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Chronopharmacokinetics: Implications for Drug Treatment

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Abstract

Nearly all functions of the human body are organized across the 24 hours of the day. This is also true for functions involved in the regulation of pharmacokinetics such as gastric absorption and emptying, gastro-intestinal perfusion, and liver and kidney functions. Several clinical studies, performed in a cross-over design, have provided evidence that the pharmacokinetics of mainly lipophilic drugs can be circadian phase-dependent. These studies show that after oral dosing, peak drug concentration (C_{max}) is, in general, higher or time-to-peak (t_{max}) shorter after morning, compared with evening application. A few studies performed with both immediate-release and sustained-release preparations (isosorbide-5-mononitrate, nifedipine) gave evidence that only the immediate-release formulation displayed circadian time-dependent pharmacokinetics, but not the sustained-release form. Most importantly, pharmacodynamic studies performed in parallel revealed that the effects, as well as the dose–response relationship, can be circadian phase-dependent, an observation which has an impact on pharmacokinetic/pharmacodynamic modelling. Moreover, this can be of relevance because the onset of certain diseases (e.g., bronchial asthma, coronary infarction, angina pectoris, rheumatic complaints) is not randomly distributed across the 24-h scale. In conclusion, there is now convincing evidence that the time-of-day has to be taken into account both in clinical pharmacokinetic and pharmacodynamic studies.

Pharmacokinetics deals with absorption, distribution, metabolism and elimination of drugs. The different steps in pharmacokinetics are determined and influenced by physiological functions of the body. Pharmacokinetic parameters such as peak drug concentration (C_{max}), time to C_{max} (t_{max}), volume of distribution, area under the curve, bioavailability, plasma protein binding and elimination half-life are conventionally not considered to be influenced by the time of day. However, this paradigm can no longer be justified as it has been convincingly demonstrated that bodily functions, including those influencing pharmacokinetics, are not constant in time (see Table 1). Numerous studies in man and in experimental animals have provided convincing evidence for the existence of daily or circadian (driven by an internal clock) rhythms in nearly every physiological function such as blood flow, stroke volume, peripheral resistance, parameters monitored by ECG recordings, in the plasma concentrations of hormones such as cortisol, melatonin, insulin, prolactin, noradrenaline, renin, angiotensin, aldosterone, in atrial natriuretic hormone and plasma cAMP concentration, in blood viscosity, aggregability and fibrinolytic activity, plasma concentration of glucose, electrolytes, plasma proteins, enzymes, and in the number of circulating red and white blood cells and blood platelets. Moreover, various functions of the lung (minute volume, peak flow, FEV_1, dynamic compliance), of the liver (metabolism, blood flow, first-pass effect) and of the kidneys (glomerular filtration, renal plasma flow, pH, urine volume, electrolyte excretion) can vary pronouncedly with time of day (for reviews see Minors & Waterhouse 1981; Redfern & Lemmer 1997; Lemmer 1998). Also gastric acid secretion exhibits a circadian

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variation with peak values in the late afternoon in normal subjects as well as in patients suffering from peptic ulcer disease (Moore & Englert 1979). Moreover, the onset and symptoms of certain diseases do not occur at random within the 24-h cycle. As early as 1698 John Floyer (1698, 1761) reported that asthma attacks are more frequent during the night time hours than at other times of day, an observation which has nicely been confirmed in modern epidemiologic studies in asthmatic patients (Neuenkirchen et al 1985). Similarly, the occurrence of coronary infarction, sudden cardiac death as well as of angina pectoris attacks and of pathologic ECG-recordings is unevenly distributed over the 24 hours (Muller et al 1985; Mulcahy et al 1988, for review see Willich & Muller 1996). In animal experiments significant circadian rhythms have been demonstrated at the cellular and subcellular level of various neurotransmitter receptors, signal transduction processes and enzyme activities (Wirz-Justice 1987; Lemmer 1989a, b; Witte & Lemmer 1991). Moreover, the genetics of the circadian clock have been demonstrated in *Drosophila melongaster*, *Neurospora*, the golden hamster and the mouse.

In the light of the chronobiologic and chronopathologic findings described above it is not surprising that the pharmacokinetics and the effects of drugs may also not be constant within the 24 hours of a day. This has been convincingly demonstrated in experimental animals as well as in clinical studies (for reviews see Lemmer & Bruguerolle 1994; Lemmer 1997, 1998; Redfern & Lemmer 1997). In the present review only some representative findings will be described to demonstrate that pharmacokinetics may be modified by the rhythmic circadian organization of the body and that daily variation in pharmacokinetics can have an impact on the therapeutic use of drugs. This paper will concentrate on circadian or daily variations; others have reviewed methodological problems as well as dealt with other periodicities, including menstrual and circannual rhythms (Bruguerolle & Lemmer 1993).

Chronopharmacokinetics

As shown in Table 1, all functions involved in the pharmacokinetic steps–from drug absorption to drug elimination—can be circadian phase-dependent. Thus, gastric emptying time of solids is faster in the morning than in the afternoon (Goo et al 1987). Also, the perfusion of the gastrointestinal tract varies with time of day, being more pronounced at midnight and the early morning hours than around noon and in the late afternoon (Lemmer & Nold 1991). Since drugs are mainly absorbed by passive diffusion these rhythmic patterns must have implications for the pharmacokinetics. These observations would nicely explain why, in general, drugs are more rapidly absorbed and more rapidly reach the systemic circulation when taken in the morning. Accordingly, clinical studies showed—mainly for lipophilic drugs—that t_{max} can be shorter and C_{max} can be higher after morning than evening drug dosing. Some data are compiled in Table 2.

