Pharmacokinetics of trapidil, an antagonist of platelet derived growth factor, in healthy subjects and in patients with liver cirrhosis

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- 1 Pharmacokinetic parameters of trapidil (an antagonist of platelet derived growth factor) were evaluated in 12 healthy male subjects (study I) and in a group of 10 patients with liver cirrhosis (Child B) and five control subjects, respectively (study II).
- 2 Investigations were carried out after a single dose trapidil (200 mg) and at steady state after application of 200 mg trapidil three times daily for 5 days (study I) or 4 days (study II).
- 3 *Study I*: The concentration-time curves of the terminal elimination phase of trapidil exhibited a slight convexity which might reflect nonlinear kinetics. The AUC of trapidil obtained after the first dose ($20.5 [\pm 7.0 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$) was markedly higher than the AUC determined at steady state ($13.2 [\pm 3.8 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$), the non-parametric 90% confidence intervals of the ratio day 5/day 1 was 0.58–0.73 (point estimator 0.64).
- 4 *Study II*: AUC averaged ($21.4 [\pm 9.1 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$) in controls and ($34.4 [\pm 14.9 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$) in cirrhotic patients. The 90% confidence intervals for the difference group 1 *vs* group 2 was 0.95–2.97 (point estimator 1.48, $P = 0.066$). At steady state, AUC averaged ($13.7 [\pm 5.7 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$) in controls and ($20.8 [\pm 6.8 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$) in cirrhotic patients (90% confidence intervals group 1 *vs* group 2: 0.88–2.20 [point estimator 1.45, $P = 0.05$]). As seen in study I, the AUC of trapidil obtained after the first dose was markedly higher than the AUC determined at steady state, the non-parametric 90% confidence intervals of the ratio day 5/day 1 was 0.48–0.84 (point estimator 0.66) in control subjects and 0.54–0.72 (point estimator 0.64) in cirrhotic patients, respectively.
- 5 An inverse correlation was seen between the results of the monoethylglycin-xilidid (MEGX)-test and the AUC of trapidil (single dose: $r = -0.516$, $P = 0.048$; steady state: $r = -0.548$, $P = 0.042$).
- 6 Results of study I and study II indicate an autoinduction of trapidil metabolism after repeated oral doses. Although trapidil elimination is decreased in patients with liver cirrhosis (study II), the elimination half-life at steady state is relatively short ($2.4 [\pm 1.1 \text{ s.d.}] \text{ h}$) and therefore should prevent cumulation of trapidil even in cirrhotic patients.

Keywords trapidil pharmacokinetics cirrhosis autoinduction

This paper is dedicated to Professor Dr H. Kewitz on the occasion of his 75th Birthday

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Introduction

Trapidil, a triazolopyrimidine derivative, is currently used for treatment of chronic stable angina in several European countries and in Japan. Trapidil has also been shown as effective as aspirin in preventing restenosis after percutaneous transluminal coronary angioplasty (PTCA) [1, 2]. Pharmacological effects of trapidil include vasodilatation mediated by phosphodiesterase (PDE)-inhibition [3] and reduction of platelet aggregation due to thromboxane (TXA₂)-inhibition [4] and antagonism of platelet derived growth factor (PDGF)[5]. In patients with coronary artery disease, arterial vasodilation and a decrease in diastolic filling pressure has been observed after trapidil administration [6] resulting in antianginal activity [7–9].

Despite its long-term use in former East European countries and in Japan, little is known about the pharmacokinetic properties of trapidil, and only data after single dose application have been reported [10]. Trapidil is completely absorbed and does not undergo first-pass metabolism [10]. Trapidil is primarily dealkylated to desethyltrapidil which has similar, but about 10-fold weaker pharmacological properties with respect to platelet aggregation [11]. CYP450 isozymes involved in the degradation of trapidil have not yet been determined. This paper comprises the first studies reported on the single dose and steady state pharmacokinetics of trapidil in healthy subjects and in patients with impaired liver function.

Methods

Study I was performed to investigate the pharmacokinetics of trapidil in 12 healthy male subjects after a 200 mg single dose given on day 1 and day 5 following 200 mg three times daily trapidil during days 2 to 4. Study II was carried out to assess the pharmacokinetics of trapidil in 10 patients with liver cirrhosis and five age-matched subjects without liver disease after a 200 mg single dose given on day 1 and day 4 following 200 mg three times daily trapidil during days 2 and 3. The shorter treatment period in study II—carried out in in-house patients—was due to logistic reasons.

