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 1) 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 [± 7.0 s.d.] μg ml⁻¹ h) was markedly higher than the AUC determined at steady state (13.2 [± 3.8 s.d.] μg ml⁻¹ 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 [± 9.1 s.d.] μg ml⁻¹ h) in controls and (34.4 [± 14.9 s.d.] μg ml⁻¹ 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 [± 5.7 s.d.] μg ml⁻¹ h) in controls and (20.8 [± 6.8 s.d.] μg ml⁻¹ 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 monoethylglycinexilid (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 [± 1.1 s.d.] 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 vasodilatation 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 isoenzymes 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 pharmacokinetic properties 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. On each of the pharmacokinetic study days (i.e. days 1 and 5), trapidil intake followed a last single dose (200 mg) of trapidil plasma samples were drawn 36 h after the last drug intake on day 4.age-matched subjects without liver disease after a 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 \(\text{µg} \cdot \text{ml}^{-1}\) for trapidil, linearity was proven up to 16 \(\text{µg} \cdot \text{ml}^{-1}\). For M1, LLQ was 0.001 \(\text{µg} \cdot \text{ml}^{-1}\) and linearity was obtained within 0.001 and 5 \(\text{µg} \cdot \text{ml}^{-1}\). 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. \(C_{\text{max}}\), \(t_{\text{max}}\) and \(C_{\text{min}}\) (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].

\[ \text{AUC} = \text{AUC}(0, t) + C_m \lambda_z \]  
(1)

where AUC(0, t) is the area under the concentration-time curve from time zero to the last quantifiable concentration value \( C_m \), and \( \lambda_z \) 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.

\[ \text{AUC}(t) \quad \text{(steady state)} \]  
(2)

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

The elimination half-life of trapidil was derived by

\[ t_{1/2,z} = \ln(2) / \lambda_z \]  
(3)

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

\[ \text{CL}_{app} = D / \text{AUC} \]  
(4)

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

\[ \text{AUC}_{M1} / \text{AUC}_{trapidil} \]  
(5)

Statistical analysis

**Single dose vs steady state** Primary target variables were the AUC, \( C_{\text{max}} \), and \( t_{1/2,z} \) of trapidil and the AUC of desethyltrapidil. 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 (±0.3 s.d.) h after the first dose to 1.1 (±0.2 s.d.) 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 accumulation of M1 (\( C_{\text{max}} \) 1.79 [±1.09 s.d.] µg ml–1) (Figure 1b, Table 2). \( t_{\text{max}} \) 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.

**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 (±1.01 s.d.) µg 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 (±0.22 s.d.) µg ml–1, \( C_{\text{max}} \) at day 5 was determined to 5.01 (±1.3 s.d.) µg 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 [±7.0 s.d.] µg ml–1 h) was markedly higher than the AUC determined at steady state (13.2 [±3.8 s.d.] µg ml–1 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 (±0.3 s.d.) h after the first dose to 1.1 (±0.2 s.d.) 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 accumulation of M1 (\( C_{\text{max}} \) 1.79 [±1.09 s.d.] µg ml–1) (Figure 1b, Table 2). \( t_{\text{max}} \) 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]); (b) Plasma concentration vs time profile of desethyltrapidil (–) first dose day 1, ● steady state day 5 [200 mg trapidil three times a day]).
explored, but no deviations from the medication patterns

The principal findings of the two studies reported here

After the first dose, maximal plasma levels of
tone) could be determined. However, the patient with

Study II: Pharmacokinetic parameters of trapidil and M1 at day 1 (single dose

Table 1

<table>
<thead>
<tr>
<th>Trapidil</th>
<th>Day 1</th>
<th>Day 5</th>
<th>90% CI (PE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µg ml⁻¹ h)</td>
<td>20.5±7.0</td>
<td>13.2±3.8</td>
<td>0.58–0.73 (0.64)</td>
</tr>
<tr>
<td>Cmax (µg ml⁻¹)</td>
<td>5.14±1.01</td>
<td>5.01±1.33</td>
<td>0.83–1.08 (0.94)</td>
</tr>
<tr>
<td>Cmax (µg ml⁻¹)</td>
<td>0.50±0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td>1.0 (0.5–2.0)</td>
<td>1.0 (0.5–1.5)</td>
<td></td>
</tr>
<tr>
<td>C1 (µg ml⁻¹)</td>
<td>1.31±0.28</td>
<td>1.14±0.16</td>
<td>0.75–0.98 (0.83)</td>
</tr>
<tr>
<td>CLavg (ml min⁻¹)</td>
<td>179±58</td>
<td>273±77</td>
<td>1.28–2.01 (1.58)</td>
</tr>
</tbody>
</table>

