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Mind the time : 24-hour rhythms in drug exposure and effect

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CHAPTER

General introduction

1

A thorough understanding of the underlying physiological processes that determine a drug's exposure and effect is required to address the challenges encountered during the development or optimisation of new and existing drug therapies. A ubiquitous feature of many physiological processes is their systematic variation over the course of the 24-hour day. As a result of the rhythmic nature of physiology, the exposure and effect of drugs could be influenced by the time of day that they are administered. In this chapter, the origin of these 24-hour rhythms will be discussed first. Next, an overview is given of the 24-hour variation in physiological processes and how these impact the exposure and effect of drugs. The current approaches of chronopharmacology, the branch of chronobiology that studies the effect of dosing time on drug treatments, will be summarized and some of the challenges will be identified. Finally, it will be discussed how the tools that have been developed within the field of pharmacometrics can be applied to benefit chronopharmacological research. This chapter lays the foundation for the research presented in this thesis.

THE ORGANISATION OF THE BIOLOGICAL CLOCK

Organisms across all kingdoms of life, from bacteria to mammals, possess an endogenous timing system that generates daily variations in biological processes. This timing system, termed the circadian clock, is thought to have emerged early in evolutionary history as an adaptation to the cyclic changes in light, temperature and food availability present on Earth (Schibler and Sassone-Corsi, 2002). The current understanding of the complex organisation of the circadian clock will be briefly summarised here.

As shown in Figure 1A, the circadian timing system consists of an input pathway that detects cyclic changes in the environment, a central clock where this input is integrated and an output pathway that conveys this information from the central clock to the periphery. A major input signal of the circadian timing system in mammals is light, which is transmitted from the retina to the central clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus (Dibner et al., 2010).

Cells in the SCN show a self-sustained circadian rhythm. These rhythms are generated by a molecular transcriptional/translational feedback loop that consists of positive and negative limbs (Mohawk et al., 2012). In short, a heterodimer consisting of CLOCK and BMAL1 proteins binds to E-box domains of *per* and *cry* genes (among others), thereby activating the transcription of these genes. After translation, PER and CRY proteins dimerize, translocate to the nucleus and suppress the activity of CLOCK and BMAL1, thereby effectively inhibiting their own transcription. PER and CRY are degraded and, as a results of their declining levels, the CLOCK:BMAL1 dimer can resume its transcriptional activity. A variety of auxiliary core clock components and post-translational modifications add to the robustness of this mechanism, creating a molecular feedback loop in each SCN neuron that autonomously sustains a rhythm with a period of approximately 24 hours (Figure 1B).

The translational/transcriptional feedback loop is not unique to the cells of the SCN. In fact, most cell types in the body express a similar set of clock genes (Balsalobre et al., 1998; Zylka et al., 1998) that can oscillate autonomously (Welsh et al., 2004). However,

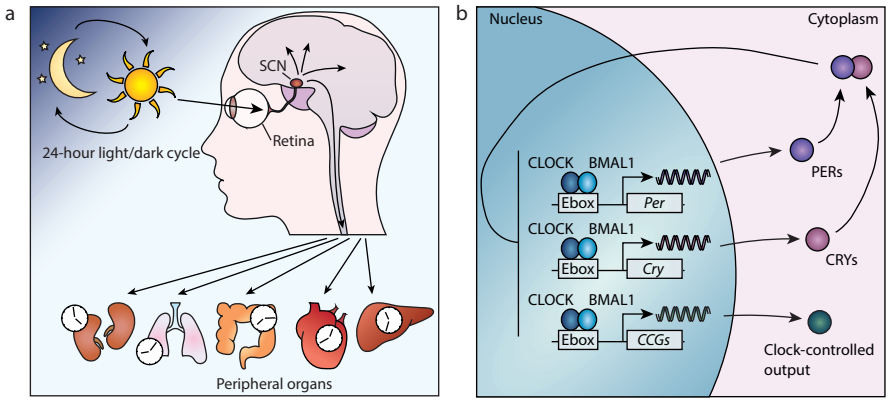

Figure 1 Organisation of the circadian timing system at (A) the level of the organism and (B) of the cell. **(A)** The biological clock is located in the suprachiasmatic nuclei (SCN). Light information from the environment is transmitted from the retina to the SCN in the hypothalamus. Neuronal and humoral signals from the SCN synchronize the circadian oscillators in peripheral organs. **(B)** At the cellular level, a 24-hour rhythm is generated by a translational/transcriptional feedback loop. The transcription factors CLOCK and BMAL1 bind to E-box elements in the promotor of other clock genes (period1,2 and cryptochrome1,2) and of clock-controlled genes (CCGs), thereby activating their transcription. After translation in the cytoplasm, PER and CRY dimerize and translocate to the nucleus, where they inhibit the transcriptional activity of CLOCK and BMAL1. Hereby, they downregulate their own transcription. This (simplified) process creates oscillations in gene expression with a period of approximately 24 hours.

