Drug Safety 2003; 26 (14): 999-1010
0114-5916/03/0014-0999/$30.00/0

© Adis Data Information BV 2003. All rights reserved.

Changes in Toxicity and Effectiveness with Timing of Drug Administration

Implications for Drug Safety

Shigehiro Ohdo

Division of Clinical Pharmacy, Department of Medico-Pharmaceutical Sciences, Clinical Pharmacokinetics, Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan

Abstract

The effectiveness and toxicity of many drugs can vary depending on the time of administration in relation to 24-hour rhythms of biochemical, physiological and behavioural processes under the control of the circadian clock. Such chronopharmacological phenomena are influenced by not only the pharmacokinetics but also pharmacodynamics of medications. Chronotherapy is especially relevant when 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. Morning, once-daily administration of corticosteroids results in little adrenocortical suppression, while the same daily dose split into four equal doses to coincide with daily meals and bedtime results in significant hypothalamus-pituitary-adrenal axis suppression. In a randomised, multicentre trial involving patients with previously untreated metastases from colorectal cancer, the chronomodulated infusion of oxaliplatin, fluorouracil and folinic acid was compared with a constant-rate infusion method. Adverse effects such as stomatitis and peripheral sensory neuropathy were lower and objective response was higher with chronotherapy as compared with the fixed-rate infusion. The merit of chronomodulated infusion is supported by the 24-hour rhythm of DNA synthesis and the activity of dehydropyrimidine dehydrogenase, which brings about the intracellular catabolism of fluorouracil. On the other hand, haloperidol and selective serotonin reuptake inhibitors have diverse effects on sleep continuity and nocturnal arousals. Although interferon also alters the clock function, this disruptive effect can be overcome by devising an administration regimen that minimises adverse drug effects on clock function. Thus, 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.

Studying the individualisation of pharmacotherapy has been undertaken with the aim of further improving pharmacotherapy. The individualisation of pharmacotherapy has been achieved mainly by monitoring drug concentrations. However, pharmacogenetic approaches, such as genetic diagnosis, have become a very attractive field because of the recent rapid progress in molecular biology.[1] Consequently, dosage adjustment has been based on the interindividual differences in drug pharmacokinetics; however, intra- as well as interindividual variability should be considered to aim at further

improving rational pharmacotherapy. This is because many drugs vary in potency and/or toxicity in association with the rhythmicity of biochemical, physiological and behavioural processes.[2-5] It has been argued that drug administration at certain times of the day should theoretically improve the outcome of pharmacotherapy.

Knowledge of 24-hour rhythm in the risk of disease, plus evidence of a 24-hour rhythm dependency in drug pharmacokinetics, therapeutic effects and safety constitutes the rationale for pharmacotherapy. 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 application of biological rhythm to pharmacotherapy may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the use of special drug delivery systems to synchronise drug concentrations to rhythms in disease activity. Within the past few years, developments in a number of pharmaceutical companies and bioengineering industries have kept pace with recent chronopharmacological advances.[6] Pharmaceutical companies have focused on investigation of underlying mechanisms as well as the conduct of multicentre clinical investigations involving numerous patients with the purpose of devising chronotherapeutic interventions with a variety of medications. New technology for delivering medications precisely in a time-modulated fashion by bedside or ambulatory pumps is developing for the management of human diseases. Chronopharmacologists are responsible for carefully evaluating and using this new technology to ensure that the devices and clinical findings are well accepted by colleagues currently involved in more classical research.

Several drugs are not only influenced by biological rhythms, but also act on them.[7] On the horizon are drugs that will 'fix' broken biological clocks, a condition which, in the opinion of some physicians, is perhaps a factor in all illness. In contrast, several drugs cause alterations in the 24-hour rhythms of biochemical, physiological and behavioural processes. The alteration of rhythmicity is sometimes associated with therapeutic effects (i.e. antidepressant drugs), or may lead to illness and altered homeostatic regulation.

In all living organisms, one of the most indispensable biological functions is the circadian clock (suprachiasmatic nuclei [SCN]), which acts like a multifunction timer to regulate homeostatic systems such as sleep and activity, hormone levels, appetite and other bodily functions that operate with 24-hour cycles.[8] Recently, clock genes are identified as the genes that ultimately control a vast array of circadian rhythms in physiology and behaviour.[9,10] The knowledge of clock genes may be important for the clinical practice.

The aim of this article is to provide an overview of drug administration time-dependent alterations in drug safety and therapeutic outcome.

1. Biological Time Structure

Biological time structure describes the sum of nonrandom, and thus predictable, time-dependent biological changes, including, with growth, development and ageing, a spectrum of rhythms with different frequencies.[2,3] Basically, the concept of biology is based on the construct of homeostasis, which is maintained in relative constancy over time by specific feedback mechanisms. However, important findings from the new science of biological rhythms clearly reveal that biological functions are not static over time. Namely, biological functions are variable in a predictable manner as rhythms of defined periods. Rhythms of very short period, in the order of a second or so, are evident in electrocardiographic and encephalographic tracings. Ultradian rhythms having periods in the range of 30 minutes to 20 hours are seen in many endocrine glands and sleep stages. A rhythm with about a 24-hour period (circadian) has been most investigated with applications now being incorporated into clinical medicine. Longer period rhythms of 7 days (circaseptan), a month (circatrigintan) and a year (circannual) are also known. Rhythms of approximately a month include the menstrual cycle in sexually mature women. Many of these rhythms appear to be genetically fixed and thus endogenous in nature. Endoge-

© Adis Data Information BV 2003. All rights reserved.

nous rhythms may or may not be adjusted in their timing by environmental factors, the so-called synchronisers. The science of objectively quantifying and investigating mechanisms of biologic time structure, including rhythmic manifestations of life, is called chronobiology.

