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Circadian changes in estimated hepatic blood flow in healthy subjects

B. LEMMER & G. NOLD
Zentrum der Pharmakologie, J. W. Goethe-Universität, Frankfurt/M, Germany

Intravenous injections of indocyanine green (ICG) were given to 10 healthy supine subjects at 02.00, 08.00, 14.00 and 20.00 h. ICG plasma half-life, plasma clearance and estimated hepatic blood flow (EHBF), but not volume of distribution, varied significantly with time of day with EHBF being greatest at 08.00 h. This circadian rhythm in EHBF should be considered when evaluating the kinetics of high-clearance drugs at different times of day.

Keywords liver blood flow indocyanine green kinetics circadian rhythm

Introduction

Hepatic enzyme activity and hepatic blood flow are major determinants of the clearance of lipophilic drugs. Liver blood flow is most important with respect to high-clearance compounds. Recently, the pharmacokinetics of such drugs, including propranolol, isosorbide-5-mononitrate and nifedipine (Langner & Lemmer, 1988; Lemmer *et al.*, 1990, 1991), were shown to be dependent on the time of day at which they were administered. Whereas physiological variables such as posture and exercise are well known to influence hepatic blood flow (Daneshmend *et al.*, 1981), no data are available concerning daily variation in estimated hepatic blood flow (EHBF). On the other hand, blood pressure and cardiac output are known to vary significantly with time of day (Lemmer, 1989). Therefore, apparent hepatic blood flow, estimated from indocyanine green (ICG) kinetics was measured in healthy subjects in the supine position at four different times of day.

Methods

Ten healthy, drug-free male volunteers (mean age 25.9 ± 3.2 years, range 23 to 32 years; mean weight 72.3 ± 7.8 kg, range 61 to 86 kg) participated in this study which was approved by the Ethics Committee of the J.W. Goethe-University Frankfurt/M. All subjects gave written informed consent. The study was performed from 12 February to 23 March 1991. Investigations in a single subject were done on 2 different days with two studies performed per day. On day 1 rapid i.v. injections of ICG (Cardio Green®, 0.5 mg kg^{-1}) were administered at 08.00 h and at 20.00 h. On the second day ICG was injected at 14.00 h and at 02.00 h. The subjects were studied after a 6 h fast in the supine position 30 min before and up to 20 min after injection of ICG. Blood samples were taken from the contralateral antecubital vein through an indwelling catheter before and at 2, 5, 10 and 15 min after injection of ICG. On each day the subject's haematocrit was measured. Plasma concentrations of ICG were measured immediately by spectrophotometry at a wavelength of 805 nm (Caesar *et al.*, 1961).

Plasma half-life, volume of distribution and plasma clearance of ICG were calculated from the individual log concentration-time data. Volume of distribution was calculated from the dose of dye divided by the extrapolated zero-time plasma concentration, plasma clearance from the ratio of the ICG dose and the area under the plasma dye concentration-time curve (AUC) and the ICG plasma half-life from $\ln 2/k$, where k is the elimination rate constant. EHBF was calculated from k times volume of distribution based on dye in blood. The latter was calculated from the plasma value corrected by the haematocrit. Statistical analysis of daily variations was done by one-way ANOVA and by cosinor analysis with PHARMFIT (Mattes *et al.*, 1991). PHARMFIT was also used to calculate k values by log-linear regression. All data are presented as mean ± s.d.

Results

The results are shown in Table 1. Significant diurnal variations were found in the plasma half-life and the plasma clearance of ICG as well as in EHBF. Elimina-

Correspondence: Professor Dr Björn Lemmer, Zentrum der Pharmakologie, J.W. Goethe-Universität, Theodor-Stern-Kai 7, D-6000 Frankfurt/M 70, Germany

Table 1 Parameters (mean ± s.d.) describing the kinetics of indocyanine green at four different times of day in 10 supine subjects

	Indocyanine green (0.5 mg kg^{-1} i.v.)			
Time of injection (h)	*Volume of distribution (l)*	*Plasma half-life (min)*	*Plasma clearance (l min^{-1})*	*Estimated hepatic blood flow (l min^{-1})*
08.00	3.70 ± 0.67	2.69 ± 0.39	0.98 ± 0.22	1.54 ± 0.38
14.00	3.51 ± 0.68	3.47 ± 0.78	0.74 ± 0.17	1.14 ± 0.28
20.00	3.84 ± 0.79	3.16 ± 0.62	0.87 ± 0.16	1.35 ± 0.24
02.00	3.71 ± 0.55	2.78 ± 0.59	0.95 ± 0.14	1.49 ± 0.24
Rhythm analysis *P*	0.72	0.017	0.018	0.019
ANOVA *P*	NS	< 0.05	< 0.025	< 0.025

Daily variation was tested by one-way ANOVA and cosinor analysis (Mattes *et al.*, 1991).

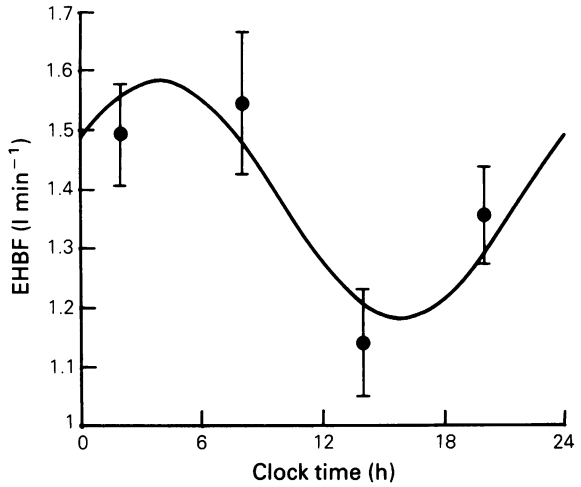

Figure 1 Circadian rhythm in estimated hepatic blood flow in 10 healthy male subjects as estimated from indocyanine green clearance measured at 02.00, 08.00, 14.00 and 20.00 h. Data were fitted by a cosine function with a period of 24 h. Values are shown as mean and s.e. mean.

tion half-life was longest at 14.00 h (3.47 ± 0.78 min) and reached a minimum at 08.00 h (2.69 ± 0.39 min). Plasma clearance and EHBF displayed a circadian rhythm ($P < 0.025$) with a rhythm-estimated peak at 04.00 h (Figure 1). No significant daily changes were found in the volume of distribution of ICG.

Discussion

The findings provide evidence for a circadian phase-dependency in EHBF in healthy subjects in the supine position. Previous studies have shown that other factors such as postural changes and exercise (Daneshmend *et al.*, 1981) and food (Svensson *et al.*, 1983) can greatly alter liver blood flow as estimated from ICG kinetics. In addition it can also be influenced by drugs. Thus, nifedipine increases and glyceryltrinitrate decreases EHBF (Feely, 1984). Olanoff *et al.* (1986) showed that food-induced increases in hepatic blood flow lead to increased systemic clearance and oral bioavailability of propranolol. These data in conjunction with the present results may explain why significantly higher plasma propranolol concentrations were observed when the drug was taken at 08.00 h than at other times of day (Langner & Lemmer, 1988). Similarly, higher plasma concentrations of nifedipine were found in the morning than in the evening (Lemmer *et al.*, 1990). Based on the present data, it seems likely that the nifedipine-induced increase in EHBF is circadian phase-dependent. Circadian variation in EHBF may be of considerable importance for the interpretation of the pharmacokinetics of drugs exhibiting hepatic blood flow-dependent clearance.

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