease and the pharmacokinetics and pharmacodynamics of medications constitutes a challenge to drug-discovery and drug-delivery scientists. We must strive to develop intelligent drug-delivery systems that can affect a target cell or organ system at that circadian time when it is possible to optimize desired therapeutic outcomes and minimize or avert adverse effects. There is a critical and urgent need at least in cases such as asthma, cancer and heart diseases for novel chronopharmaceutical drug products either for therapy or prevention. Such novel drug dosage forms should be effective, safe, robust (predictable drug release rate in biological systems) and clinically justified, with spatial and temporal control ability after administration by different routes. Theoretically, such ideal drug delivery system (preferably a noninvasive system with affordable cost) would potentially improve the safety, efficacy and patient compliance of old and new drugs.

Keywords: Chronopharmacokinetics, circadian rhythms, chronotherapeutics, asthma, intelligent drug delivery systems.

INTRODUCTION

Mammalians circadian pacemaker resides in CNS and influences a multitude of biological processes, including the sleep–wake rhythm. The circadian clock acts like a multifunction timer to regulate homeostatic systems such as sleep and activity, hormone levels, appetite, and other bodily functions with 24 h cycles. Clock genes are identified as the genes that ultimately control a vast array of circadian rhythms in physiology and behavior. Biological rhythms not only impact the function of physiology, but the pathophysiology of diseases.[1] *Chronopharmacokinetics* describes biologic time-related changes in the pharmacokinetics of an agent. *Chronotherapeutics* is the delivery of medications in the right concentration to the right targeted tissues at the right time to meet biological rhythm-determined needs, e.g., rhythms in the mechanisms of disease, symptom intensity, and/ or patient tolerance, to optimize desired and minimize and avert adverse effects.

Biological rhythms

A biological rhythm is a self-sustaining oscillation of endogenous origin. The spectrum of biological rhythms is broad as displayed in Table 1. Short-period rhythms of a second or so are quite common; the high frequency oscillations in the electrical impulses of the central and autonomic nervous systems and the high frequency pulsatile secretions of the neuroendocrine system are but a few examples. Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian (<20 h), circadian (~24 h), and infradian (>28 h) rhythms. Finally, long-period rhythms show oscillations of roughly a week, month, and year.[2]

Table 1: Spectrum of biological rhythms

Period (τ)	Major rhythmic components
Short [τ<0.5 h]	0.1s < τ < 1s τ~min Pulsatiles
Intermediate [0.5 h<τ<6 days]	Ultradian (0.5 h <τ< 20 h) Circadian (20 h <τ< 28 h) Infradian (28 h <τ< 6 days)
Long [τ>6 days]	Circaseptan (τ ~7 days) Circamensual (τ~30 days) Circannual (τ~1 year)

Circadian time structure

Circadian rhythms are controlled by an inherited master clock network composed of the paired suprachiasmatic nuclei (SCN) that are situated in the hypothalamus and the pineal gland.[3] The rhythmic activities of specific, so-called, clock genes, like per1, per2, per3, bmal, clock, and CRY, among others, and their gene products, plus the cyclic (nocturnal) secretion of melatonin from the pineal gland comprise the central timekeeping mechanism. This master clock network orchestrates the period and phase of the multitude of subservient peripheral circadian clocks located in cells, tissues, and organ-systems. The end-effect is a rather exquisite temporal organization of biological processes and functions. The daily changes in

light intensities are thought to be the major environmental cue involved in circadian entrainment. Light- signals are perceived by photoreceptor cells in the retina and transmitted to neurons of the SCN via the retinohypothalamic tract. A great deal of research shows that the inherited period of the human pacemaker clock is not precisely 24 h. In fact, in most people, it is somewhat longer, closer to 25 h. Environmental time cues, termed synchronizers or zeitgebers, the strongest one being the daily light–dark cycle occurring in conjunction with the wake–sleep routine, set the inherited pacemaker circadian timekeeping systems to 24 h each day. The human circadian time structure was depicted in Figure 1.
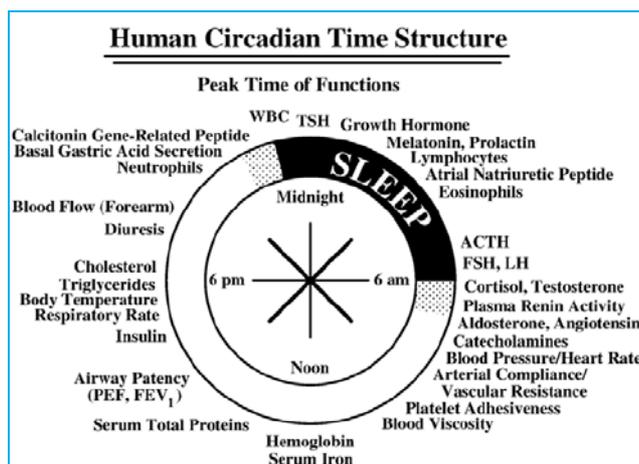

Figure 1: Human circadian time structure. Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (~6–7 a.m. to ~10–11 p.m.) alternating with nighttime sleep.