2. Circadian Time Structure

The SCN of the anterior hypothalamus are the site of the circadian pacemaker in mammals.[8] The inherited period of the human pacemaker clock is not precisely 24 hours; it is somewhat longer, closer to 25 hours. Environmental time cues, termed synchronisers or zeitgebers, the strongest one being the daily light-dark cycle, set the inherited pacemaker circadian time-keeping systems to 24 hours each day. Many rhythms are genetically determined (endogenous). Some endogenous rhythms are adjusted in time (synchronised) by environmental factors, a process that adapts the human organism to its periodic surroundings. The genetic environmental interactions in the establishment and the maintenance of rhythms begin in early intrauterine life. They continue during infancy and childhood with the development of the mature time structure similar to that seen in the adult during the first l–2 years of extrauterine life.[5] Among the most prominent changes found in the course of ageing is the reduction of the amplitude of many circadian rhythms, which appears to be an important part in the ageing process.

Like any timing system, the circadian clock is made up of three components: an input pathway adjusting the time, a central oscillator generating the circadian signal and an output pathway manifesting itself in circadian physiology and behaviour. The daily changes in light intensities are thought to be the major environmental cue involved in circadian entrainment. Clock genes are the genes that control the circadian rhythms in physiology and behaviour.[9,10] The heterodimers of CLOCK-BMAL1 (MOP3) act through an E-box enhancer to activate the transcription of clock genes and clock-controlled genes (figure 1). The cryptochrome genes proteins shut down CLOCK-BMAL1 transcription in the nucleus, forming a negative feedback loop. Period (*PER*) gene 2 protein stimulates the transcription of BMAL1, forming a positive feedback loop. The phosphorylation of PER1 and PER2 by casein kinase I epsilon (CKIε) may regulate their cellular location and stability. Clock-controlled genes products, which include PER3, D-element binding protein (DBP) and arginine vasopressin, transduce the core oscillation to downstream output systems. A circadian rhythm in the expression of *PER* mRNA is discovered not only in the SCN but also in other tissues.[11] The circadian rhythm in the periphery is governed by that in the SCN, since the circadian rhythm in physiological function and expression of PER mRNA expression are abolished in SCN-lesioned rats[11] and *CLOCK* mutant mice.[12] Such a cascade of clock genes may contribute to the organisation of biological rhythms in the whole body. However, the mechanisms employed by circadian output pathways are poorly understood but are likely to involve both nervous and humoral signals.[13,14]

The mammalian circadian system[15,16] is much more complicated anatomically than the schematic representation shown in figure 2, but even a simplified version is enough to illustrate the point that there are a number of potential sites of action for drugs, which acts on the circadian clock or its inputs to alter timekeeping function. The principal entrainment pathway is the retinohypothalamic tract, a glutamatergic projection from the retina to the SCN and intergeniculate leaflet (IGL). There are two other inputs to the SCN core that transmit photic information, the IGL-geniculohypothalamic tract (GHT) projection, which is a γ-aminobutyric acid (GABA)-neuropeptide Y projection, and a pretectal-hypothalamic pathway, which is also probably GABAergic. The other inputs to the SCN core are a serotonin-containing projection from the raphe and a glutamate projection from the paraventricular nucleus that terminates in both the shell and core.

The 24-hour rhythms of physiology and behaviour are influenced by various environmental factors such as lighting condition, feeding schedules, social interactions and several drugs.[17-19] Since the period of the central circadian pacemaker in humans is slightly longer than 24 hours, synchronisation of

© Adis Data Information BV 2003. All rights reserved.