three properties unique to SCN cells have led to the distinction of the central clock in the SCN and peripheral clocks in other brain regions and organs (Welsh et al., 2010). Firstly, the phase of SCN neurons is directly modulated by photic input; that is, these cells can be entrained by environmental light information that is conveyed from the retina via the retinohypothalamic tract to the SCN. Secondly, SCN neurons are tightly coupled, so their rhythm remains synchronized even in the absence of any oscillating input. Thirdly, their firing rate shows pronounced circadian variation, by which they directly and indirectly synchronize other cells in the body (Welsh et al., 2010). Other cell types in the body do not share these properties. Instead, synchronisation among cells within a tissue, and of a tissue with the external light/dark cycle, relies on the rhythmic output generated by the SCN, which is transmitted via various mechanisms, including neuronal connections, endocrine signalling and indirect cues conveyed by oscillations in body temperature or behaviour (Dibner et al., 2010). In the absence of synchronizing signals, tissues as a whole rapidly lose their rhythmicity due to subtle differences in the period length between the individual cells (Nagoshi et al., 2004; Welsh et al., 2004).

The core clock genes do not only regulate their own expression, but also that of clock controlled genes. Early microarray studies revealed that up to 10% of genes in the SCN and the liver show circadian expression patterns (Panda et al., 2002). More recently, it was shown that 43% of all genes in mice are rhythmically transcribed in at least one organ (Zhang et al., 2014). Through these fluctuations in gene expression, the circadian timing system controls a wide range of physiological processes, such as metabolism, heart rate, renal function and hormone levels (Duguay and Cermakian, 2009).

In the context of this thesis, it is important to emphasize the correct use of the word "circadian". Although frequently used more loosely outside the field of chronobiology, a circadian rhythm refers, by definition, to a rhythm with a period of approximately 24 hours that is autonomous and therefore persists under constant conditions. The terms "diurnal", "daily" or "24-hour" can be used to describe any rhythm with a period of 24 hours, regardless of whether it is endogenously generated or caused by rhythms in light exposure, social cues, or activity (Klerman, 2005). Therefore, research on the effect of time of day in any biological process that is conducted in the presence of environmental cues that exhibit a 24-hour variation, like most clinical trials, do not study circadian rhythmicity, but rather 24-hour, diurnal or daily rhythmicity. This distinction is important for the correct understanding and interpretation of chronobiological research (Klerman, 2005).

THE EFFECT OF PHYSIOLOGICAL RHYTHMS ON DRUG TREATMENTS

Twenty-four hour rhythms in physiological processes are known to influence the exposure and effect of numerous drugs (Dallmann et al., 2014). The existence of these rhythms implies that the effectiveness of a drug may depend on dosing time and that there may be an optimal time of administration for any given drug. Therefore, although often overlooked, the rhythmic nature of mammalian physiology is a source of variation that could have

