Special issue: chronopharmacometrics

Wojciech Krzyzanski¹

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Biorhythms are inherent parts of many biological systems. By far, the most prevalent is the circadian rhythm defined by its 24-h cycle that is entrained by the light–dark daily changes. Circadian rhythms influence both the disposition and actions of various drugs and can affect therapeutic efficacy and toxicity. Chronotherapeutics is the science of preventing or treating illnesses according to biologic rhythms [1]. It involves the timing of pharmacological and nonpharmacological interventions in order to minimize toxicity or adverse events, and to optimize treatment efficacy. Pharmacometrics is a scientific discipline developing and applying mathematical, statistical, and computational methods to characterize, understand, and predict a drug's pharmacokinetics and pharmacodynamics [2]. Chronopharmacometrics encompasses pharmacometric methods relevant to chronotherapeutics. A key feature of a chronopharmacometric model is quantification of the impact of a biorhythm on the modeling endpoints. The purpose of this special issue is to present current modeling approaches that address the presence of biorhythms in biomarkers used in drug development and therapeutics.

The issue begins with a series of reviews providing an overview of modeling approaches currently applied in chronopharmacometrics, followed by original articles reporting results of selected studies involving circadian rhythms. The influence of the circadian clock system on human physiology, disease, drug disposition and action, as well as a brief introduction to chronopharmacometrics and systems pharmacotherapeutics are provided in the opening review. The principles of cosinor rhythmometry and their applications to chronobiologic study designs, testing for anticipated rhythms and estimation of their parameters, and treatment of different disease conditions are presented in the next review. The model-based approaches that have

been used to explore circadian genomic systems of mammals are reviewed in the subsequent article. The first study applies a pathway-based analysis technique to identify how individual genes come together to generate orchestrated rhythmic patterns and how these may vary within and across tissues. Indirect response pharmacodynamic models are used to describe corticosteroid effects on biomarkers exhibiting profound circadian rhythms such as immune response cells, cortisol, and glucose in healthy women. A simulation study assesses the role of heart rate circadian rhythmicity in the prediction of drug effects on QT interval length in a healthy subject population. Ultradian oscillations of heart rate and body temperature, as well as the sleep cycle in preterm neonates are characterized by mathematical models and signal processing methods. The special issue closes with a report of comparison of a deconvolution-analysis approach with several standard statistical methods to model pulsatile growth hormone data in a simulated clinical trial.

The modeling techniques presented in this special issue employ classic pharmacokinetic/pharmacodynamic, physiologically based, nonlinear mixed effects, and system pharmacology models to quantify biorhythms. In this issue, some novel approaches that emerge in chronopharmacometrics are introduced. We missed examples of other techniques such as machine learning methods for quantification of circadian rhythms [3]. Chronopharmacometrics extends beyond modeling longitudinal data reported in this special issue. The cosinor model has been adopted in the proportional hazards model to describe the survival of breast cancer patients [4]. Our expectation is that the field of chronopharmacometrics will advance novel mathematical and statistical tools as new biomarkers of biorhythms emerge in drug development and therapeutics.

✉ Wojciech Krzyzanski
wk@buffalo.edu

¹ Department of Pharmaceutical Sciences, University at Buffalo, Buffalo, NY, USA

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