CIRCADIAN RHYTHMS IN OCCURRENCE AND SEVERITY OF DISEASE

The symptom intensity of many medical conditions and the occurrence of life-threatening medical emergencies exhibit rather precise timings. Gout, gallbladder, and peptic ulcer attacks are most frequent at night. Acute pulmonary edema, congestive heart failure, and asthma worsen nocturnally. Sudden infant death and the symptoms of allergic rhinitis and rheumatoid arthritis are either most intense overnight or in the morning upon wakening. Migraine headache typically is triggered during rapid eyeball movement (REM) episodes during nighttime sleep or in the early morning hours after awakening. Angina pectoris, ventricular arrhythmia, acute myocardial infarction, sudden cardiac death, stroke, fatal pulmonary embolism, and hypertensive crises all are most frequent in the morning as are other cardiovascular conditions. Depression is most severe in the morning. Symptoms of osteoarthritis worsen during the course of daily activity, being most intense typically in the late afternoon and evening. Perforated and bleeding ulcer is reported to be most common in the afternoon. Some seizure disorders are triggered during specific sleep stages and/or by

transitions between sleep and wakefulness. Figure 2 depicts the circadian rhythm in human diseases.
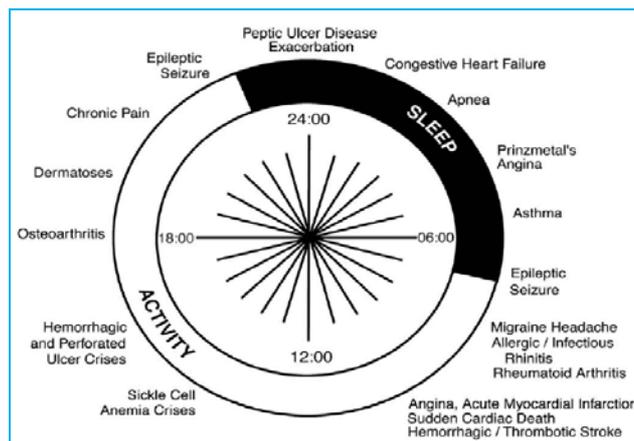
Figure 2: Display in the form of a 24 h clock diagram of the approximate time, in human following the diurnal activity/nocturnal sleep routine, when symptoms or events of diseases are worst or most frequent[2].

The following are the diseases with established oscillatory rhythm in their pathogenesis,

1) *Asthma*

   Symptoms of asthma occur 50 to 100 times more often at night than during the day. Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms.[4] For example, cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am.

2) *Pain*

   Pain threshold does not follow the same pattern in all tissues. The sensitivity threshold of the gingiva to a cold stimulus was maximal at 18:00 h and reached a peak at 03:00 h (35% difference). Tooth sensitivity was lowest between 15:00 and 18:00 h, with a peak in pain intensity at 08:00 h (160% increase). Circadian rhythms in acute pain have been also recorded, such as in dental surgery, with a morning peak during the first postoperative day. The peak of *morphine* use occurred at 09:00 h and was the least at 15:00 h in patients undergoing elective surgery. The peak demand for morphine or hydromorphone occurred in the early morning and was lowest during the night in postoperative gynecologic patients.

3) *Arthritis*

   Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAID's such as ibuprofen should be timed to ensure that the

highest blood levels of the drug coincide with peak pain. For osteoarthritis sufferers, the optimal time for a nonsteroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal.[5] There is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 of patients with rheumatoid arthritis.

4) Cardiovascular diseases

Several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood.[6] It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. Cardiac events also occur with a circadian pattern. Numerous studies have shown an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia[6]. BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile. They have quite a marked rise in blood pressure upon awakening - called 'the morning surge' – that increase can be 3 mm Hg/hour (systolic) and 2 mm Hg/hour (diastolic) for the first four to six hours after waking up. This is due to high catecholamine concentrtion in the early morning.

5) Duodenal ulcer

In peptic ulcer patients, gastric acid secretion is highest during the night[7]. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for H_2 antagonists. At nighttime, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower.

6) Cancer

Chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue[8]. The rhythmic circadian changes in tumor blood flow and cancer growth are relevant both when tumors are small and growing most rapidly and when they are larger and growing more slowly. The blood flow to tumors and tumor growth rate are each up to threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. Normal human bone marrow DNA synthesis peaks around noon, DNA synthesis in malignant lymphoma cells peaks near midnight. By treatment at mid night, more tumor cell kill could be achieved with same dose of S-phase active cytotoxic therapy and with relatively little bone marrow damage.

7) Hypercholesterolemia

A circadian rhythm occurs during hepatic cholesterol synthesis. However, this rhythm varies according to individuals. Indeed, there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis. Many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight; however the maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing[9].

8) Diabetes

The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been previously discussed[10]. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion. Providing basal insulin exogenously to patients with diabetes inhibits hepatic glucose production. Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release.