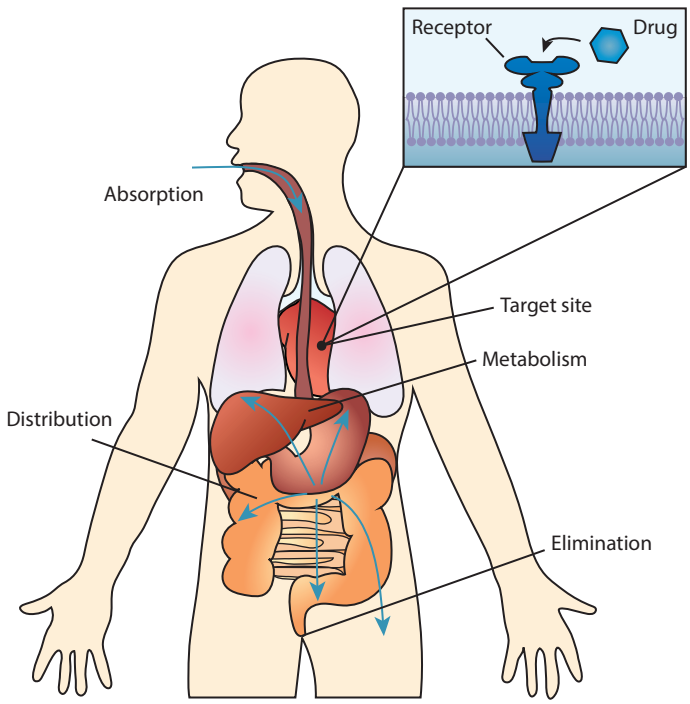

Figure 2 Overview of the processes that determine the exposure (pharmacokinetics) and effect (pharmacodynamics) of a drug. The exposure to a drug in the body is determined by the rate and extent of absorption, distribution, metabolism and elimination. The effect is determined by the interaction between the drug and its receptor at the target site.

important implications for the design of new and existing drug therapies. This section will give an overview of the rhythms in physiological processes and provide some examples of how the exposure (pharmacokinetics) and effect (pharmacodynamics) of a drug (Figure 2) are influenced by the time of day.

Pharmacokinetics

Pharmacokinetics refers to the fate of a drug in the body from the moment it is administered until it is eliminated. The pharmacokinetics of a drug is defined by its absorption, distribution, metabolism and elimination. Collectively known as ADME, these properties determine the exposure and the shape of the concentration-time profile of a drug in the body. The four ADME properties and the extent to which they show 24-hour variation will be briefly discussed here.

Absorption

Depending on the route of administration, a drug needs to be absorbed before it reaches the systemic circulation. Following oral administration, a compound passes through the gastrointestinal tract, crosses the intestinal wall and reaches the liver via the portal vein, after which it enters the bloodstream. Absorption is affected by system- and drug-specific factors, such as gastric emptying time, the pH of the gastrointestinal tract, gastrointestinal blood flow, intestinal motility, function of transporter enzymes, first-pass effects, as well as the solubility and permeability of the compound (Martinez and Amidon, 2002).

Many processes involved in drug absorption show 24-hour or circadian variation (Baraldo, 2008). For example, in humans, intestinal motility (Keller et al., 2001; Kumar et al., 1986; Rao et al., 2001), gastric emptying rate (Goo et al., 1987) and hepatic blood flow (Lemmer and Nold, 1991) are higher in the morning than in the evening or night. In line with these findings, many drugs, including roflumilast, nifedipine, cilostazol, and paracetamol, are absorbed most rapidly in the morning (Bethke et al., 2010; Kamali et al., 1987; Lee et al., 2014; Lemmer et al., 1991). Daily variation in the rate of drug absorption influences the peak concentration (C_{max}) and the time to the peak concentration (T_{max}) (Baraldo, 2008). This could be relevant for drugs with a narrow therapeutic window, or for drugs whose effect depends on the C_{max} or the period of time that the concentration is above a critical concentration, as is the case for many antibiotics (Drusano, 2004). Additionally, there is some evidence that dosing time affects the bioavailability of a drug after oral administration. The bioavailability of an immediate-release formulation of nifedipine, a calcium channel blocker used for the treatment of hypertension, was 40% lower after administration in the evening compared to the morning (Lemmer et al., 1991). This reduction was attributed to diurnal variation in the absorption of the drug, because neither a sustained-release formulation nor an intravenous solution of nifedipine showed dosing time dependent variations in exposure, excluding the effect of rhythmic metabolism (Lemmer et al., 1991). In theory, daily variations in the extent or rate of absorption may provide a rationale to adapt the dose depending on the time of day, but this has not been applied clinically.

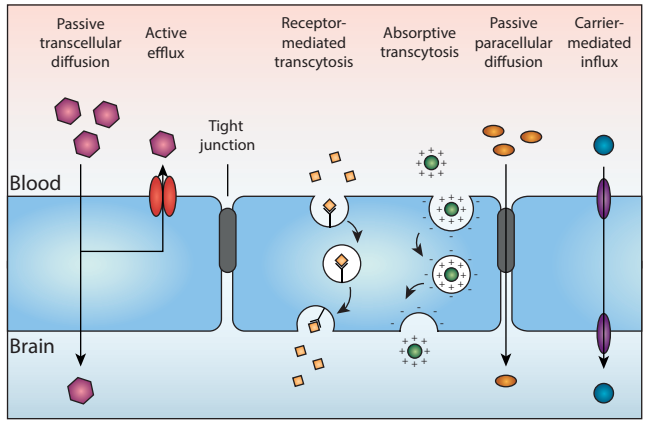

Figure 3 Routes of transport across the blood-brain barrier. Molecules, including therapeutic drugs, may enter the brain via passive transcellular or paracellular diffusion. Efflux transporters actively pump their substrates out of the brain through an energy-dependent process. Molecules, including hormones and albumin, also enter via receptor-mediated or absorptive transcytosis. Specialized influx transporters facilitate the entry of their substrates to the brain.

