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

Kervezee, L.

CHAPTER

Scope and intent of investigation

2

The aim of this thesis is to provide a structured framework for chronopharmacological studies, while concurrently touching upon several critical issues encountered during the development and optimization of new and existing drug treatments.

The general approach taken in this thesis to study the effect of the time of day on the pharmacokinetics, pharmacodynamics and/or side-effects of a drug involves the following three elements:

- The use of model compounds that can be used to study a physiological process;
- A strict study design that is optimally suited to evaluate the chronopharmacology of a drug, consisting of a sufficient number of dosing times distributed throughout the day and night;
- The use of PKPD modelling to characterize and quantify the extent of 24-hour variation in the time, concentration and effect relationships of a drug.

Chapter 3 exemplifies the methodological framework on which the research described in this thesis is based. In this chapter, the 24-hour variation in the pharmacokinetics of the benzodiazepine midazolam is studied. Midazolam was used as a model compound to study CYP3A-mediated metabolism (Lee et al., 2002). A large proportion of the clinically used drugs are metabolized by the two CYP3A isozymes involved in xenobiotic metabolism (CYP3A4 and CYP3A5) (Benedetti et al., 2009). Therefore, evaluation of the 24-hour variation in midazolam pharmacokinetics provides insight into the pharmacokinetics of the numerous other CYP3A substrates as well.

In contrast to many examples available in the literature (as described in the introduction), the clinical trial described in **Chapter 3** was prospectively designed to study the 24-hour variation in the pharmacokinetics of midazolam, using six dosing times, appropriate control for stable diurnal rhythmicity before and during the study as well as a semi-simultaneous oral and intravenous administration. This yields detailed information about the effect of time of administration on the resulting concentration-time profile of the drug, which were subsequently analyzed by population pharmacokinetic (pop-PK) modelling. Hereby, the research described in **Chapter 3** demonstrates how pop-PK modelling can be used to study the effect of time of drug administration as an additional source of variation.

A similar strategy was used to study the 24-hour variation in the pharmacokinetics of the antibiotic levofloxacin in the clinical trial described in **Chapter 4**. Levofloxacin, being subject to minimal metabolism and active transport processes, was selected as a model compound for solubility and permeability independent absorption as well as passive renal elimination (Fish and Chow, 1997). These are two of the main pathways by which drugs are taken up and excreted by the body. Again combining a strict design that controls for the influences of food and fluid intake, posture and daily patterns in behavior with population pharmacokinetic modelling, the effect of dosing time on each of the pharmacokinetic parameters is precisely determined.

Delayed ventricular repolarization, manifested as a prolonged QT interval on an

electrocardiogram (ECG) recording, is one of the side-effects associated with the use of levofloxacin (Taubel et al., 2010). QT prolongation is a common side effect of a wide variety of cardiac and non-cardiac drugs that has potentially serious consequences, such as Torsade de Pointes and cardiac arrest (Kannankeril et al., 2010). For the proper evaluation of its safety profile, it is crucial to understand the factors that influence the relationship between the concentration of a drug and the QT interval. At present, it is unknown whether the effect of a drug on the length of the QT interval is influenced by the time of day. Building upon the pharmacokinetic model presented in **Chapter 4**, the effect of time of drug administration on the extent of levofloxacin-induced QT prolongation is investigated in **Chapter 5**.

Another important aspect of the development and optimization of drug treatments is to determine the concentration of a drug at its target site. As described in Chapter 1, this holds especially true for drugs targeted at the central nervous system, which is protected from the entry of exogenous compounds by a series of barriers, such as the blood brain barrier and the blood CSF barrier. Efflux transporters that drive their substrates from the brain back into the circulation, such as P-glycoprotein (P-gp), serve as an additional protective mechanism (Abbott et al., 2010). Twenty-four hour variation in the activity of P-gp may result in differences in brain concentrations depending on the time of drug administration, which could be exploited to either enhance or reduce the distribution of a P-gp substrate to the brain. Being a potent and specific substrate for P-gp (Kusuhara et al., 1997; Sziráki et al., 2011), quinidine was used in **Chapter 6** as a model drug to investigate whether P-gp mediated brain distribution shows 24-hour variation. **Chapter 6** also provides an example of the use of semi-physiologically based pharmacokinetic modelling in a chronobiological framework.

The objective of the study presented in **Chapter 7** was to apply the findings presented in Chapter 6 to a more clinically relevant drug. To this end, we investigated the brain distribution of morphine, a substrate of P-gp as well as of probenecid-sensitive transporters such as multidrug resistance-associated protein (Mrp) transporters, after administration at different dosing times.

In **Chapter 8**, the results of the work presented in Chapter 3-7 are summarized and placed in a broader perspective. The relevance of the findings will be discussed, as well as the possibilities for future research.

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