Subject selection and study protocol

Both studies were approved by the Institutional Review Board of the Frankfurt University Hospital, and study subjects gave their written informed consent.

Subjects in study I had a mean age of 29 years (range 26–35 years), mean weight was 77 kg (range 65–98) and mean height was 178 cm (range 165–192 cm). All volunteers had normal renal and hepatic function as assessed by physical examination and appropriate biochemical tests. They all were non-smokers and did not take any other medication for 2 weeks before and during the study. Electrocardiographic (12-lead) examination revealed no signs of conduction abnormalities.

Subjects in study II were divided in two groups. Five patients without clinical or biochemical signs of liver damage were used as age-matched control group (group 1). All group 1 subjects had normal renal and hepatic function as assessed by physical examination and appropriate biochemical tests. Two of the control subjects used oral contraceptives, two other control subjects received heparin. Group 2 comprised five patients suffering from ethanol-induced liver cirrhosis and five patients with liver cirrhosis after previous infection with hepatitis B or C. Severity of liver disease of patients in group 2 was classified as Child B; eight patients had oesophageal varicosis. Active comedication was spironolactone in all patients, three patients received insulin.

The following tests were carried out within a 2 week period before the study began to assess liver function with regard to xenobiotic biotransformation: antipyrine (AP) clearance [12], monoethylglycinoxylid-(MEGX) test [13], indocyaninegreen (ICG) clearance [14]. Demographic data of patients and controls in study II and the results of the quantitative tests for assessment of the liver function are given in Table 2.

Investigations

Study I. On day 1, plasma samples were obtained before and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after application of a single dose (capsule) containing 200 mg trapidil. From day 2 to day 4, trapidil was administered 200 mg three times daily. On day 5, after application of a last single dose (200 mg) of trapidil plasma samples were drawn as on day 1. On each of the pharmacokinetic study days (i.e. days 1 and 5), trapidil intake followed an overnight fast, and a standardized breakfast was served after 2 h.

Study II. Investigations followed the same schedule as in study I, except there was a shorter treatment period (3 instead of 4 days) and an additional blood sample was drawn 36 h after the last drug intake on day 4.

Trapidil assay

Trapidil and desethyltrapidil (M1) were determined in plasma by an h.p.l.c.-method and u.v.-detection. Lower limit of quantification (LLQ) was 0.004 µg ml⁻¹ for trapidil, linearity was proven up to 16 µg ml⁻¹. For M1, LLQ was 0.001 µg ml⁻¹ and linearity was obtained within 0.001 and 5 µg ml⁻¹. Samples containing higher concentrations were re-analysed after dilution. Day-to-day variability was below 5%.

Pharmacokinetic evaluation

All pharmacokinetic calculations were based on plasma concentrations which were above the LLQ. C_{max} , t_{max} and C_{min} (i.e. pre-dose plasma concentration at day 5 [study I] or day 4 [study II]) were read directly

from the plasma concentration-time curves of trapidil and M1. The following pharmacokinetic parameters were obtained by using the non-compartmental analysis module of TOPFIT® [15].

$$\text{AUC} = \text{AUC}(0, t) + C_t/\lambda_z \quad (\text{first dose}), \quad (1)$$

where $\text{AUC}(0, t)$ is the area under the concentration-time curve from time zero to the last quantifiable concentration value C_t , and λ_z is the log-linear disposition rate constant derived from the slope of the regression line of the last three or four non-zero concentration values.

$$\text{AUC}(\tau) \quad (\text{steady state}) \quad (2)$$

describes the area under the concentration-time curves from time zero (pre-dose) over the time span of the dosing interval τ (obtained with the logarithmic trapezoidal rule).

The elimination half-life of trapidil was derived by

$$t_{1/2,z} = \ln(2)/\lambda_z \quad (3)$$

The apparent clearance (assuming complete bioavailability of trapidil [10]) of trapidil was determined by

$$\text{CL}_{\text{app}} = D/\text{AUC} \quad (4)$$

The relative clearance of trapidil to M1 [16] was determined as ratio

$$\text{AUC}_{\text{M1}}/\text{AUC}_{\text{trapidil}} \quad (5)$$

Statistical analysis

Single dose vs steady state Primary target variables were the AUC, C_{max} and $t_{1/2,z}$ of trapidil and the AUC of desethyltrapidil. Confidence intervals of the ratio day 5 [or day 4, resp.]/day 1 were assessed after determination of the distribution of the log-transformed data.