Distribution

After reaching the circulation, a drug travels through the bloodstream and moves into and out of the various sites of the body, a process known as distribution. The distribution of a drug is a critical determinant of its concentration at the target site and thereby, ultimately, of its effectiveness. Whether a drug is primarily retained in the blood or whether it mainly concentrates in organs or tissues depends partly on its physicochemical properties, like lipophilicity and molecular size. However, physiological processes such as organ blood flow, active transport and plasma protein binding, also play an important role in the rate and extent of distribution (Danhof et al., 2007). Given the focus of this thesis, the importance of 24-hour variation in drug distribution will be discussed here in the context of drugs targeted at the central nervous system (CNS).

A better understanding of the underlying mechanisms that regulate the transport of drugs between the blood to the brain is required to increase the success rate of treatments targeted at CNS disorders (de Lange and Hammarlund-Udenaes, 2015). More specifically, knowledge on 24-hour variation in the processes that regulate drug distribution in the CNS may lead to better informed dosing decisions by providing insight into the effect of dosing time on the concentration at the target site.

Unlike most peripheral tissues, the distribution of drugs and other potentially toxic compounds to and within the brain is limited because of the existence of a specialized barrier called the blood-brain barrier (BBB). The BBB is made up of a layer of endothelial cells that line the wall of the brain capillaries and that are connected by tight junctions. Tight junctions are multiprotein complexes that effectively restrict the paracellular diffusion of drugs and other molecules (Keaney and Campbell, 2015). Therefore, the transport of molecules to and from the brain takes place primarily via transcellular pathways (Figure 3). These pathways include passive or facilitated diffusion, active influx and efflux by membrane transporters

and receptor- or adsorptive-mediated transcytosis (Abbott, 2013). Active efflux transport involves the movement of molecules from the CNS back into the circulation by specialized transporter proteins. One of the best-studied efflux transporters is P-glycoprotein (P-gp), which is expressed in the BBB as well as in the blood-cerebral spinal fluid (BCSFB) and in various parenchymal cell types such as neurons and glial cells (de Lange, 2013; Stieger and Gao, 2015). P-gp has broad substrate specificity and restricts the distribution of a wide variety of drugs to the brain, forming a major challenge for the development of effective therapies for neurological disorders (Miller, 2010).

It is becoming increasingly clear that the transport across the BBB is highly dynamic and is influenced by both physiological processes such as the sleep-wake cycle and aging as well as pathophysiological conditions such as ischaemic stroke and infection (Keaney and Campbell, 2015). However, it is unknown if, and to what extent, the transport of drugs and endogenous compounds to and within the CNS is influenced by 24-hour variation in the mechanisms that regulate transport across this barrier.

The possibility that the transport of molecules, including therapeutic drugs, across of the BBB is influenced by the time of day is largely unexplored, but is not fully unsupported. For example, it has been shown that the effect of mannitol-induced osmotic opening of the BBB on the exposure to intravenously administered atenolol in brain extracellular fluid is 10x higher in the afternoon compared to the morning (de Lange et al., 1995). Other processes showing 24-hour variation that could conceivably influence drug distribution to the CNS depending on the time of day include cerebral blood flow (Conroy et al., 2005; Endo et al., 1990) and the production of cerebral spinal fluid (CSF) (Nilsson et al., 1992, 1994). Additionally, it has been shown in several *in vitro* and *in vivo* studies that that the expression and activity of P-gp in the liver and intestine exhibits 24-hour variation (Ando et al., 2005; Ballesta et al., 2011; Hayashi et al., 2010; Murakami et al., 2008; Okyar et al., 2012). However, it is unknown whether this applies to P-gp expression and activity in the CNS as well. Considering the large number of drugs that are a substrate for this and other efflux transporters, this question warrants further investigation.