CHRONOPHARMACOKINETICS

The time of administration of a drug or toxic agent may influence the response of the organism. Chronopharmacology examines the influence of the moment of drug administration (hour, month, and year) on the drug and body response according to the temporal structure of the organism receiving it. Thus, the quantitative response (duration or intensity of the action) of an organism, as well as the qualitative response (i.e. inhibition or induction, increase or decrease of its effect), varies with time of administration. Moreover, the different steps in pharmacokinetics, e.g. absorption, distribution, metabolism and elimination, are influenced by different physiological functions that may vary with the time of day. Thus, pharmacokinetic parameters [including the peak drug plasma concentration (Cmax),

time to reach Cmax (tmax), the area under the concentration-time curve (AUC), volume of distribution (Vd), protein binding, elimination half-life ($t_{1/2}$) and clearance (CL)] which are conventionally considered to be constant in time are circadian time-dependent[11]. More recently, Shiga et al[12] documented differences in chronopharmacokinetic profiles between propranolol, a lipophilic β-blocker, and atenolol, a hydrophilic b-blocker, in patients with hypertension. Their results showed that propranolol, but not atenolol, is absorbed more rapidly after morning administration compared with evening administration. This confirms that the absorption rate of a lipophilic, but not a hydrophilic, drug is faster after the morning dosage in humans.

CIRCADIAN DEPENDENCE OF DRUG PHARMACOKINETICS

Time-dependent changes in kinetics may result from circadian variations at each step, e.g. absorption, distribution, metabolism and elimination. At each of these steps, biological rhythms may influence the kinetics of a drug, as indicated in Table 2.

Table 2: Possible physiological factors influencing circadian stage-dependent pharmacokinetics of drugs

Absorption
Oral: Gastric pH, gastric motility, gastric emptying time, gastrointestinal blood flow, transporter. *Parenteral:* Transdermal permeability, ocular permeability, pulmonary permeability.
Distribution
Blood flow, albumin, α1-acid glycoprotein, red blood cells, transporter.
Metabolism
Liver enzyme activity, hepatic blood flow, gastrointestinal enzyme.
Elimination
Renal, biliary, intestinal, Glomerular filtration, renal blood flow, urinary pH, electrolytes, tubular resorption, transporter.

Each process is also influenced by life style such as active–rest cycle, posture and feeding schedule, and physico-chemical properties of a drug (lipophilicity or hydrophilicity).

- *Drug absorption*

    Several factors, such as the physico-chemical properties of the drug (lipophilicity or hydrophilicity), the area and the structure of the biomembrane, gastric emptying, pH and motility, and gastrointestinal blood flow, may influence the absorption process after oral drug administration[13]. For example, circadian changes of pH may induce circadian modifications of drug ionization according to its physicochemical properties. Most lipophilic drugs seem to be absorbed faster when the drug is taken in the morning compared with the evening, but this has not been reported for highly water-soluble drugs. The mechanisms underlying the

chronopharmacokinetics of lipophilic drugs involve a faster gastric emptying time and a higher gastrointestinal perfusion in the morning. Feeding conditions also contribute to dosing time-dependent difference in drug absorption. Drug absorption by other than oral route of administration is also influenced by biological rhythms. For example, skin permeability shows circadian time-dependent difference. For instance, in children, the skin penetration of an eutectic mixture of lidocaine (lignocaine) and prilocaine was reported to depend on the time of administration, with a higher rate of penetration occurring in the evening. Ocular absorption of topically applied beta-blockers is also demonstrated to be circadian time-dependent difference.

- *Drug distribution*

    Circadian changes in biological fluids and tissues related to drug distribution are documented to vary according to time of day. Blood flow depends on several regulatory factors including sympathetic and parasympathetic systems which activities are known to be circadian time dependent with a predominant diurnal effect of the sympathetic system. Thus, diurnal increase and nocturnal decrease of blood flow may explain a possible difference in drug distribution depending on dosing time. Plasma proteins such as albumin or alpha 1 glycoprotein acid have been documented to be circadian time-dependent. The plasma concentrations of albumin and alpha 1 glycoprotein acid show peak around noon. As a result, daily variations have been reported for drug protein binding. Temporal variations in plasma drug binding may have clinical implications only for drugs that are characterized by a high protein binding (>80%) and a small apparent Vd.

- *Drug metabolism*

    Hepatic drug metabolism is generally assumed to depend on liver enzyme activity and/or hepatic blood flow: both have been shown to be circadian time-dependent[14]. Enzyme activities show circadian time-dependent difference in many tissues such as brain, kidney, and liver. Conjugation, hydrolysis and oxidation were shown to be circadian time dependent. For drugs with a high extraction ratio, hepatic metabolism depends on hepatic blood flow. Circadian variations in hepatic blood flow induce changes in liver perfusion and, thus, temporal variations in the clearance of such drugs. Clearance in healthy volunteers shows the highest values in the early morning.