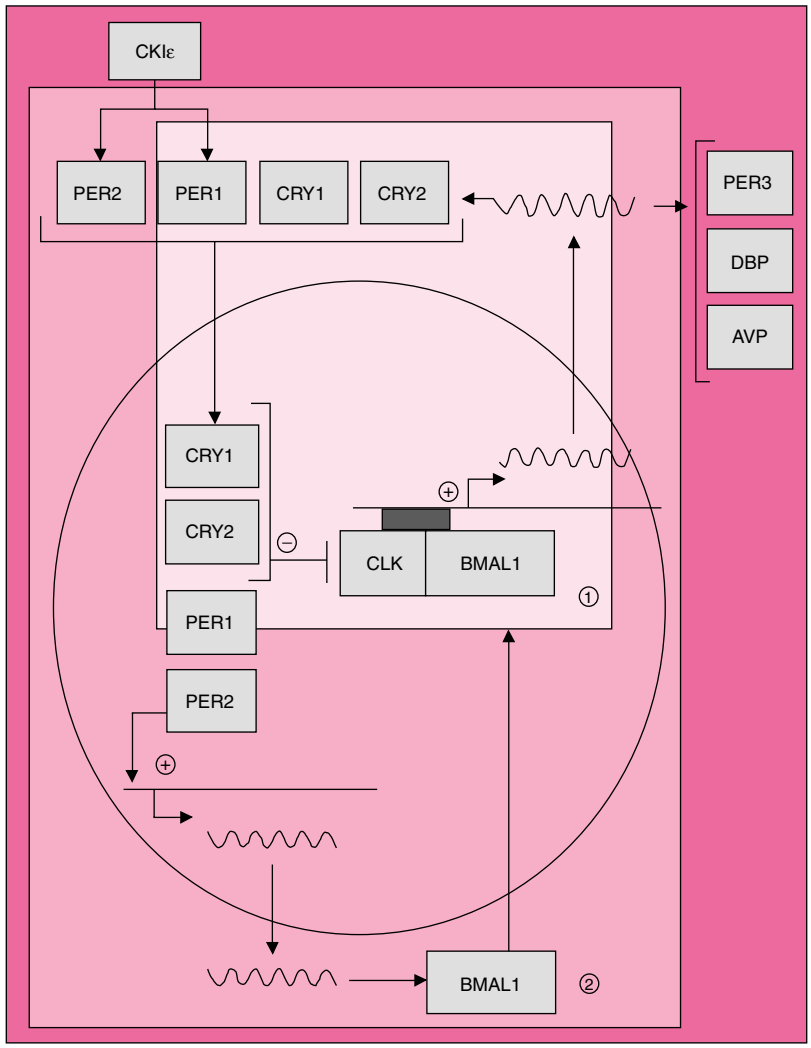

Fig. 1. A model of the molecular clockwork in a suprachiasmatic nuclei neuron.[10] Heterodimers of CLOCK (CLK) and BMAL1 (MOP3) activate transcription of clock genes and clock-controlled genes. The cryptochrome (CRY) proteins shut down CLOCK-BMAL1 transcription in the nucleus (circle), forming a negative feedback loop (small rectangle [1]). Period (PER) 2 stimulates the transcription of BMAL1, forming a positive feedback loop (middle rectangle [2]). The phosphorylation of PER1 and PER2 by casein kinase I epsilon (CKIε) may regulate their cellular location and stability. Clock-controlled genes products, which include PER3, D-element binding protein (DBP), and arginine vasopressin (AVP), transduce the core oscillation to downstream output systems.

the circadian system with the light-dark cycle occurs by daily phase advances of the circadian clock. In humans, the time-of-day–dependent phase-shifting effects of light are summarised in a phase-response curve (PRC).[20] In the first half of the night, light exposure causes phase delays and in the second half of the night it causes phase advances. Physiological doses of melatonin (nonphotic effect) have been used to describe a PRC that is about 12 hours out of phase with the PRC to light. Photic and nonphotic (i.e. extrinsic timekeeping) effects on intrinsic timekeeping may be important components of disordered timekeeping in depressive illness.

© Adis Data Information BV 2003. All rights reserved.

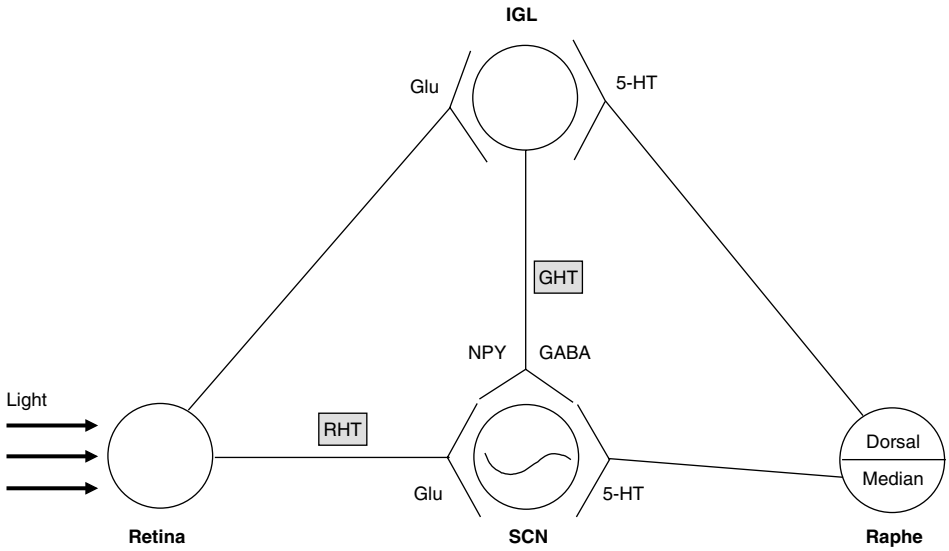

Fig. 2. Schematic and simplified diagram of the circadian system in mammals.[15,16] **GABA** = γ-aminobutyric acid; **GHT** = geniculohypothalamic tract; **Glu** = glutamate; **IGL** = intergeniculate leaflet; **NPY** = neuropeptide Y; **RHT** = retinohypothalamic tract; **SCN** = suprachiasmatic nuclei; **5-HT** = serotonin.

PER1 and *PER2* transcription is rapidly induced by light in a time-of-day–dependent manner in rodents.[17] The responsiveness of *PER1* mRNA to light is closely related to behavioural phase delays induced by light. Light-induced phase delays in locomotor activity during subjective night are significantly inhibited when mice are pretreated with *PER1* antisense phosphorothioate oligodeoxynucleotide.[21] Therefore, the gated expression of *PER1* may be an important step in causing photic entrainment. On the other hand, the acute and circadian time-dependent reduction of *PER1* and/or *PER2* mRNA in the hamster SCN by serotonin 5-$HT_{1A/7}$ receptor agonists is strongly correlated with the phase resetting in response to the drug.[22] Therefore, nonphotic shifts may involve change in *PER1* and/or *PER2* mRNA levels in the SCN.

3. Definition of Chronopharmacology

Chronopharmacology describes the results of a chronobiological approach to pharmacological phenomena.[2,3] Chronobiological methodology involves less risk of error and/or false information than the conventional homeostatic approach. Chronopharmacology includes the chronotoxicology describing undesired or harmful effects from chemical, physical or other agents including poisons, pollutants and overdoses of drugs upon biological temporal characteristics and as a function of biological timing and the chronotherapy endeavouring to cure or prevent disease, with proper regard to temporal characteristics, for example corticosteroid therapy timed to simulate the adrenocortical cycle in Addison's disease.