Table 2. Chronokinetics after morning (a.m.) versus evening (p.m.) dosing.

Drug	C_{max} ($\mu g\,L^{-1}$)		t_{max} (h)	
	a.m.	p.m.	a.m.	p.m.
Digoxin	3·6*	1·8	1·2	3·2
Enalaprilat	46·7	53·5	3·5*	5·6
IS-5-MN i.r.	1605·0	1588·0	0·9*	2·1
IS-5-MN s.r.	509·0	530·0	5·2	4·9
Nifedipine i.r.	82·0*	45·7	0·4*	0·6
Nifedipine s.r.	48·5	50·1	2·3	2·8
Oxprenolol	507·0[a]	375·0	1·0	1·1
Molsidomine	27·0	23·5	1·7	1·9
Propranolol	38·6*	26·2	2·5	3·0
Verapamil i.r.	59·4*	25·6	1·3	2·0
Verapamil s.r.	389·0	386·0	7·2*	10·6
Theophylline	a.m. ≥ p.m.		a.m. ≤ p.m.	
Terbutaline	24*	10	3·5*	6·2
Diazepam	250*	170	1*	2
NSAID	a.m. ≥ p.m.		a.m. < p.m.	

*$P < 0{\cdot}05$, [a]significant difference in half-life. IS-5-MN = isosorbide dinitrate, i.r. = immediate release, s.r. = sustained release.

Table 1. Biological rhythms and oral pharmacokinetics.

Liberation	Absorption (GI tract)	Distribution	Metabolism (liver)	Elimination (kidney)
Time-specified release, programmable	Perfusion	Perfusion	Perfusion	Perfusion
	Gastric pH	Blood distribution	First-pass effect (enzyme activity)	Renal plasma flow
	Acid secretion	Peripheral resistance		Glomerular filtration
	Motility	Blood cells		Urinary excretion
	Gastric emptying	Serum proteins		Urine pH
		Protein binding		Electrolytes
	Rest – Activity	Rest – Activity		

In the last few years, several studies have been performed to investigate the pharmacokinetics in cross-over designs.

Mostly, the pharmacokinetics were studied both after morning and evening dosing, sometimes 4–6 different circadian times were used. Studies were performed in healthy volunteers or in various disease entities such as bronchial asthma, hypertension, gastric ulcer disease, pain, cancer, and psychiatric diseases.

However, a circadian phase-dependency was not always found. Table 2 shows that in some cases C_{max} or t_{max} was not significantly modified by the time of day of drug ingestion. This holds true for some sustained-release preparations such as those of isosorbide-5-mononitrate, the dihydropyridine calcium channel blocker nifedipine, and also for molsidomine (Nold & Lemmer 1998) (Table 2). This clearly indicates that we need more data from circadian phase-dependent designed studies with different groups of drugs, differing in physicochemical properties (lipophilic vs hydrophilic drugs), differing in the rates of absorption and the main mechanisms of elimination (i.e. kidneys and liver). Moreover, an immediate-release preparation of a drug should be studied in comparison with a sustained-release one.

Implications for Therapy?

As mentioned above, the onset and the degree of certain diseases can be circadian phase-dependent as shown for bronchial asthma, myocardial infarction, angina pectoris (including silent ischaemia), rheumatic disease, ulcer disease, and for the 24-h blood pressure profile in essential hypertension (dippers) and the disturbed pattern in forms of secondary hypertension (non-dippers, e.g. in renal and endocrine diseases, gestation) (see Lemmer & Portaluppi 1997). Since both the need for an adequate drug concentration and the dose–response relationship can be dependent on the time of day (Redfern & Lemmer 1997; Lemmer 1998), it is conceivable that the pharmacokinetic profile at the given time of day has implications for drug treatment. Thus, it has been nicely shown that in nocturnal asthma, evening dosing of theophylline or β-agonists can be of advantage in treating the asthma attacks (Lemmer 1996a; Smolensky & D'Alonzo 1997). Histamine$_2$-receptor antagonists for ulcer disease are recommended for evening dosing (Moore & Merki 1997). In dippers, antihypertensive drugs are in general dosed in the morning, whereas in non-dippers evening dosing might not only reduce high blood pressure but also normalize the disturbed blood pressure profile as shown for isradipine (Portaluppi et al 1995; Lemmer 1996b; Lemmer & Portaluppi 1997). Finally, non-steroidal antiinflammatory drugs (NSAIDs) (see Table 2) may be better given in the evening when treating rheumatic patients (Labrecque et al 1997). Chronopharmacokinetics and its implications for cancer therapy is discussed in the contribution to this symposium by F. Lévi (Lévi 1999).

Conclusions

The chronopharmacological studies published in recent years gave evidence that both the pharmacokinetics and the effects of drugs can be circadian phase-dependent. In the light of the circadian organization of the onset and 24 h pattern of various diseases, the knowledge about possible chronokinetics and a circadian phase-dependency in the dose–response relationship are of utmost importance for increasing drug efficacy and reducing side effects. It is of interest to note that recently consideration of the time-of-day for the diagnosis and treatment of asthma has been implemented in international recommendations (The National Institutes of Health 1997).

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