- *Drug elimination*

    Renal physiological functions such as glomerular filtration, renal blood flow, urinary pH and tubular resorption show circadian time-dependent

difference with higher values during daytime. These rhythmic variations in renal functions may contribute to circadian dependent change in drug urinary excretion. The rhythmicity in urinary pH modifies drug ionization and may explain that acidic drugs are excreted faster after an evening administration as demonstrated for sodium salicylate and sulfasalazine. Such variations are obviously more pronounced for hydrophilic drugs.

CHRONOPHARMACOKINETICS OF DRUGS

- *Antiasthmatic Drugs*

  Antiasthmatic drugs such as theophylline and beta-sympathomimetics may/ should be dosed higher in the evening than during daytime when asthma is predominantly nocturnal. The theophylline concentration peak height (Cmax) is greater and time to peak (Tmax) shorter with dosing at 08:00 than at 20:00[15]. Both the first and second-generation H1-receptor antagonists of cyproheptadine, terfenadine, clemastine, and mequitazine exerted a statistically significantly longer duration of action when they were ingested in the morning (7 a.m.) than evening (7 p.m.).

- *Antibiotics*

  Administration-time-dependent differences in the pharmacokinetics and toxicity of antimicrobial agents have been documented in Table 3.

Table 3: Circadian variations in the pharmacokinetics of antibiotics in human beings

Results	Antibiotics
Higher mean serum levels at 5 a.m. Higher trough serum levels at 9 a.m.	Netilmicin
Higher serum levels at 9 p.m.	Amikacin
Longer serum half-life between 8 pm. and midnight Lower renal clearance between 8 p.m. and midnight Higher AUC (serum) between 8 p.m. and midnight	Gentamicin and isepamicin
Lower renal clearance at 8 p.m. Higher renal cortex accumulation at 1:30 a.m. Lower renal clearance at 1:30 a.m.	Amikacin
Higher AUC (serum) at midnight	Cefodizime
Longer serum half-life at midnight	Sulfamethoxazole
Lower urine excretion at 10 p.m.	Ciprofloxine
No significant circadian difference in serum half-life and renal clearance	Netilmicin
No significant circadian difference in renal clearance	Vancomycin

This is particularly true for the aminoglycosides, as their nephrotoxicity is greatest when administered during the resting period. Food intake and low urinary pH has been found to be protective of the toxicity of aminoglycosides at this time of the day[16]. Knowledge of the administration-time-dependence of aminoglycosides and the underlying mechanisms can be used to develop once-a-day formulations that are significantly less toxic, in particular to the kidney,

in patients who require around-the-clock antimicrobial therapy.

- *Anticancer Drugs*

  In human bone marrow, skin, and oral and rectal mucosae, DNA synthesis, a stage of the cell-division cycle associated with increased susceptibility to S-phase-specific agents, decreases by 50% or more between 00:00 and 04:00 compared with daytime. The activity of dehydropyrimidine dehydrogenase in human mononuclear cells increases by 40% around midnight. This enzyme brings about the intracellular catabolism of 5-FU and contributes to improved tolerability of this drug between 00:00 and 04:00. In contrast, cisplatin are better tolerated between 16:00 and 20:00 than 12 h apart. The chronopharmacokinetic finding of cisplatin seems to contribute to the decreased renal toxicity during evening administration. These findings show that the circadian stage at which anticancer drugs are given to patients should be carefully considered. One approach to increasing the efficiency of pharmacotherapy is administering drugs at times during which they are best tolerated given in Table 4.

Table 4: Tolerance to Circadian-based Cancer Chemotherapy in Humans

Drug	Cancer type	Time of optimal host tolerance
Doxorubicin	Ovarian Bladder	06.00 hr (>18.00 hr) 06.00 hr (>18.00 hr)
4-Tetrahydropyranyl adriamycin	Ovarian	06.00 hr (>18.00 hr)
Cisplatin	Ovarian Bladder	16.00 hr-20.00 hr (>4.00-08.00 hr) 18.00 hr (>6.00 hr)
Etoposide	Solid Tumors	07.00 hr (>19.00 hr)
5-FU		02.00- 10.00 hr
Methotrexate		08.00 hr
Anthracyclins		early morning

- *Antiulcer Drugs*

  H2-blockers (ranitidine, cimetidine, famotidine, roxatidine, nizatidine) should be taken once a day in the late afternoon or early night when acid secretion is increasing, independently of whether the compounds have a short or a long half-life. In contrast to H2-blockers proton pump inhibitors (PPI) should be dosed in the morning[17] since the increase by lansoprazole and omeprazole in intragastric pH is more pronounced after morning than evening administration.

- *Antihypertensive drugs*

  Cardiovascular drugs such as nifedipine, oral nitrates and propranolol, plasma peak concentration is twice as high and time to reach peak concentration is shorter after morning dosing compared with evening dosing[18]. Such a variation was not detected when sustained release dosage forms of nifedipine and isosorbide mononitrate were used. The underlying mechanisms of their chronopharmacokinetic pattern

involve a faster gastric emptying time and a greater gastrointestinal perfusion in the morning. Shiga et al documented that atenolol, in contrast to propranolol, is not absorbed more rapidly after morning administration compared with post-evening administration.[32] This confirms that the absorption rate of a lipophilic, but not hydrophilic, drugs is faster after morning dosing .