Chronopharmacokinetics describes biological time-related changes in the pharmacokinetics of an agent quantified by parameters of one or several curve patterns (models). Chronopharmacokinetic studies have been reported for many drugs in an attempt to explain chronopharmacological phenomena and demonstrate that the time of administration is a possible factor of variation in the pharmacokinetics of a drug. Time-dependent changes in pharmacokinetics may proceed from 24-hour rhythms at each process, for example absorption, distribution, metabolism and elimination. Thus, 24-hour rhythms in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow, drug protein binding, liver enzyme activity and/or hepatic blood flow, glomerular filtra-

© Adis Data Information BV 2003. All rights reserved.

tion, renal blood flow, urinary pH and tubular resorption may play a role in such pharmacokinetic variations.[4] Chronopharmacokinetics can, but may not always, be responsible for daily variation in drug effects and/or adverse effects.

Chronesthesy describes rhythmic (predictable-in-time) differences in the susceptibility or sensitivity of a biological target (e.g. receptors, membrane permeability, cells, tissues, organ, organ systems) to an agent. Chronesthesy emphasises predictable, rather than randomly distributed, biological time-related differences of such a target. When healthy organisms are concerned and metabolic processes are documented, the term chronopharmacodynamics is used by certain authors instead of chronesthesy. Biological rhythms at the cellular and subcellular level can give rise to significant dosing-time differences in the pharmacodynamics of medications that are unrelated to their pharmacokinetics. This phenomenon is termed chronesthesy. Rhythms in receptor number or conformation, second messengers, metabolic pathways and/or free-to-bound fraction of medications help explain this phenomenon.

Chronergy describes time-dependent effects of drugs on the organism as a whole. Chronergy pertains to rhythmic changes in both the desired and undesired effects of medications. It depends on both the chronesthesy of affected biological targets and the chronopharmacokinetics of a given drug.

4. 24-Hour Rhythm in Disease Occurrence or Severity

Chronobiological approach has clarified the presence of 24-hour rhythms in physiological functions and diseases. The examples described below show the approximate peak time of 24-hour rhythms relative to the diurnally active human beings.[2,3,6] The peak in serum cortisol, aldosterone, testosterone, platelet adhesiveness, blood viscosity and natural killer-cell activity is observed during the initial hours of daytime. Haematocrit is greatest and airway calibre (forced expiratory volume in 1 second) best around the middle and afternoon hours, respectively. Insulin, cholesterol, triglyceride and uric acid levels and platelet numbers and peak later during the day and evening. The rhythms of basal gastric acid secretion, white blood cells, lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle-stimulating hormone and luteinizing hormone show a peak at specific times during the night-time.

Twenty-four–hour rhythms in the processes that make up the pathophysiology of diseases cause prominent day-night patterns in the manifestation and severity of many medical conditions.[2,3,6] The onset of migraine is most frequent in the morning around the time of awakening from sleep. The sneezing, runny nose and stuffy nose in allergic and infectious rhinitis are worst in the morning upon waking up. The risk of asthma attack is greatest while the patient is asleep at night. The symptoms of rheumatoid arthritis are worst when awakening in the morning from sleep, while those of osteoarthritis are worst later in the day. The morbid and mortal events of myocardial infarction are greatest during the initial hours of daytime. The incidence of thrombotic and haemorrhagic stroke is greatest in the morning around the time of commencing diurnal activity. The ischaemic events, chest pain, and ST-segment depression of angina are strongest during the initial 3–5 hours of daytime. The symptoms of congestive heart failure are worse nocturnally. The manifestation of ST-segment elevation in Prinzmetal's angina is most frequent during the middle to later half of night-time. The pain and gastric distress at the onset and acute exacerbation of peptic ulcer disease are most likely in the late evening and early morning. The seizures of epilepsy are common around sleep onset at night and offset in the morning.

5. Chronotherapy in Clinical Practice

The knowledge of 24-hour rhythm in the risk of disease plus evidence of 24-hour rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for 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 accom-

© Adis Data Information BV 2003. All rights reserved.

plished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronise drug concentrations to rhythms in disease activity. Chronotherapy is especially relevant in the following cases. 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 antitumour medications. The pharmacokinetics and pharmacodynamics of a medication vary depending on biological rhythms. The goal hormonal substitution is to mimic the rhythmic variation of hormone levels in healthy individuals. Several examples for chronopharmacotherapy have been described.[2,3,6] The first chronotherapy to be incorporated into clinical practice is the administration of methylprednisolone in the morning on a daily or alternate-day basis. Some examples include:

- once-daily administration in the evening of specially formulated theophylline tablets for treatment of nocturnal asthma;
- before-bedtime administration of verapamil HCL as a unique controlled-onset extended-release 24-hour dosage form to optimise the treatment of patients with ischaemic heart disease and/or essential hypertension;
- evening administration of HMG-coenzyme A reductase inhibitors for the management of hyperlipidaemia;
- once-daily evening administration of conventional histamine H_2 receptor antagonists or once-daily morning administration of proton pump antagonists for the management of peptic ulcer disease;
- before-bedtime administration of hypnosedatives for sleep induction and maintenance;
- morning application of testosterone drug delivery patch systems to achieve a physiological androgen replacement therapy;
- programmed-in-time infusion of antitumour medications according to biological rhythms to moderate toxicity and enhance dose intensity in cancer treatment; and
- programmed-in-time administration of tocolytic medication relative to the 24-hour rhythm in uterine contractility to avert preterm labour and birth.