Cirrhosis vs controls For study II, data of group 1 were compared with those of group 2 using the Mann-Whitney *U*-test. For the AUC of trapidil, non-parametric confidence intervals and the Hodges-Lehmann point estimator were obtained. The correlation between the quantitative liver function tests and the AUC of trapidil was assessed by linear regression analysis.

Results

Pharmacokinetic parameters

Study I After application of the first dose, maximal plasma levels of trapidil were $5.14 (\pm 1.01 \text{ s.d.}) \mu\text{g ml}^{-1}$, reached at 0.5–2 h. At day 5, after 4 days treatment with 200 mg trapidil three times daily, trough levels of trapidil averaged $0.50 (\pm 0.22 \text{ s.d.}) \mu\text{g ml}^{-1}$. C_{max} at day 5 was determined to $5.01 (\pm 1.3 \text{ s.d.}) \mu\text{g ml}^{-1}$,

measured at 0.50 to 1.5 h after drug intake (Figure 1a, Table 1). The AUC of trapidil obtained after the first dose ($20.5 [\pm 7.0 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$) was markedly higher than the AUC determined at steady state ($13.2 [\pm 3.8 \text{ s.d.}] \mu\text{g ml}^{-1} \text{ h}$), the non-parametric 90% confidence intervals of the ratio day 5/day 1 was 0.58–0.73 (point estimator 0.64). This change in the apparent oral clearance of trapidil seems to be due to an enhanced $t_{1/2,z}$ which decreased from $1.3 (\pm 0.3 \text{ s.d.}) \text{ h}$ after the first dose to $1.1 (\pm 0.2 \text{ s.d.}) \text{ h}$ at steady state (90%-confidence interval 0.75–0.98 [point estimator 0.83]). The plasma concentration-time profile of desethyltrapidil (M1) obtained after the steady state investigation indicated cumulation of M1 ($C_{\text{min}} 1.79 [\pm 1.09 \text{ s.d.}] \mu\text{g ml}^{-1}$) (Figure 1b, Table 2). t_{max} was reached earlier at steady state (2–6 h *vs* 3–12 h). The AUC-ratio (M1/trapidil) increased from 0.68 to 1.28 at steady state (Table 1), indicating an induction of this degradation step [16]. However, AUC values of M1 obtained after the first dose and at steady state were not different suggesting that the apparent clearance of M1 is not changed during steady state.

Figure 1 (study I): (a) Plasma concentration *vs* time profile of trapidil in healthy subjects (○ first dose [200 mg] day 1, ● steady state day 5 [200 mg trapidil three times a day]). Inset: log-linear profiles showing a slight convexity as seen with nonlinear elimination kinetics. (b) Plasma concentration *vs* time profile of desethyltrapidil (○ first dose day 1, ● steady state day 5 [200 mg trapidil three times a day]).

Table 1 Study I: Pharmacokinetic parameters of trapidil and M1 at day 1 (single dose application 200 mg) and day 5 (steady state 200 mg trapidil three times daily, dose interval) (mean $\pm$ s.d. or median and range, 90% confidence intervals [CI] and point estimator [PE] for the ratio day 5/day 1)

Trapidil	Day 1	Day 5	90%-CI (PE)
AUC ($\mu\text{g ml}^{-1}\text{ h}$)	20.5 $\pm$ 7.0	13.2 $\pm$ 3.8	0.58–0.73 (0.64)
C_{max} ($\mu\text{g ml}^{-1}$)	5.14 $\pm$ 1.01	5.01 $\pm$ 1.33	0.83–1.08 (0.94)
C_{min} ($\mu\text{g ml}^{-1}$)		0.50 $\pm$ 0.22	
t_{max} (h)	1.0 (0.5–2.0)	1.0 (0.5–1.5)	
$t_{\frac{1}{2},z}$	1.31 $\pm$ 0.28	1.14 $\pm$ 0.16	0.75–0.98 (0.83)
CL_{app} (ml min^{-1})	179 $\pm$ 58	273 $\pm$ 77	1.28–2.01 (1.58)
<i>Desethyltrapidil</i>			
AUC ($\mu\text{g ml}^{-1}\text{ h}$)	16.2 $\pm$ 4.5	16.9 $\pm$ 6.6	0.88–1.05 (0.97)
C_{max} ($\mu\text{g ml}^{-1}$)	1.50 $\pm$ 0.24	2.70 $\pm$ 0.90	1.42–2.11 (1.78)
C_{min} ($\mu\text{g ml}^{-1}$)		1.79 $\pm$ 1.09	
t_{max} (h)	6.0 (3.0–12.0)	3.0 (2.0–6.0)	
$\text{AUC}_{\text{M1}}/\text{AUC}_{\text{trapidil}}$	0.68 $\pm$ 0.29	1.28 $\pm$ 0.53	0.40–1.80 (0.83)

Table 2 Study II (liver cirrhosis): Antropometric data (mean, range) and liver function tests (mean, s.d.)