Metabolism

Xenobiotic metabolism is mediated by two groups of enzymes that have distinct functional roles (Xu et al., 2005). The first group of enzymes activate or inactivate drugs through oxidation, reduction or hydroxylation. The cytochrome P450 (CYP) microsomal enzymes, which are mainly found in the liver, gastrointestinal tract, lung and kidney, are an important family of this group. The second group of enzymes catalyses conjugation reactions. This makes lipophilic compounds more hydrophilic, thereby facilitating their excretion into urine, faeces or bile. The expression of many of these metabolizing enzymes in the liver shows profound 24-hour variation, which is regulated by clock-controlled transcription factors (Gachon et al., 2006; Takiguchi et al., 2007). As a result, the metabolism of many drugs is influenced by the time of day (Dallmann et al., 2014). For example, acetaminophen (paracetamol) bioactivation and toxicity in mice, which is controlled by CYP enzymes,

shows 24-hour variation that appears to be at least partly regulated by the autonomous hepatocyte circadian clock (DeBruyne et al., 2014; Johnson et al., 2014). Also in humans, CYP3A activity, as measured by 6β-hydroxycortisol to cortisol ratio in urine, shows 24-hour variation with 2.8 fold higher activity between 17:00 and 21:00 than between 9:00 and 13:00 (Ohno et al., 2000).

Elimination

Drugs, and their metabolites, are excreted from the body through renal, biliary, pulmonary or faecal elimination. Diurnal rhythms have been found in many physiological processes that underlie renal elimination, the predominant route of drug excretion, including glomerular filtration rate, renal plasma flow, urine volume and the excretion of electrolytes in urine (Stow and Gumz, 2011). Of note, the variation in glomerular filtration rate and renal plasma flow persist when food and fluid intake as well as posture kept constant for the entire study duration, indicating the endogenous nature of these rhythms (Buijsen et al., 1994; Koopman et al., 1989; Voogel et al., 2001). In line with these findings, the renal clearance of various antibiotics, including amikacin and gentamicin, has been reported to depend on the time of day, with generally higher clearance during the day and lower clearance during the night in human subjects (Beauchamp and Labrecque, 2007). However, mechanistic links between the 24-hour variation in renal physiology and drug clearance at different times of the day have not been reported (Paschos et al., 2010).

Pharmacodynamics

Pharmacodynamics is the result of the interaction of a drug with its target. Recently, it was reported that the majority of best-selling drugs directly target the product of a gene that is rhythmically transcribed, suggesting that the effect of these drugs could depend on the time of day (Zhang et al., 2014). Indeed, the most successful examples of chronopharmacological interventions involve rhythmic targets and/or symptoms (Dallmann et al., 2014). For example, blood pressure shows clear 24-hour variation with a marked decrease during the night. In patients with hypertension, the absence of this night-time dip is associated with an increased risk of cardiac events (Ohkubo et al., 2002; Staessen, 1999; Verdecchia et al., 1994). It has been shown that patients that take at least one antihypertensive medication at bedtime, instead of upon awakening, have better blood pressure control and lower risk of developing cardiovascular events (Hermida et al., 2008, 2010).

The chronopharmacology of pain management has also received considerable attention due to the rhythmic nature of pain intensity (Junker and Wirz, 2010). Indeed, numerous studies have reported an effect of time-of-day on the action of analgesic drugs in humans, although the results with regards to the timing of these effects has been conflicting (Potts et al., 2011). Furthermore, the translation of these findings to clinical practice is difficult due to the heterogeneity in the nature and causes of pain, the large variation in pain among individuals as well as the difficulty to obtain an objective measure.

Toxicity

The toxicity of many types of drugs, such as aminoglycosides, anti-cancer drugs and acetaminophen (paracetamol), also varies over the 24-hour period, which should be considered when determining the most optimal time of drug administration (Paschos et al., 2010). Time-of-day dependent toxicity may arise from variation in the exposure to a drug or its toxic metabolites or from variation in the sensitivity of target cells. To discriminate between these two possibilities with regard to the anticancer drug cyclophosphamide, Gorbacheva et al (2005) combined pharmacokinetic analysis of this drug and its metabolites with measurements of the sensitivity of the hematopoietic system, the main target of cyclophosphamide toxicity, at different dosing times (Gorbacheva et al., 2005). Through an elegant series of experiments, the authors found that the 24-hour rhythm in the toxicity of cyclophosphamide is not related to variation in the exposure to this drug, but rather to the 24-hour rhythms in the sensitivity of B cells to cyclophosphamide, which is influenced by the activity of the clock genes CLOCK and BMAL1.