6. Relevance of Chronobiology and Chronopharmacological Concepts to Drug Safety

The relevance of chronobiology and chronopharmacological concepts to drug safety have been exemplified in terms of drug testing and post-approval drug surveillance. The findings of human circadian rhythms in chronotoxicity have been identified by the conventional endpoints of response as shown in classical toxic manifestation during corticosteroid and cancer therapy, and the unconventional ways as shown in altered circadian staging of human rhythms (e.g. with selective serotonin reuptake inhibitors [SSRIs], lithium, haloperidol, melatonin). The term chronotoxicity refers specifically to predictable-in-time variation in patient vulnerability to the adverse effects of medications due to biological rhythm determinants. Several examples are described in sections 6.1 to 6.3.

6.1 Corticosteroids

The circadian rhythm of serum cortisol in day-active persons shows a peak in the morning around the time of awakening from night-time sleep, generally around 08.00. Time-dependent differences in the effects of corticosteroids on adrenal suppression have been investigated after administration of a single infusion of methylprednisolone at different clock times to diurnally active healthy subjects.[23,24] When methylprednisolone is infused between 08.00 and l6.00, cortisol secretion remains normal. In contrast, when methylprednisolone is infused during the late afternoon and early evening, between l6.00 and 20.00, cortisol suppression is moderate. When methylprednisolone is infused between 00.00 and 04.00, cortisol secretion is markedly suppressed. The administration time-dependent inhibitory effect of methylprednisolone on cortisol secretion is due to the circadian rhythm in drug-induced hypothala-

© Adis Data Information BV 2003. All rights reserved.

mus-pituitary-adrenal (HPA) axis inhibition. By contrast, ACTH inhibition is more likely when methylprednisolone is infused late in the day and at night rather than during the morning and early afternoon hours. Morning once-daily administration of corticosteroids results in little adrenocortical suppression.[25,26] On the other hand, the same daily dose split into four equal administrations to coincide with daily meals and bedtime results in very significant HPA axis suppression.

6.2 Antitumour Drugs

Chronotoxicities are known, especially for antitumour agents.[27-31] In a randomised multicentre trial involving patients with previously untreated metastases from colorectal cancer, 93 patients were assigned chronotherapy and 93 were assigned constant-rate infusion via multichannel programmable ambulatory pumps.[27,28] The chronomodulated infusion of oxaliplatin (peak at 16.00), fluorouracil (peak at 04.00) and folinic acid (peak at 04.00) was compared with a constant-rate infusion method. Severe stomatitis was seen in 76% of the patients receiving the fixed-rate infusion and 14% of those on chronotherapy. Cumulative peripheral sensory neuropathy with functional impairment was reported in 31% patients on the fixed-rate infusion and in 16% patients on chronotherapy. The objective response rate was 51% for chronotherapy and 29% for the fixed-rate infusion. According to this multicentre randomised trial, therefore, the most active chronomodulated schedule is also the least toxic one. Median survival was 16 months in both modalities, possibly because 24% of the patients crossed over from the flat schedule to chronotherapy. The merit of chronomodulated infusion described here is supported by the following evidence. 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 during daytime.[27] The activity of dehydropyrimidine dehydrogenase in human mononuclear cells increases by 40% around midnight.[27] This enzyme brings about the intracellular catabolism of fluorouracil and contributes to improved tolerability of this drug between 00.00 and 04.00.

Two clinical trials compared the toxicity of two dosage administration times of anthracyclines and cisplatin in 30 patients with advanced ovarian cancer. Both studies demonstrated that doxorubicin is better tolerated where administered around 06.00 and cisplatin is better tolerated when given between 16.00 and 20.00 compared with when the agents are given 12 hours apart.[29] The chronopharmacokinetic finding for cisplatin seems to contribute to the decreased renal toxicity seen with this agent 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.

6.3 Psychotropic Drugs

Circadian rhythm sleep disorders (CRSDs) are a group of sleep disorders characterised by age-synchronisation between a person's biological clock and the environmental 24-hour schedule.[32-36] There are four main types of CRSD: delayed sleep phase syndrome (the most common); advanced sleep phase syndrome; non–24-hour sleep-wake syndrome (free-running pattern); and irregular (or disorganised) sleep wake pattern. These disorders lead to harmful psychological and functional difficulties and certain personality disorders may also be related to them. It has been found that psychotropic drugs such as haloperidol can cause CRSD, and this is also true for some cases of minor head trauma. For example, a patient with Gilles de la Tourette syndrome treated with haloperidol, ingested once daily after awakening from sleep, exhibited an irregular sleep-wake pattern with a free-running component of approximately 48 hours.[36] Transfer to risperidone, ingested once daily after awakening from sleep, was beneficial, resulting in a sleep-wake cycle more synchronised at the appropriate phase to the external zeitgebers and fewer nocturnal disturbances. The circadian sleep-wake schedule was ful-

© Adis Data Information BV 2003. All rights reserved.

ly synchronised when the patient was subsequently treated with melatonin at 21.00, before intended nocturnal sleep, in addition to risperidone in the morning. Restoration of the sleep-wake circadian pattern was accompanied by the patient's subjective report of significant improvement in his quality of life, social interactions and occupational status. This observation suggests that CRSDs can be related to use of the typical antipsychotic haloperidol and restored by switching to use of the atypical antipsychotic risperidone.