	Group 1 (Control)	Group 2 (Cirrhosis)	95%-CI
<i>n</i> (male/female)	2/3	6/4	
Age (years)	39 (28–45)	45 (35–56)	
Height (cm)	168 (156–182)	168 (158–185)	
Weight (kg)	68 (55–74)	69 (55–82)	
ICG-CL ($\text{ml min}^{-1}\text{ kg}$)	9.2 $\pm$ 2.3	3.2 $\pm$ 2.1	2.8–8.9 ($P < 0.001$)
AP-CL ($\text{ml min}^{-1}\text{ kg}$)	1.74 $\pm$ 1.04	1.00 $\pm$ 0.51	0.18–2.5 ($P < 0.01$)
MEGX ($\mu\text{g l}^{-1}$)	85 $\pm$ 33	35 $\pm$ 17	10.9–83.7 ($P < 0.001$)

ICG-CL = Indocyaninegreen clearance, AP = Antipyrine clearance, MEGX = Monoethylglycinxylylidid-concentration. 95%-CI = 95%-Confidence intervals of the difference in the mean value between group 1 and group 2 (Mann–Whitney *U*-test)

Study II After the first dose, maximal plasma levels of trapidil were not significantly different between cirrhotic patients and control subjects (5.32 [± 1.06 s.d.] $\mu\text{g ml}^{-1}$ and 5.73 [± 1.02 s.d.] $\mu\text{g ml}^{-1}$, respectively). AUC averaged (21.4 [± 9.1 s.d.] $\mu\text{g ml}^{-1}\text{ h}$) in controls and (34.4 [± 14.9 s.d.] $\mu\text{g ml}^{-1}\text{ h}$) in cirrhotic patients (Figure 2a, Table 3). The 90% confidence intervals for the difference group 1 *vs* group 2 was 0.95–2.97 (point estimator 1.48, *U*-test: $P = 0.066$). The decrease in the clearance of trapidil between cirrhotic patients and controls seems due to a longer elimination half-life (1.9 [± 0.6 s.d.] h *vs* 3.9 [± 1.6 s.d.] h).

At steady state, AUC averaged (13.7 [± 5.7 s.d.] $\mu\text{g ml}^{-1}\text{ h}$) in controls and (20.8 [± 6.8 s.d.] $\mu\text{g ml}^{-1}\text{ h}$) in cirrhotic patients (Figure 2b, Table 3). The 90% confidence intervals for the difference group 1 *vs* group 2 was 0.88–2.20 (point estimator 1.45, *U*-test: $P = 0.05$). However, the pattern of autoinduction seen in study I was also present in study II in control subjects as well as in cirrhotic patients. Plasma levels of desethyltrapidil at trough were higher in cirrhotic patients (3.80 [± 3.15 s.d.] $\mu\text{g ml}^{-1}$) when compared with control subjects (1.29 [± 1.09 s.d.] $\mu\text{g ml}^{-1}$) and subjects from study I (Table 1).

Active comedication of two patients with outstanding high AUC values (> 2 s.d. of the mean of group 2) was explored, but no deviations from the medication patterns of the remaining subjects (comedication with spironolac-

tone) could be determined. However, the patient with the highest AUC value during the single dose trial (but not at the steady state investigation) received propranolol. A significant inverse correlation could be demonstrated between the results of the MEGX-test and the AUC of trapidil (single dose: $r = -0.516$, $P = 0.048$; steady state: $r = -0.548$, $P = 0.042$) (Figure 3). No correlations could be detected between ICG clearance or AP clearance and the AUC of trapidil.

Tolerability

In both studies, no differences were seen between the pre- and post-study laboratory tests. In study I, no adverse events were recorded. One patient in study II (group 2) experienced a transient episode of weakness after the intake of the morning drug dose at days 2 and 3 without further haemodynamic symptoms. Pharmacokinetic parameters of trapidil in this patient were not outstanding from the mean of his group.