CHRONOPHARMACOLOGY: APPROACHES & CHALLENGES

The previous section highlighted the ubiquitous nature of 24-hour rhythms in physiology and provided examples of its effect on the pharmacokinetics, pharmacodynamics and toxicity of drugs. Although the relevance of these rhythms to the optimisation of drug treatments has been recognized within the field of chronobiology, this body of knowledge has yet to reach clinical practice (Paschos et al., 2010). In this section, the current approaches that are used in chronopharmacology and the challenges pertaining to the translation of the findings to the clinic are discussed.

To study the effect of time of day on the pharmacokinetics, pharmacodynamics or toxicity of a drug, the most obvious approach is to administer the drug of interest at various times of the day and subsequently measure the exposure or effect of the drug at those time points. Although continuous infusions of more than 24 hours are occasionally used instead (Bienert et al., 2013; Elting et al., 1990; Fleming et al., 2015), most chronopharmacological research described in the previous section took this former approach. With such a study design, the ability to detect a significant time-of-day effect greatly depends on the choice and number of dosing times. As many studies only use two dosing times in the morning and the afternoon or evening (for instance: (Bethke et al., 2010; Bleyzac et al., 2000; Cao et al., 2010; Lee et al., 2014; Martin et al., 2002)), it is possible that the peak and trough of the variable of interest are outside the studied intervals. Hence, if no effect of dosing time is detected, this may either be due to absence of 24-hour variation on the pharmacokinetic or pharmacodynamic parameter(s) of interest, or due to an unfortunate choice of time-points, rendering the study inconclusive. This should be considered in the design of prospective chronopharmacological studies.

Another factor to take into consideration in chronopharmacological research in humans is the large degree of heterogeneity among the population. Individuals differ in their

amplitude and phase, introducing a source of variability to any chronopharmacological study. This interindividual variability is associated with chronotype (morningness/eveningness), demographic variables, or circadian rhythm disturbance due to shift work or transmeridian travel (Kerkhof, 1985). Although these factors can be – at least partly – controlled for in order to minimize the degree of unexplained interindividual variability, this is usually not reported and/or included in chronopharmacological studies.

Another limitation of many chronopharmacological studies is that typically one drug is investigated without paying attention to the implications of the findings to other drugs. However, given the large number of drugs used in clinical practice, it is virtually impossible to investigate the effect of time of day on all available drugs. As the pharmacokinetic and pharmacodynamic properties are a function of the underlying physiological processes that are shared between many different types of drugs, as described in the previous section, this raises the possibility of studying 24-hour variation in physiological process(es) using a model compound that represents a group of drugs.

A relative recent development within the field of drug discovery and development is the use of statistical and mathematical methods to model the pharmacokinetics and pharmacodynamics of a drug and the associated sources of variability (Milligan et al., 2013). Many of the challenges in chronopharmacology that were discussed above, including the characterization of interindividual variability and quantification of the effect of time of day on pharmacokinetic of pharmacodynamic parameters, can be addressed by the field of pharmacometrics. The next section will highlight the potential benefits of applying this field to chronopharmacology.

PHARMACOMETRICS AND CHRONOPHARMACOLOGY

Having evolved over the past four decades, pharmacometrics is a relatively new scientific discipline that is becoming an increasingly important tool in the development and optimisation of new and existing drug therapies (Milligan et al., 2013). Pharmacometrics is the science of developing and applying statistical and mathematical models to analyse the fate and effect of drugs in a biological system. Within the field of pharmacometrics, population pharmacokinetic-pharmacodynamic (PKPD) modelling is used to quantitatively describe the time course of drug exposure (pharmacokinetics), the relationship between exposure and effect (pharmacodynamics) and the associated sources of variability among the population (Mould and Upton, 2012). In this section, the application of PKPD modelling to the field of chronopharmacology is discussed.

Effect of time of day in PKPD models

As discussed above, time of day may affect the pharmacokinetics and pharmacodynamics of a drug, thereby introducing a significant source of variation in the data. Although frequently overlooked in PKPD models, there are several examples available in the literature that show how the effect of time of day can be incorporated in such a model.

Baseline variation in pharmacodynamic models

In general, a pharmacodynamic model describes the link between the concentration or dose and the drug effect. Functions used to describe continuous pharmacodynamic effects can, for example, be linear or E_{max} and can be either directly connected to the measured drug concentration or modelled as an indirect effect to account for a delay between the concentration and the effect (Mould and Upton, 2012). A pharmacodynamic model generally involves a function to describe the baseline of the measured response as well.