- *Anti-inflammatory drugs*

  Studies on NSAIDs, e.g., indomethacin and ketoprofen, have also shown that these drugs have a greater rate and/or extent of bioavailability when they are given in the morning than when they are given in the evening due to better morning absorption. Earlier and higher peak concentrations were obtained when ketoprofen and indomethacin was given at 07:00 and 07:00 or 11:00 respectively than at other times of the day or night[19]. Greater blood flow of the gastrointestinal tract in the morning than in the evening may explain this phenomenon. Circadian changes in renal function, plasma protein binding or hepatic blood flow could also explain temporal variation in drug plasma levels. Many variables are known to influence pharmacokinetics.

- *Opiod analgesics*

  Stronger analgesic effects were observed when tramadol and dihydrocodeine were applied in the evening to relieve painful stimuli. Peak morphine use occurred at 9 a.m. and least use at 3 a.m. In postoperative patients undergoing elective cholecystectomies, the need for fentanyl was lower when the surgery was done between 8 and 10 a.m. than between 11 a.m. and 3 p.m.[20]. Finally, a recent study of meperidine reveals a circadian variation of meperidine-induced analgesia in sickle cell anemia patients, with maximal analgesic effect occurring with the morning dose. A prospective study reported the existence of circadian variation in the distribution of lethal opiate overdoses in drug abusers, with a high death risk in the evening hours (03:00–09:00 h).

- *Local anesthetics*

  The duration of local anesthesia was longest when amide-type local anesthetic agents (lidocaine, ropivacaine, mepivacaine and betoxycaine) were applied around 3 p.m.[21] Area under the lidocaine plasma concentration curves (AUC) was largest in the afternoon. A 60%change was found in the 24-hour plasma clearance of bupivacaine, the clearance being greatest at 6 a.m. An administration-time-dependent variation in the transcutaneous passage of a medication was also studied. The plasma levels of lidocaine were significantly higher in the evening than at any other time of day.

- *General anesthetics*

  Barbiturates

  Higher brain pentobarbital or hexobarbital concentrations occurred when injected during the dark phase. Postsynaptic type A GABAergic activity is increased during nocturnal hours, corresponding to the duration of the maximal efficacy of barbiturates.

  Benzodiazepines

  The elimination half-life of midazolam was found to be at its shortest at 14:00 h and at its longest at 02:00 h

  Ketamine, Etomidate, Propofol, and Halogenated Agents

  Action longer during the night than during the day. This circadian rhythm also followed a seasonal pattern between 115% in January to 54% in May–June.

  Halothane

  Greatest efficacy of halothane occurred between 24:00 and 06:00 h.

- *Anti-Migraine drugs*

  Sumatriptan is a drug of choice in migraine treatment. The meanpeak serum concentration following the 0700 h administration was significantly higher than after the 1900 h administration. AUC and AUMC were significantly higher following the 0700 and 0100 h administrations than after the 1900 h administration. Following administration at 0700 h, the mean oral clearance and the apparent volume of distribution were significantly lower than after the 1900 h administration.

- *Immunosupressants*

  A slightly increased AUC and AUMC resulting from decreased apparent clearance during the resting (PM) versus activity (AM) period were observed for cyclosporine. A significant delay in mean residence time was observed after the PM dose, and the PM area under the moment curve was larger than the AM value. These trends and differences suggest that more sophisticated time-dependent cyclosporine dosing methods are needed to balance AM and PM drug exposure and thereby improve immunosuppression.

CHRONOTHERAPEUTICS

The knowledge of 24 h rhythm in the risk of disease plus evidence of 24 h rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for pharmacotherapy (chronotherapy). One approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated. The chronotherapy of a medication may be accomplished by the appropriate

timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The risk and/or intensity of the symptoms of disease vary predictably over time as exemplified by allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke, and peptic ulcer disease. The therapeutic-to-toxicity ratio of a medication varies predictably according to chronobiological determinants as exemplified by antitumor medications. The pharmacokinetics and pharmacodynamics of a medication vary depending on biological rhythms.

Chronotherapy to be incorporated into clinical practice,

- The morning daily or alternate-day dosing strategy for methylprednisolone that was introduced during the 1960s constitutes the first chronotherapy to be incorporated into clinical practice.

- Evening, once-daily dosing of especially formulated theophylline tablets for treatment of nocturnal asthma.

- Before-bedtime administration of verapamil HCL as a unique controlled onset extended release 24 h dosage form to optimize the treatment of patients with ischemic heart disease and/or essential hypertension.

- Evening administration of HMG-CoA-reductase antagonists for the management of hyperlipidemia.

- Evening, once-daily dosing of conventional H2-receptor antagonist or morning once-daily administration of proton pump antagonist tablet medications for the management of peptic ulcer disease.