Discussion

The principal findings of the two studies reported here were that (1) trapidil metabolism exhibits autoinduction

Figure 2 (study II): (a) Plasma concentration *vs* time profile of trapidil after the first dose (200 mg) (● group 1 [control subjects]1, ■ group 2 [liver cirrhosis]). Inset: plasma concentration *vs* time profile of desethyltrapidil after the first dose (200 mg) (● group 1 [control subjects]1, ■ group 2 [liver cirrhosis]). (b) Plasma concentration *vs* time profile of trapidil at day 4 (steady state 200 mg three times a day) (● group 1 [control subjects]1, ■ group 2 [liver cirrhosis]). Inset: Plasma concentration *vs* time profile of desethyltrapidil after the first dose (200 mg) (● group 1 [control subjects]1, ■ group 2 [liver cirrhosis]).

after repeated oral dosing, and (2) patients with liver cirrhosis exhibit a longer elimination half-life and reduced clearance of trapidil than healthy subjects.

Pharmacokinetic studies in patients with impaired renal or hepatic function are formally required by drug approval authorities in order to exclude possible risks in these patient groups, e.g. due to cumulation. Since trapidil is metabolized extensively, an investigation in patients with liver cirrhosis was mandatory. In a further study trapidil kinetics were shown not to be affected by decreased renal function (glomerular filtration rate <30 ml⁻¹ min) [17].

The concentration-time curves of the terminal elimination phase of trapidil exhibited a slight convexity (see inset of Figure 1a) which might reflect non-linear kinetics. Non-linear kinetics have already been suggested from a single dose study with ascending oral doses, where the relative bioavailability of a 300 mg dose

Figure 3 (study II): Linear regression (Pearson's correlation coefficient) between MEGX-test (concentration of the principal metabolite of lignocaine, monoethylglycin-xylylid 30 min after injection of 1 mg kg⁻¹ lignocaine [13]) and the AUC of trapidil obtained after single dose administration (left panel) and at steady state (right panel). Control subjects (□), patients with liver cirrhosis (■).

compared with a 100 mg dose came up to 150% [data not published]. However, an explorative analysis of our data with non-linear models supplied within the TOPFIT software was not successful due to the only marginally visible convexity in the concentration-time curves and the lack of a validation procedure, e.g. by employing different dose levels per individual (for which similar V_{max} and k_d -values should be obtained).

Trapidil metabolism is mainly due to *N*-dealkylation and hydroxylation [18, 19]. Data from study II indicate that the clearance of trapidil is reduced in patients with liver cirrhosis by about 35%. The fact that we could not detect a relationship between trapidil clearance and ICG clearance, the latter reflecting liver blood flow and hence the decrease in the intrinsic clearance of a drug [14], is in accordance with the complete bioavailability of trapidil without considerable first pass metabolism.

Table 3 Study II: Pharmacokinetic parameters after single dose application of 200 mg trapidil in patients with and without liver cirrhosis (mean $\pm$ s.d. or median, range)

	Control patients (n=5)			Cirrhotic patients (n=10)		
	Day 1	Day 4	90%-CI (PE)	Day 1	Day 4	90%-CI (PE)
<i>Trapidil</i>						
AUC ($\mu\text{g ml}^{-1} \text{ h}$)#	21.4 $\pm$ 9.1	13.7 $\pm$ 5.7	0.48–0.84 (0.66)	34.4 $\pm$ 14.9	20.8 $\pm$ 6.8	0.54–0.72 (0.64)
$C_{\min}$ ($\mu\text{g ml}^{-1}$)		0.17 $\pm$ 0.25			0.55 $\pm$ 0.64	
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	5.73 $\pm$ 1.02	5.73 $\pm$ 1.02	0.86–1.53 (0.96)	5.32 $\pm$ 1.06	5.67 $\pm$ 1.16	0.90–1.24 (1.10)
$t_{\max}$ (h)	1.0 (0.5–2.0)	1.0 (0.5–1.5)		1.0 (0.5–1.5)	1.0 (0.5–1.5)	
$t_{\frac{1}{2},z}$	1.85 $\pm$ 0.64	1.19 $\pm$ 0.26	0.51–0.84 (0.66)	3.88 $\pm$ 1.60	2.41 $\pm$ 1.09	0.51–0.74 (0.66)
CL_{app} (ml min^{-1})	166 $\pm$ 59	251 $\pm$ 79		105 $\pm$ 42	163 $\pm$ 52	1.38–1.83 (1.52)
<i>Desethyltrapidil</i>						
AUC ($\mu\text{g ml}^{-1} \text{ h}$)	22.7 $\pm$ 9.1	18.0 $\pm$ 8.8	0.77–1.13 (0.90)	29.8 $\pm$ 14.4	34.5 $\pm$ 23.9	0.72–1.09 (0.85)
$C_{\min}$ ($\mu\text{g ml}^{-1}$)		1.29 $\pm$ 1.09			3.80 $\pm$ 3.15	
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	2.09 $\pm$ 0.44	2.83 $\pm$ 1.10		1.93 $\pm$ 0.70	4.74 $\pm$ 3.16	2.45 (1.40–3.20)
$t_{\max}$ (h)	6.0 (3.0–12.0)	4.0 (2.0–6.0)		12 (8.0–24.0)	3.0 (1.0–6.0)	
AUC _{M1} /AUC _{trapidil}	1.01 $\pm$ 0.32	1.28 $\pm$ 0.41		0.85 $\pm$ 0.31	1.51 $\pm$ 0.71	1.72 (1.32–2.41)

