From the Biological Clock to Chronopharmacology: 
Implications for Chronotherapy

Björn Lemmer*

Circadian rhythms have been documented throughout the plan and animal 
kingdom at every level of eukariotic organization. Circadian rhythms are 
endogenous in nature, driven by oscillators or clocks, and persist under 
free-running (e.g. constant darkness) conditions. The genes expressing the 
biological clock have been identified in various species (Drosophila 
melangaster, Neurospora, Mouse, Golden hamster). The important feature 
of endogeneous biological rhythms is their anticipatory character. 
Rhythmicity inherent to all living systems, allows them to adapt more easily 
and to better survive under changing environmental conditions during the 24 
hours of a day as well as during changing seasons. Having this in mind it is 
easy to conceive that not only must the right amount of the right substance 
be at the right place, but also this must occur at the right time.

Thus, in man nearly all functions of the body including those influencing 
pharmacokinetic parameters such as drug absorption and distribution, drug 
metabolism and renal elimination display significant daily variations (liver: 
metabolism, hepatic blood flow, first pass effect; kidneys: glomerular 
filtration renal plasma flow, urine volume and pH; cardiovascular system: 
blood pressure, heart rate, peripheral resistance, organ perfusion; gastro-
intestinal tract: acid secretion, gastric emptying time). Also the onset and 
symptoms of diseases such as asthma attacks, coronary infarction,angina 
pectoris, stroke, ventricular tachycardia are circadian phase dependent. 
Asthma attacks predominately occur around 4 o’clock at night. Myocardial 
infarction and angina attacks as well as silent ischemias (ST-segment 
depression) in stable angina pectoris have an early morning peak between 8 -
12 h. In contrast, ECG abnormalities and angina attacks in variant angina mainly occur at night. Blood pressure and heart rate in normotensives and essential (primary) hypertensive patients display highest values during daytime followed by a nightly drop and an early morning rise. In about 70% of forms of secondary hypertension (e.g. renal disease, hyperthyroidisms, hormonal diseases, gestational hypertension), however, this rhythmic pattern is abolished or even reversed exhibiting nightly peaks in blood pressure. This form of hypertension is accompanied by increased end organ damages. Thus, different subtypes of a disease (angina pectoris, hypertension) can display different circadian patterns in symptoms. These observations are a challenge for basic and clinical research to get a better understanding on the underlying mechanisms of regulation. Moreover, they call for a circadian time-specified drug treatment. In nocturnal asthma, therefore, unequal dosing of antiasthmatic drugs (theophylline, β-agonists) with a higher dose at night or even a single evening dose are recommended. In secondary hypertension not only the elevated blood pressure must be reduced but there is first evidence that the disturbed blood pressure profile should be normalized, too, possibly best achieved by evening dosing.

From above it is evident that pharmacokinetics may also not be constant within a day. Chronopharmacokinetics have been shown for cardiovascular active drugs (propranolol, nifedipine, verapamil, enalapril, isosorbide-5-mononitrate, digoxin), antiasthmatics (theophylline, terbutaline), anticancer drugs, psychotropics, analgesics and local anesthetics, antibiotics to mention but a few. Far more drugs were shown to display significant daily variations in their effects (chronopharmacodynamics, chronotoxicology) even after chronic application or constant infusion.

In conclusion, there is clear evidence that the dose/concentration-response relationship of drugs can be significantly dependent on the time of day. Thus, circadian time has to be taken into account as an important variable influencing a drug’s pharmacokinetics and/or its effects or side effects.