In pharmacodynamic models, the effect of time of day is most commonly incorporated when the baseline parameter of interest exhibits 24-hour variation. A well-known example is the 24-hour variation in the QT interval on an ECG recording. This variation can be accounted for by describing the baseline as a cosine function with one or multiple harmonics (Chain et al., 2011; Piotrovsky, 2005). Furthermore, 24-hour variation of endogenous cortisol levels have been described by an indirect response model with a synthesis rate that exhibits 24-hour variation (Krzyzanski et al., 2000). Other rhythmic baseline parameters that have been implemented in PKPD models include intraocular pressure (Luu et al., 2010), mevalonic acid concentration in plasma as a marker for cholesterol synthesis (Aoyama et al., 2010), gastric acid secretion (Puchalski et al., 2001), acetylcholinesterase activity (Han et al., 2012) and prolactin release (Friberg et al., 2009). Although informative, these studies did not regard the notion that the pharmacokinetics or the concentration-effect relationship may also exhibit 24-hour variation.

Rhythmic variation in exposure or effect

While characterisation of a rhythmic pharmacodynamic baseline can be performed by analysing off-drug data that are commonly collected in clinical trials, identification of rhythmic variation in the exposure or effect of a drug requires a more specialized study design that involves either the use of multiple dosing times (Krzyzanski et al., 2000) or prolonged exposure to a drug (i.e. sustained exposure for at least 24 hours). Therefore, potential 24-hour variation in the pharmacokinetics or in the response to a drug is investigated less frequently. However, several examples are available in the literature, among which two main approaches can be distinguished.

The first approach involves the use of covariates. In general, covariates are factors that influence pharmacokinetic of pharmacodynamic parameters, such as demographic variables, laboratory values or disease state (Mould and Upton, 2012). For example, inclusion of the effect of body weight in a model allows for dosing adjustments based on weight in order to reach a more consistent drug exposure or effect among the population (Mould and Upton, 2012). In (pre-)clinical studies that involve multiple time-points of drug administration, different dosing times can also be investigated as potential covariates on the pharmacokinetic (Bienert et al., 2014; Chen et al., 2013; Musuamba et al., 2009; Salem et al., 2014) and/or pharmacodynamic (Fisher et al., 1992) parameters. Although often employed, this approach is of limited use as it only provides information at the discrete time points that were investigated in the study and therefore lacks predictive value for other time points.

Moreover, the notion that the time-dependent parameter may continue to change after dosing is neglected.

A second approach to study the 24-hour variation in the pharmacokinetics or pharmacodynamics of a drug is the addition of a trigonometric function with a fundamental component of 24 hours and - if supported by the data - multiple harmonic components, to a model parameter. This approach has been used previously in both population pharmacokinetic models (Bressolle et al., 1999; Lee et al., 2014; Tomalik-Scharte et al., 2014) as well as in a population pharmacodynamic model studying the effect of dosing time on the analgesic effect of fentanyl (Boom et al., 2010). In general, this approach enhances the predictive value of a model by providing a continuous description of a model parameter over the 24-hour period. Using this approach, the exposure or effect of a drug can be predicted or simulated at any time of the day instead of only at the dosing times used in the study.

Population PKPD model development in a chronopharmacological context

Typically, the development of any PKPD model starts by fitting a relatively simple model to a data set. By evaluating the model, misspecifications or biases can be identified and the model can subsequently be updated in an attempt to find a model that provides a better fit of the data. Like any mathematical model, a PKPD model is by definition a simplification of a real system and therefore no "true" or "right" model exists (Bonate, 2011). Certainly, some models are better representations of the real system than others, raising the question how one is to judge which model is "better" than another.

The general steps that are taken during the development of a PKPD model and the criteria to evaluate and compare the fit of these models have been extensively described elsewhere (Bonate, 2011; Mould and Upton, 2013; Upton and Mould, 2014). In this section, it will be discussed how to determine if there is an effect of time of day in pharmacokinetic or pharmacodynamic parameters.

Time of day as a source of variation

In a PKPD model, different sources of variability in the data, including interindividual variability, interoccasion variability (in a crossover design) and residual unexplained variability, can be distinguished and quantified. The degree of interindividual variability (IIV) on a model parameter shows the extent to which this parameter varies from individual to individual in the study population, whereas the degree of interoccasion variability (IOV) shows to what extent the parameter varies within an individual from one occasion to the next occasion (Bonate, 2011). The quantification of these different sources of variation are an important advantage of a PKPD model compared to traditional statistical methods that are commonly used to analyse the results of a clinical trial.

