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Chronopharmacokinetics

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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 [Cmax], time to Cmax [tmax], 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 not be hold any longer because it has been convincingly demonstrated that bodily functions, including those influencing pharmacokinetics, are not constant in time, see Table 1. Accordingly, clinical studies showed that—mainly for lipophilic drugs—tmax can be shorter and/or Cmax can be higher after morning than evening drug dosing. Some data are compiled in Table 2.

Since drugs are mainly absorbed by passive diffusion the delay in tmax after evening application indicate that drug absorption can be circadian phase dependent. Two main mechanisms being rhythmic may be involved: Gastric emptying time and gastrointestinal perfusion. A delayed gastric emptying time for solids in the evening was described (Goo et al., 1987). Of greater importance may be that the gastro-intestinal and hepatic perfusion changes with time of day as indicated by a greater estimated hepatic blood flow in the morning than around noon or in the afternoon (Lemmer & Nold, 1991), thereby modifying the velocity of drug absorption.

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	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
NSAR	a.m.	≥p.m.	a.m.	< p.m.

*$P < 0.05$; [a] sign. difference in half-life.

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Table 1. Biological rhythms and oral pharmacokinetics.

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