Desethyltrapidil

| AUC (µg ml⁻¹ h) | 16.2±4.5 | 16.9±6.6 | 0.88–1.05 (0.97) |
| Cmax (µg ml⁻¹) | 1.50±0.24 | 2.70±0.90 | 1.42–2.11 (1.78) |
| Cmax (µg ml⁻¹) | 1.79±1.09 | |
| tmax (h) | 6.0 (3.0–12.0) | 3.0 (2.0–6.0) | |
| AUC_{trapidil} | 0.68±0.29 | 1.28±0.55 | 0.40–1.80 (0.83) |

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Control)</th>
<th>Group 2 (Cirrhosis)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male/female)</td>
<td>2/3</td>
<td>6/4</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 (28–45)</td>
<td>45 (35–56)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 (156–182)</td>
<td>168 (158–185)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 (55–74)</td>
<td>69 (55–82)</td>
<td></td>
</tr>
<tr>
<td>ICG-CL (ml min⁻¹ kg)</td>
<td>9.2±2.3</td>
<td>3.2±2.1</td>
<td>2.8–8.9 (P&lt;0.001)</td>
</tr>
<tr>
<td>AP-CL (ml min⁻¹ kg)</td>
<td>1.74±1.04</td>
<td>1.00±0.51</td>
<td>0.18—2.5 (P&lt;0.001)</td>
</tr>
<tr>
<td>MEGX (µg l⁻¹)</td>
<td>85±33</td>
<td>39±17</td>
<td>10.9–33.7 (P&lt;0.001)</td>
</tr>
</tbody>
</table>

ICG-CL = Indocyaninegreen clearance, AP = Antipyrine clearance, MEGX = Monoethylglycinexylidide
clearance, 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.] µg ml⁻¹ and
5.73 [± 1.02 s.d.] µg ml⁻¹, respectively). AUC
averaged (21.4 [± 9.1 s.d.] µg ml⁻¹ h) in controls and
(34.4 [± 14.9 s.d.] µg ml⁻¹ 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).

At steady state, AUC averaged (13.7 [± 5.7 s.d.] µg ml⁻¹ h) in controls and (20.8 [± 6.8 s.d.] µg ml⁻¹ 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.] µg ml⁻¹) when compared with control subjects (1.29
[± 1.09 s.d.] µg ml⁻¹) and subjects from study 1 (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 proprano-
lool. 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
Trapidil kinetics in healthy and in cirrhotic subjects

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

Figure 3 (study II): Linear regression (Pearson's correlation coefficient) between MEGX-test (concentration of the principal metabolite of lignocaine, monoethylglycin-xylidid 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 (■).

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$^{-1}$) [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 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.

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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 cumulation even in cirrhotic patients.

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

<table>
<thead>
<tr>
<th></th>
<th>Control patients (n=5)</th>
<th>Cirrhotic patients (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 4</td>
</tr>
<tr>
<td>Trapidil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (µg ml⁻¹ h)</td>
<td>21.4±9.1</td>
<td>13.7±5.7</td>
</tr>
<tr>
<td>Cmax (µg ml⁻¹)</td>
<td>5.73±1.10</td>
<td>5.73±1.10</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>10 (0.5–20)</td>
<td>10 (0.5–15)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.85±0.64</td>
<td>1.19±0.26</td>
</tr>
<tr>
<td>CLapp (ml min⁻¹)</td>
<td>166±59</td>
<td>251±79</td>
</tr>
<tr>
<td>Desethyltrapidil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (µg ml⁻¹ h)</td>
<td>22.7±9.1</td>
<td>18.0±8.8</td>
</tr>
<tr>
<td>Cmax (µg ml⁻¹)</td>
<td>1.29±0.90</td>
<td>2.83±1.10</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>6.0 (3.0–12.0)</td>
<td>4.0 (2.0–6.0)</td>
</tr>
<tr>
<td>AUCmax/AUCinitial</td>
<td>1.01±0.32</td>
<td>1.28±0.41</td>
</tr>
</tbody>
</table>

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: 0.038–2.28; (point estimator 1.45, \( P = 0.050 \) [U-Test])

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 \( t_{1/2} \) 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 vitro concentrations of about 10 µg 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. Trapidil 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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