#90% confidence intervals for the difference between group 1 and group 2: Day 1: 0.95–2.97; (point estimator 1.48, $P=0.066$ [U-Test]); Day 4 0.88–2.20; (point estimator 1.45, $P=0.050$ [U-Test])

The inverse correlation between the AUC of trapidil and the MEGX concentration suggests a decrease of phase-I-metabolism of trapidil, since MEGX is produced by CYP4503A4 dependent dealkylation and production rate is reduced not only with decreased liver blood flow but also when the metabolic capacity is restricted [13]. However, no correlation was observed between trapidil AUC and antipyrine-clearance, although antipyrine is also a low extraction drug metabolized by *N*-dealkylation and hydroxylation [12]. Since the database of our study is small and CYP450 isozymes involved in the degradation of trapidil have not yet been determined, we can only speculate that trapidil degradation pathways are not closely related to antipyrine metabolism (mainly CYP2C9 and CYP3A4 [20]).

Induction of liver enzymes by trapidil has been suggested from early studies in rats and in rat liver preparations, where trapidil as well as desethyltrapidil have been shown to decrease the hexobarbitone-induced sleeping time of rats [19,21] and to induce the *N*-demethylation of aminophenazone and the *O*-demethylation of codeine phosphate [19]. Autoinduction could not be confirmed by these *in vitro* experiments [21]. However, both of our human studies showed clearly that the apparent oral clearance of trapidil is enhanced by about 20% after a treatment period of 3–4 days with 200 mg trapidil three times daily. It is suggested that the enhanced metabolism of trapidil during steady state is reflected by the earlier $C_{\max}$ of M1 and the increase in the ratio AUC_{M1}/AUC_{trapidil} [16]. In contrast, further degradation of M1 seems not to be affected by autoinduction, as the AUC values for M1 were not different when comparing single dose and steady state investigations.

The extent of the autoinduction in cirrhotic patients seems comparable with that observed in healthy subjects of study I and the control group of study II. The clinical relevance of the decreased clearance of trapidil in cirrhotic

patients cannot be judged. Maximal plasma levels of trapidil are comparable between patients and controls, suggesting that any adverse effects due to extensive plasma peaks will not occur. Although trapidil elimination half-life is increased, the relative short duration of $t_{\frac{1}{2},z}$ and the autoinduction during steady state should prevent cumulation even in cirrhotic patients.

The results of our studies raise the question whether the short elimination half-life of trapidil, combined with the autoinduction of its metabolism, allows for sustained plasma levels to maintain clinical efficacy. Unfortunately, we were not able to determine pharmacodynamic parameters during our studies. Clinical investigations in patients with coronary artery disease receiving chronic trapidil treatment showed that haemodynamic effects measured at the time of peak plasma levels were comparable with those obtained after a single dose [7], but no trough effects with regard to haemodynamics and exercise duration could be detected. In addition to the presumably PDE-dependent vasodilating effects, trapidil inhibits biosynthesis and action of TXA₂ [22] by 25% as well as PDGF activity [5] by 20% at *in vivo* concentrations of about 10 $\mu\text{g ml}^{-1}$. However, plasma levels of trapidil might not necessarily be maintained throughout the dosing interval to obtain a therapeutic effect on platelet aggregation. In support of this assumption the clinical efficacy of trapidil in prevention of restenosis after PTCA has been demonstrated in two studies including 72 [1] and 256 [2] patients, respectively. Trepidil given 100 mg three times daily [2] and 200 mg three times daily [1], respectively, was compared with aspirin 300 mg day⁻¹ over 6 months, resulting in restenosis rates of 19% and 24 % under trapidil compared with 48% and 40% under aspirin.

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