- Before-bedtime administration of hypnotics for sleep induction and maintenance.

- Morning application of testosterone drug delivery patches systems to achieve a physiologic androgen-replacement therapy.

- Programmed-in-time infusion of antitumor medications according to biological rhythms to moderate toxicity and enhance dose-intensity in cancer treatment.

- Programmed-in-time administration of tocolytic medication relative to the circadian rhythm in uterine contractility to avert preterm labor and birth.

CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM (CDDS)

The effectiveness and toxicity of many drugs vary depending on the relationship between the dosing schedule and the 24 h rhythms of biochemical, physiological and behavioral processes. In addition, several drugs can cause alterations to the 24 h rhythms leading to illness and altered homeostatic regulation. The alteration of biological rhythm is a new concept of adverse effects. The disruption of circadian rhythm can be minimized by optimizing the dosing schedule[22]. A major aim of chronopharmaceutics is to deliver the drug in higher concentrations during the time of greatest need and in lesser concentrations when the need is less to minimize side effects. Examples of Chrono-DDS on the market, are given in Table 5 [23]. Most data have been compiled from FDA electronic orange book, specific product package inserts and United States patents and specific pharmaceutical company websites.

Table 5: Examples of chrono-drug delivery system on the market in USA and Japan

Active pharmaceutical ingredient (API)	Proprietary name dosages form	Proprietary chronopharmaceutical technology	Disease
USA			
Theophylline	Uniphyl® extended release tablets	CONTIN®	Asthma
Famotidine	Pepcid® Tablets	Physico-chemical modification of API	Ulcer
Simvastatin	Zocor® tablets	Physico-chemical modification of API	Hyperlipidemia
Verapamil HCl	Covera-HS® extended release tablets	OROS®	Hypertension
Verapamil HCl	Verelan®PM extended release capsules	CODAS®	Hypertension
Diltiazem HCl	Cardizem® LA extended release tablets	CEFORM®	Hypertension
Propranolol HCl	InnoPran® XL	DIFFUCAPS®	Hypertension
Japan			
Famotidine	Gaster® tablets	Physico-chemical modification of API	Ulcer
Simvastatin	Lipovas® tablets	Physico-chemical modification of API	Hyperlipidemia
Theophylline	Uniphyl® extended release tablets	CONTIN® Transdermal chrono delivery system	Asthma
Tulobuterol	Hokunalin® tape		Asthma

1) *CONTIN® technology*

In this technology, molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex

having utility as a matrix in controlled release formulations since it has a uniform porosity (semipermeable matrixes) which may be varied [24].

E.g.: Evening administration of Uniphyl® (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased bronchoconstriction in the morning.

2) *Physico-chemical modification of the API*

In this strategy, a proprietary method is used to modify the physicochemical properties (e.g. solubility, partition coefficient, membrane permeability, etc.) of the API to achieve the chronopharmaceutical objective. Typical examples of the use of this strategy in chronotherapy are those of antihyperlipidemic statins (HMG-CoA reductase inhibitors) [25] and antiulcerative agents (histamine H2 receptor-antagonists).

3) *OROS® technology*

OROS® technology[26] uses an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract.

Ex: OROS® Delayed Push– Pull System, also known as controlled onset extended release (COER) was used to design Covera- HSR, a novel anti hypertensive product. It actually enabled delayed, overnight release of verapamil to help prevent the potentially dangerous surge in BP that can occur in the early morning.[27]

4) *CODAS® technology*

The Chronotherapeutic Oral Drug Absorption System (CODAS®)[28] is a multiparticular system which is designed for bedtime drug dosing, incorporating a 4–5 h delay in drug delivery. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads.

E.g.: The CODAS®- verapamil extended release capsules (Verelan® PM) as ChrDDS actually provided enhanced BP reduction during the morning period when compared with other time intervals of the 24-h dosing period.[29]

5) *CEFORM® technology*

The CEFORM® technology[45] allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This ChrDDS approach is based on ''melt-spinning'', which means subjecting solid feedstock i.e. biodegradable polymer/bioactive agents combinations to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/ slow release combination.

E.g.: CardizemR LA, 1-day diltiazem formulation as ChrDDS.

6) *DIFFUCAPS® technology*

In the DIFFUCAPS® technology,[30] a unidosage form, such as a capsule for delivering drugs into the body in a circadian release fashion, is comprising of one or more populations of drug-containing particles (beads, pellets, granules, etc..). Each bead population exhibits a pre designed rapid or sustained release profile with or without a predetermined lag time of 3–5 h.

E.g.: Propranolol-containing ChrDDS (InnopranR XL) for the management of hypertension.

7) *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, electric fields, temperature, light and mechanical stimulation have been developed.[31]

E.g.: The Melodie®, programmable Synchromed®, Panomat® V5 infusion, and the Rhythmic® pumps.