Haloperidol is not the only psychotropic drug that can provoke CRSD. Typical delayed sleep phase syndrome was observed in ten patients during treatment with the SSRI fluvoxamine, prescribed for obsessive-compulsive disorder.[37] The delay in falling asleep was seen to range from between 2.5 and 4 hours later than the patients' normal sleep routine. Emergence of DSPS induced by fluvoxamine was not immediate, and at least 5 days of treatment with no less than 100 mg/day of fluvoxamine occurred before patients first noticed the change in their normal sleep pattern. Additional treatment with melatonin 5mg taken at 21.00 can reorganise the sleep-wake schedule of these patients enabling them to continue with the fluvoxamine treatment. Furthermore, SSRIs have diverse effects on sleep continuity and nocturnal arousals.[7] The SSRI fluoxetine has been shown to increase arousals and the amount of stage 1 sleep, and to have a tendency to reduce slow wave sleep in depressed patients.[7] Fluvoxamine has been shown to diminish sleep continuity more than the tricyclic antidepressant (TCA) desipramine; this was thought to be related to its rapid eye movement sleep–suppressing properties.[7] Neither drug consistently affected sleep latency or delta sleep during chronic administration. Acute treatment with fluoxetine has been shown to increase, whereas the TCA trimipramine has been shown to decrease nocturnal wakefulness compared with placebo treatment.[7] The SSRI zimelidine has also been shown to diminish sleep continuity compared with amitriptyline and to increase arousals and awake time compared with amitriptyline and nortriptyline.[7] The SSRI citalopram delayed sleep onset in a patient with seasonal affective disorder.[7] The SSRI clomipramine advanced the acrophase of sleep and rectal temperature.[7] Attention should be paid to the alteration of sleep-wake cycle when prescribing psychotropic drugs.

Sleep disorders are a common symptom and characteristic of numerous psycho-pathologies, such as depression, anxiety or post-traumatic stress disorder. However, it should be emphasised that no existing psychopathology is characterised by a sleep disorder of the circadian type. Similar findings reported in patients with other disorders support the hypothesis that the described disruption of the sleep-wake schedule is medication rather than illness-related. Therefore, it is very important to realise that CRSDs may be an adverse effect of psychotropic drugs.

7. Administration Time-Dependent Alteration of Clock Function

Interferons (IFNs) have been widely used as antiviral and antitumour agents. However, IFNs cause adverse neuropsychiatric effects such as depression and neurosis and they are reported to sometimes lead to suicide.[38,39] When IFNs are administered during the early active phase in diurnally active humans, alterations in the 24-hour rhythm are suggested by the changes in the lymphocyte counts and cortisol levels.[40] However, the mechanism has not been clarified from the viewpoint of the disruptive effect of the drug on the clock genes. Figure 3 shows the disruptive effect of IFN-α on the rhythm of mRNA expression by *PER* genes in the SCN of mice.[41,42] These findings are supported by the inhibitory effect of IFN-α on the mRNA expression of *Clock* and *BMAL1*, which are important factors in activating the transcription of *PERs*, vasopressin and the *DBP* gene showing specific output function from SCN to the periphery.[10-12] Interestingly, an inhibitory effect of mRNA expression of each clock gene in the SCN is observed by the repetitive administration of IFN-α during the early active phase, but not the early rest phase. Similar administration schedule-dependent inhibition of *PER1* mRNA expression is demonstrated during the repetitive ad-

© Adis Data Information BV 2003. All rights reserved.

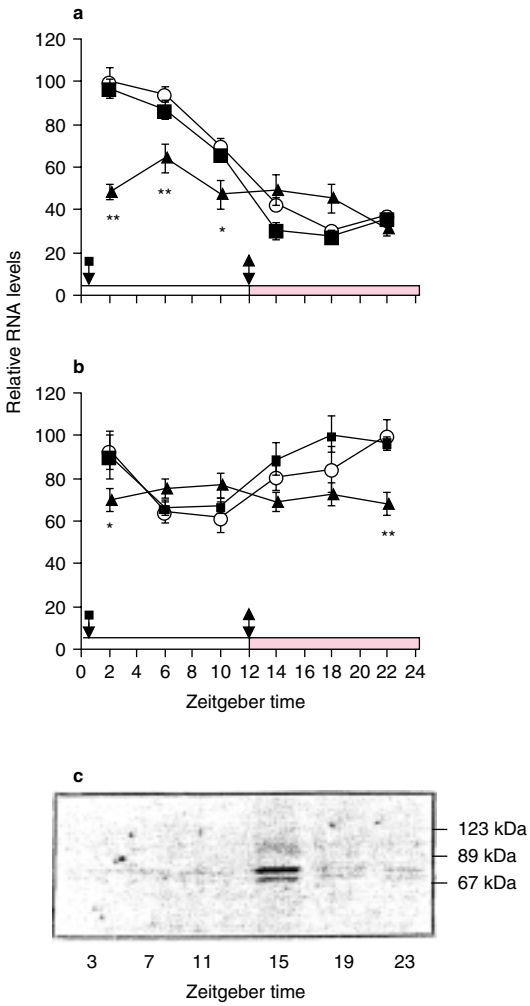

Fig. 3. Influence of interferon (IFN)-α dose schedule on mRNA expression of clock genes in the suprachiasmatic nuclei (SCN) [**a**] and (**b**)[41] and the time-dependent expression of interferon (IFN)-γ receptor (**c**).[44] In panels (**a**) and (**b**), RNA levels for the *PER* (**a**) or *BMAL1* (**b**) in the SCN of mice after a single dose of IFN-α (2 MIU/kg subcutaneously) at zeitgeber time 0 (ZT0) [closed square] or ZT12 (closed triangle), or saline (open circle) daily for 6 days. Each point represents the mean ± SEM of six observations. All mRNAs except for *BMAL1* in groups injected with IFN-α at ZT12 show significant 24-hour rhythms (*PER1* in groups injected with IFN-α at ZT12; $p < 0.05$, respectively, others; $p < 0.01$, respectively, ANOVA). White bars indicate the light period, and blue bars indicate the dark period. In panel (**c**), immunoblots of SCN whole extracts, probed with an anti–IFN-γ receptor antiserum (C-20) raised against amino acids 466–485 at the carboxyterminus of the α-chain of the receptor, show a major band of ~75 kDa: lane 1, ZT3; lane 2, ZT7; lane 3, ZT11; lane 4, ZT15; lane 5, ZT19; lane 6, ZT23. ** $p < 0.01$, * $p < 0.05$, compared with the value of controls at corresponding ZTs (Bonferroni's test).