Time of day can also be regarded as a source of variation. In PKPD models based on studies involving multiple times of drug administration, boxplots of each parameter's interindividual variability (in studies with a parallel design) or interoccasion variability

(in studies with a crossover design) over dosing time may be informative. In theory, any bias present in these plots provides a rationale for investigating the inclusion of 24-hour variation in a model parameter. However, in most PKPD models in which a time-of-day effect is studied, the use of these types of plots to facilitate the identification of 24-hour variation in the model parameters is generally not reported.

Time-of-day dependent bias in diagnostic plots

An important aspect of model evaluation is the graphical examination of its goodness of fit. This includes the assessment of scatter plots of observed data versus population and individual predicted data and of the distribution of conditional weighted residuals with interaction (CWRESI) versus concentration or time after dose (Byon et al., 2013; Karlsson and Savic, 2007). In a chronopharmacological context, model diagnostic plots can be used to identify biases or misspecifications with regard to the time of day. For example, if 24-hour variation in any model parameter is not accounted for, a scatter plot of CWRESI over the time of day may show a time-dependent bias, indicating that the observed values are over-predicted at some time points and under-predicted at other time points. Such a bias was observed in a study into the chronopharmacology of cilostazol (Lee et al., 2014), which could be resolved by modelling the absorption rate constant as a cosine function with a period of 24 hours.

Model selection

An important concept in the selection of one PKPD model over the other is statistical significance: a model is generally selected if it provides a significantly better fit of the data. In population PKPD models, non-linear mixed effect modelling is used to estimate the parameter values that best fit the data. This involves a maximum likelihood approach (an extension of the least squares minimization used in linear regression), which returns an objective function value (OFV), a single numeric value that represents the fit the model (Mould and Upton, 2012). Whether a model provides a significantly better fit than another model is typically assessed by comparing their respective OFVs with the likelihood ratio test (for nested models), the Akaike information criterion or the Bayesian information criterion (Mould and Upton, 2013). These tests take into account the number of additional parameters that are added, such that a simpler model that fits the data equally well is chosen over a model which is more complex (i.e. which requires the estimation of more parameters). In a chronopharmacological context, for example, a cosine function with a fixed period of 24 hours to describe a model parameter, which requires the estimation of two additional parameters (the amplitude and the phase), is only included in a model if it provides a significantly better fit.

Physiological plausibility is another criterion for the selection of a model. For example, since renal function shows 24-hour variation (Wuerzner et al., 2014), it is biologically plausible that the clearance of a renally eliminated drug shows 24-hour variation, while a mechanistic reason for a 24-hour rhythm in the volume of distribution may be more difficult

to conceive. In case both models fit the data equally well, the model with more biological plausibility should be selected.

The clinical relevance of a model is also important. Daily variation in pharmacokinetics and/or pharmacodynamics may impact dosing decisions, as has been shown for chemotherapeutic agents in the treatment of different types of cancer (Lévi et al., 2010). However, this is not always the case. In a study investigating the chronopharmacokinetics of midazolam, it was found that the hepatic clearance of this drug shows statistically significant 24-hour variation that could be described by a single cosine function (Tomalik-Scharte et al., 2014). However, the relative amplitude of this function was 10%, which was lower than the degree of residual unexplained variability in the data. The authors therefore concluded that the effect of dosing time is not clinically relevant and does not influence therapeutic decisions.

Lastly, the predictive value of a model should be considered. In a chronopharmacological context, a model in which the 24-hour variation in a parameter is described by a continuous (e.g. sinusoidal) function allows for the estimation and simulation of the parameter at any time of the day, whereas the inclusion of different covariates representing different dosing times can only be used to estimate and simulate the parameter at the dosing times that were used in the original study.

In brief, this section provided an overview of the application of population PKPD modelling to the field of chronopharmacology, revealing several advantages over the use of traditional statistical methods. This includes a more rigorous quantification of the effect of time of day, the possibility of performing simulations as well as characterization of interindividual and interoccasion variability in the data.

CONCLUSION

This chapter provided an overview of the influence of 24-hour rhythmicity in physiological processes on the pharmacokinetics and pharmacodynamics of drugs. From the extensive body of chronopharmacological research discussed in this chapter, a rather reductionist picture emerges. There are many examples that reveal the potential relevance of the 24-hour rhythms in physiology for the optimization of drug treatments scattered throughout the literature. However, a systematic approach to analyze and integrate these findings is lacking, which limits both the extrapolation of these findings to other types of drugs and the translation to clinical practice. In this light, PKPD modelling is a promising approach that may be able to overcome some of these limitations.

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