8) *TIMERx® technology*

The TIMERx® technology (hydrophilic system)[32] combines primarily xanthan and 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 TIMERx® gum matrix, which expands to form a gel and subsequently releases the active drug substance.

E.g.: An oral, CR opioid analgesic oxymorphone.

9) *Three-dimensional printing*

Three dimensional printing® (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals[33]. Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets.

10) *Other CR erodible polymers*

Erodible polymers have been designed in different forms (e.g. tablets, capsules, micro particles) for ChrDDS applications. An excellent review of pulsatile drug-delivery system involving erodible polymers has been made by Bussemer et al.[51] By careful selection and combination of polymeric drug carrier of different erosion/degradation kinetic, or by

manipulating the interaction energy between the drug and the polymer, it may be possible to control the release of a drug at a rate that matches the requirement of the biological rhythm of a given disease state.

11)   *Controlled-release microchip*

An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using micro fabrication technology. Santini et al.[33] reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand.

OVERVIEW OF THE CURRENT STATUS OF CHRONOPHARMACEUTICAL DRUG DELIVERY

Examples of technologies that may be used for parenteral routes in chronotherapy include chronomodulating infusion pumps (i.e. Melodie™, Panomat™ V5, Synchromed™, Rhythmic™) and controlled release microchip strategies. Examples of technologies intended for oral administration include Contin®, Chronset®, Codas®, Ceform®, Diffucaps®, TIMERx®, Chronotopic™, Egalet™, GeoClock™, Port™, Three-dimensional printing (3DP)™, methods involving physicochemical modification of the active pharmaceutical ingredient and/or the use of controlled release erodible polymer. Recently, a novel floating pulsatile system using high internal phase emulsion based porous material intended for chronotherapy have been reported. In this floating system, drug loading using a porous carrier, synthesized by high internal phase emulsion technique using styrene and divinylbenzene, was achieved via solvent evaporation method. The lack of chemical agent as release modifiers made this delivery system distinct from other technologies for chronotherapy. Overall, the concept of low density floating multiparticulate pulsed-release dosage forms have been extensively explored.[53] Moreover, the combination of floating and pulsatile principles to develop drug delivery system for chronotherapy in nocturnal acid breakthrough has been demonstrated by using a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating. The development of transdermal drug delivery system for chronopharmaceutical applications was recently reviewed[34]. Examples of such systems include ChronoDose™, crystal reservoir and thermo responsive membrane systems. For rectal routes, a novel chronopharmaceutical and rectal aminophylline delivery system for asthma therapy has been reported. It consisted of sustained release hollow-type (SR-HT) suppositories using sodium alginate, sodium polyacrylate or polyacrylate-PANa (PA-PANa) co-polymer as gelling polymers/gel agent. The SR-HT suppository, particularly using PA-PANa as a gel agent, may be useful against nocturnal symptoms of asthma, thus providing (besides transdermal strategies), potentially an alternative method for chronotherapy for patients that are unable to take oral medications. Recently novel drug loaded nanocarriers have also been investigated in chronotherapy. The chrono-administration of drug containing nanoformulation appears to be a new therapeutic strategy that can increase for example breast cancer curability with no added side effects, costs, and risks for the patients. For example, based on the fact that the periodical sex hormones during menstrual cycle regulate the cyclic expression of VEGF in breast cancer and modulate the cancer vascular permeability and since the expression of cancer VEGF varies considerably at different menstrual cycle stages, it was conceivable that the variation between the highest and lowest cancer vascular permeabilities during menstrual cycle was significant. Thus, it was shown that nanoformulations (i.e. Caelyx and/or Abraxane) given at the proper menstrual stage with predicted highest VEGF expression and cancer vascular permeability could allow significantly increased drug retention in breast cancer, and thus leading to the maximal cancer growth control and minimal cancer metastatic spread. Caelyx/Doxil is a pegylated liposomal doxorubicin and Abraxane is a nanoformulation of paclitaxel using albumin molecules forming nano-size particles (130 nm). These data further suggest that the efficacy and/or targeting ability of novel nanomedicines could be enhanced by taking into account the biological rhythm as well. Future research in this field should also embody the design of novel systems not only for improved therapy but also for the chronoprevention of diseases with potential application in markers guided chronotheranostics (integration of diagnostic and chronotherapeutic products) and vaccination/ immunization strategies.[36]

CONCLUSION

The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 h rhythms of biochemical, physiological and behavioral processes under the control of circadian clock. The knowledge of 24 h rhythm in the risk of disease plus evidence of 24 h rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for pharmacotherapy. One approach to increasing the efficiency of pharmacotherapy is administering drugs at times during which they are best tolerated. The application of biological rhythm to pharmacotherapy may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The monitoring of rhythm, overcome of rhythm disruption and manipulation of rhythm are essential to improved progress and diffusion of chronopharmacotherapy. Chrono-DDS may benefit the development of new therapeutic strategies for several diseases as well as provide insights into chronotherapy as a way to optimize current therapies.