ministration of IFN-γ, which can be induced by IFN-α or IFN-β in combination with other cytokines.[43] The expression of IFN-γ receptor in SCN follows a 24-hour rhythm with a peak at the early active phase.[44] This may be why the administration of IFN-α during the early rest phase can reduce its side effects. The effects of IFNs seen in humans correspond well to the findings indicating that alteration of the clock genes is induced by IFN-α administration during the early active phase in nocturnally active rodents. Furthermore, the 24-hour dependency of the disruptive effect of IFN-α on clock genes in SCN may be applicable to other drugs as shown in the case of IFN-γ. Thus, alteration of the clock function may be overcome by devising an administration regimen that minimises adverse effects on clock function.

8. Conclusions

The effectiveness and toxicity of many drugs vary depending on administration time associated with 24-hour rhythms of biochemical, physiological and behavioural processes under the control of circadian clock. The knowledge of 24-hour rhythm in the risk of disease plus evidence of 24-hour rhythm dependencies of drug pharmacokinetics, effects and safety constitutes the rationale for chronotherapy. To monitor the rhythmicity of pharmacokinetics and/or pharmacodynamics it may be useful to choose the most appropriate time of day for administration of drugs that may increase their therapeutic effects and/or reduce their adverse effects. Several drugs are not only influenced by biological rhythms, but also act on them.

In contrast, several drugs cause alterations in the 24-hour rhythms of biochemical, physiological and behavioural processes. The alteration of rhythmicity is sometimes associated with therapeutic effects (i.e. antidepressant drugs), or may lead to illness and altered homeostatic regulation. Attention should be paid to the alteration of the expression of clock genes and consider it an adverse effect, when it leads to altered regulation of the circadian system which is a serious problem affecting basic functioning of living organisms. The alteration of the clock func-

© Adis Data Information BV 2003. All rights reserved.

tion, a new concept of adverse effects, can be overcome by devising an administration regimen that minimises adverse drug effects on clock function.

It is very important to realise that the alteration of circadian rhythm can be an adverse effect of several drugs. Since the findings on circadian rhythm alteration are based upon a study with a small population of patients, we must be cautious in drawing broad conclusions. Naturally, well designed controlled studies are required to support the preliminary data and further clinical and basic research is needed to completely reveal the mechanism underlying the relationship between certain medications and circadian rhythm alteration. In future clinical trials, we should evaluate the alteration of the circadian time structure, such as evidenced by delayed, advanced or disrupted sleep-wake circadian rhythm, as a new side effect of medications that might show manifestation only as a result of particular administration time-schedule.

Acknowledgements

The author has provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

References

1. Ozdemir V, Shear NH, Kalow W. What will be the role of pharmacogenetics in evaluating drug safety and minimising adverse effects? Drug Saf 2001; 24 (2): 75-85
2. Halberg F. Chronobiology. Annu Rev Physiol 1969; 31: 675-725
3. Reinberg A, Halberg F. Circadian chronopharmacology. Annu Rev Pharmacol 1971; 11: 455-92
4. Labrecque G, Belanger PM. Biological rhythms in the absorption, distribution, metabolism and excretion of drugs. Pharmacol Ther 1991; 52: 95-107
5. Haus E, Touittou Y. Chronobiology of development and aging. In: Redfern PH, Lemmer B, editors. Physiology and pharmacology of biological rhythms. Berlin, Heidelberg: Springer-Verlag, 1997: 95-134
6. Smolensky MH, Labrecque G. Chronotherapeutics. Pharmaceutical News 1997; 4: 10-6
7. Duncan WC. Circadian rhythms and the pharmacology of affective illness. Pharmacol Ther 1996; 71: 253-312
8. Moore RY, Eichler VB. Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. Brain Res 1972; 42: 201-6
9. Tei H, Okamura H, Shigeyoshi Y, et al. Circadian oscillation of a mammalian homologue of the Drosophila period gene. Nature 1997; 389: 512-6
10. Chang DC, Reppert SM. The circadian clocks of mice and men. Neuron 2001; 29: 555-8
11. Sakamoto K, Nagase T, Fukui H, et al. Multitissue circadian expression of rat period homolog (rPer2) mRNA is governed by the mammalian circadian clock, the suprachiasmatic nucleus in the brain. J Biol Chem 1998; 273: 27039-42
12. Jin X, Shearman LP, Weaver DR, et al. A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. Cell 1999; 96: 57-68
13. Ueyama T, Krout KE, Nguyen XV, et al. Suprachiasmatic nucleus: a central autonomic clock. Nat Neurosci 1999; 2: 1051-3
14. Silver R, LeSauter J, Tresco PA, et al. A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. Nature 1996; 382: 810-3
15. Mrosovsky N. Problems in interpreting the effects of drugs on circadian rhythms. In: Redfern PH, Lemmer B, editors. Physiology and pharmacology of biological rhythms. Berlin, Heidelberg: Springer-Verlag, 1997: 415-34
16. Moore RY. Chemical neuroanatomy of the mammalian circadian system. In: Redfern PH, Lemmer B, editors. Physiology and pharmacology of biological rhythms. Berlin, Heidelberg: Springer-Verlag, 1997: 79-93
17. Shigeyoshi Y, Taguchi K, Yamamoto S, et al. Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. Cell 1997; 91: 1043-53
18. Ohdo S, Ogawa N, Nakano S, et al. Influence of feeding schedule on the chronopharmacological aspects of sodium valproate in mice. J Pharmacol Exp Ther 1996; 278: 74-81
19. Jones CR, Campbell SS, Zone SE, et al. Familial advanced sleep-phase syndrome: a short-period circadian rhythm variant in humans. Nat Med 1999; 5: 1062-5
20. Lewy AJ. Melatonin as a marker and phase-resetter of circadian rhythms in humans. In: Olcese J, editor. Melatonin after four decades: an assessment of its potentia. New York: Kluwer Academic/Plenum Publishers, 1999: 425-34
21. Akiyama M, Kouzu Y, Takahashi S, et al. Inhibition of light- or glutamate-induced mPer1 expression represses the phase shifts into the mouse circadian locomotor and suprachiasmatic firing rhythms. J Neurosci 1999; 19: 1115-21
22. Horikawa K, Yokota S, Fuji K, et al. Nonphotic entrainment by 5-HT1A/7 receptor agonists accompanied by reduced Per1 and Per2 mRNA levels in the suprachiasmatic nuclei. J Neurosci 2000; 20: 5867-73
23. Ceresa F, Angeli A, Boccuzzi A, et al. Once-a-day neurally stimulated and basal ACTH secretion phases in man and their responses to corticoid inhibition. J Clin Endocrinol Metab 1969; 29: 1074-82
24. Smolensky MH, D'Alozo GE. Progress in the chronotherapy of nocturnal asthma. In: Redfern PH, Lemmer B, editors. Physiology and pharmacology of biological rhythms. Berlin, Heidelberg: Springer-Verlag, 1997: 205-49
25. Reinberg A, Smolensky MH, D'Alonzo GE, et al. Chronobiology and asthma: III. Timing corticotherapy to biological rhythms to optimize treatment goals. J Asthma 1988; 25: 219-48
26. Reinberg A. Chronopharmacology of corticosteroids and ACTH. In: Lemmer B, editor. Chronopharmacology: cellular and biochemical interactions. New York: Marcel Dekker, 1989: 137-78
27. Levy F. Circadian chronotherapy for human cancers. Lancet Oncol 2001; 2: 307-15
28. Levy F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid

© Adis Data Information BV 2003. All rights reserved.

in metastatic colorectal cancer: International Organization for Cancer Chronotherapy. Lancet 1997; 350: 681-6

29. Hrushesky WJM. Circadian timing of cancer chemotherapy. Science 1985; 228: 73-5
30. Ohdo S, Makinosumi T, Ishizaki T, et al. Cell cycle-dependent chronotoxicity of irinotecan hydrochloride in mice. J Pharmacol Exp Ther 1997; 283: 1383-8
31. Takane H, Ohdo S, Yamada T, et al. Chronopharmacology of antitumor effect induced by interferon-β in tumor-bearing mice. J Pharmacol Exp Ther 2000; 294: 746-52
32. Dagan Y. Circadian rhythm sleep disorders (CRSD) in psychiatry: a review. Isr J Psychiatry Relat Sci 2002; 39 (1): 19-27
33. Wirz-Justice A, Cajochen C, Nussbaum P. A schizophrenic patient with an arrhythmic circadian rest-activity cycle. Psychiatry Res 1997; 73: 83-90
34. 34. Dagan Y. Sleep wake schedule disorders as a possible side effect of CNS medications [abstract]. Chronobiol Int 1999; 16: 25
35. Wirz-Justice A, Werth E, Savaskan E, et al. Haloperidol disrupts, clozapine reinstates the circadian rest-activity cycle in a patient with early-onset Alzheimer disease. Alzheimer Dis Assoc Disord 2000 Oct-Dec; 14: 212-215
36. Ayalon L, Hermesh H, Dagan Y. Case study of circadian rhythm sleep disorder following haloperidol treatment: reversal by risperidone and melatonin. Chronobiol Int 2002; 19 (5): 947-59
37. Hermesh H, Lemberg H, Abadi J, et al. Circadian rhythm sleep disorders (CRSD) as a possible side effect of fluvoxamine. CNS Spectr 2001; 6: 511-3
38. Fattovich G, Giustina G, Favarato S, et al. A survey of adverse events in 11241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 1996; 24: 38-47
39. Janssen HL, Brouwer JT, van der Mast RC, et al. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. J Hepatol 1994; 21: 241-3
40. Bocci V. Administration of interferon at night may increase its therapeutic index. Cancer Drug Deliv 1985; 2: 313-8
41. Ohdo S, Koyanagi S, Suyama H, et al. Changing the dosing schedule minimizes the disruptive effects of interferon on clock function. Nat Med 2001; 7: 356-60
42. Koyanagi S, Ohdo S. Alteration of intrinsic biological rhythms during interferon treatment and its possible mechanism. Mol Pharmacol 2002; 62: 1393-9
43. Hunter CA, Gabriel KE, Radzanowski T, et al. Type I interferons enhance production of IFN-γ by NK cells. Immunol Lett 1997; 59: 1-5
44. Lundkvist GB, Robertson B, Mhlanga JD, et al. Expression of an oscillating interferon-γ receptor in the suprachiasmatic nuclei. Neuroreport 1998; 9: 1059-63

Correspondence and offprints: Dr *Shigehiro Ohdo*, Division of Clinical Pharmacy, Department of Medico-Pharmaceutical Sciences, Clinical Pharmacokinetics, Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi, Higashi-Ku, Fukuoka, Fukuoka, 3-1-1, 812-8582, Japan.
E-mail: ohdo@phar.kyushu-u.ac.jp

© Adis Data Information BV 2003. All rights reserved.