REFERENCES

1. Reinberg A, Halberg F, Circadian chronopharmacology, Annu. Rev. Pharmacol., 11, 1971, 455–492.

2. Smolensky MH, Labrecque G, Chronotherapeutics, Pharm News, 4, 1997, 10–16.

3. Maronde E, Stehle EH, The mammalian pineal gland: known facts, unknown facets, Trends Endocrinol. Metab., 18, 2007, 142–149.

4. Vener KJ, Reddy A, Timed treatment of the arthritic diseases: a review and hypothesis, Arthritis Rheum, 22, 1992, 83– 97.

5. Auvil-Novak SE, The chronobiology, chronopharmacology, and chronotherapeutics of pain, Annu. Rev. Nurs. Res., 17, 1999, 133–153.

6. Anwar YA, White WB, Chronotherapeutics for cardiovascular disease, Drugs, 55, 1998, 631–643.

7. Muller JE, Tofler GH, Stone PH, Circadian variation and triggers of onset of acute cardiovascular disease, Circulation, 79, 1989,733–743.

8. Moore JG, Englert E, Circadian rhythm of gastric acid secretion in man, Nature, 226, 1970, 1261–1262.

9. Levi F, Circadian chronotherapy for human cancers, Lancet Oncol, 2, 2001, 307– 315.

10. Hori K, Zhang QH, Li HC, Saito S, Sato Y, Timing of cancer chemotherapy based on circadian variations in tumor tissue blood flow, Int. J. Cancer, 65, 1996, 360–364.

11. Simvastatin: a one-a-day treatment for hypercholesterolemia, Pebble Beach, California, Am. J. Med, 87, 1989, 1– 59.

12. Malherbe C, De Gasparo M, De Hertogh R, Hoet JJ, Circadian variations of blood sugar and plasma insulin levels in man, Diabetologia, 5, 1969, 397–404.

13. Shiga T, Fujimura A, Tateishi T, The effect of age on diurnal variation in the pharmacokinetics of propranolol in hypertensive subjects, Eur J Clin Pharmacol, 44, 1993, 489-92.

14. Bernard Bruguerolle, Chronopharmacokinetics Current Status, Clin Pharmacokinet, 35, 1998, 83-94.

15. Reinberg A, Pauchet F, Ruff F, Gervais A, Smolensky MH, Levi F, Gervais P, Comparison of once-daily evening versus morning sustained-release theophylline dosing for nocturnal asthma, Chronobiol. Int, 4, 1987, 409–419.

16. Lemmer B, Circadian rhythms and drug delivery, J J Contr Release. Controlled Release, 16, 1991, 63-74.

17. Shiga, Fujimura A, Tateishi T, Ohashi K, Ebihara A, Differences of chronopharmacokinetic profiles between propranolol and atenolol in hypertensive patients, J Clin Pharmacol, 33, 1993, 756-761.

18. Bernard Bruguerolle, Gaston Labrecque, Rhythmic pattern in pain and their chronotherapy, Adv. Drug Del Rev, 59, 2007, 883–895

19. Youan BC, Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery, J. Control. Rel, 98, 2004, 337–353.

20. FDA, Electronic Orange Book, Administration, Washington, DC, 2003 F.a. D.

21. Leslie S, Euroceltique, SA, United States, 1982, 20.

22. Hoffman W, Smith R, Willard A, Merck & Co., United States, 1984, p. 26.

23. Jao F, Wong P, Huynh H, McChesney K, Alza Corporation, United States, 1992, p. 17.

24. White WB, Mehrotra DV, Black HR, Fakouhi TD, Effects of controlled-onset extended-release verapamil on nocturnal blood pressure, Am. J. Cardiol, 80, 1997, 469– 474.

25. Panoz D, Geoghegan E, Elan Corporation, United States, 1989, p. 49.

26. Smith DH, Neutel JM, Weber MA, A new chronotherapeutic oral drug absorption system for verapamil optimizes blood pressure control in the morning, Am. J. Hypertens, 14, 2001, 14– 19.

27. Fuisz R, Fuisz Technologies Ltd, United States, 1996, p. 34.

28. Percel P, Vishnupad K, Venkatesh G, Eurand Pharmaceuticals Ltd., United States, 2002, p.13.

29. Sershen S, West J, Implantable, polymeric systems for modulated drug delivery, Adv. Drug Deliv. Rev, 54, 2002, 1225–1235.

30. Baichwal A, Staniforth J, Penwest Pharmaceuticals Co.,United States, 2002, p. 19.

31. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Cima. Oral dosage forms fabricated by three dimensional printing, J.Control.Release, 66, 2000,1– 9.

32. Santini ST, Cima MJ, Langer R, A controlled-release microchip, Nature, 397, 1999, 335–338.

33. Hradetzky D, Transdermal drug delivery devices for chronotherapy, Med. Device Technol, 19, 2008, 45– 47.

34. Youan BBC, Chronopharmaceutics: Science and Technology for Biological Rhythm Guided Therapy and Prevention of Diseases, John Wiley & Sons, Hoboken, NJ, USA, 2009.

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