Biotransformation of Tirilazad in Human: 4. Effect of Finasteride on Tirilazad Clearance and Reduced Metabolite Formation

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ABSTRACT

The effect of oral finasteride, an inhibitor of 5α-reductase, on the clearance of tirilazad, a membrane lipid peroxidation inhibitor, was assessed in eight healthy men who received: 1) 10 mg/kg tirilazad mesylate solution orally on the 7th day of a 10-day regimen of 5 mg finasteride once daily, 2) 10 mg/kg tirilazad mesylate orally, 3) 2 mg/kg tirilazad mesylate i.v. on the 7th day of a 10-day regimen of 5 mg finasteride once daily and 4) 2 mg/kg tirilazad mesylate i.v., in a four-way cross-over design. Plasma concentrations of tirilazad and its active reduced metabolites (U-89678 and U-87999) were measured by liquid chromatography with tandem mass spectrometry (LC-MS-MS). Finasteride increased mean tirilazad areas under the curve by 21 and 29% for i.v. and p.o. tirilazad, respectively.

Tirilazad is a membrane lipid peroxidation inhibitor that has been tested in animal models for the prevention of neuronal damage due to head trauma, subarachnoid hemorrhage, spinal cord injury and stroke (Braughler et al., 1989). Tirilazad has been evaluated clinically in the same disorders and has demonstrated reduced mortality in male subarachnoid hemorrhage patients (Haley et al., 1994; Bleck et al., 1995; Kassell et al., 1993; Kassell et al., 1996).

Tirilazad mesylate appears to be a medium extraction ratio compound (Fleishaker et al., 1994, 1993). The majority of tirilazad is recovered in the feces as various metabolites; less than 12% of the dose is recovered in the urine as drug-related materials (Stryd et al., 1992). One reduced metabolite has been identified that has activity similar to that of tirilazad in a rat model of subarachnoid hemorrhage (Smith et al., 1996) (U-89678, fig. 1). This metabolite exhibits AUC values on multiple dosing which may be >50% of those of the parent compound (Fleishaker et al., 1994). An additional metabolite with activity in the mouse head injury model, U-87999 (fig. 1) (Smith et al., 1996) has also been identified in human plasma, but plasma concentrations of this metabolite are generally <20% than those of U-89678 (Fleishaker et al., 1996).

Recent experiments in human liver microsome preparations suggest that the major pathways of tirilazad metabolism in humans are mediated by the 3A isozymes of cytochrome P-450 (CYP3A) (Wienkers et al., 1996). These results have been confirmed by the observation that ketoconazole, a specific CYP3A inhibitor, dramatically reduces the clearance of tirilazad in vivo (Fleishaker et al., 1996). Despite this fact, Mean U-89678 areas under the curve were decreased 92 and 75% by finasteride administration with i.v. and p.o. tirilazad, respectively, and decreases of 94 and 85% in mean U-87999 area under the curve values were observed. These differences were statistically significant. These results indicate that finasteride inhibits the metabolism of tirilazad to U-89678. However, this inhibition has only a moderate effect on the overall clearance of tirilazad. These results thus confirm earlier in vitro work that showed that tirilazad is predominantly metabolized by CYP3A4. Although the major circulating metabolites of tirilazad are formed via reduction, this represents a minor route of tirilazad elimination in man.

ABBREVIATIONS: SAH, subarachnoid hemorrhage; t½, half-life; AUC0–∞, area under the plasma concentration-time curve; AUCM0–∞, area under the first moment curve; MRT, mean residence time; T, infusion duration; CL, systemic clearance; CLPO, oral clearance; Vss, volume of distribution at steady-state; Cin, concentration at the end of infusion; Cmax, maximal plasma concentration; Tmax, time of maximal plasma concentration; F, absolute bioavailability; ANOVA, analysis of variance; E, extraction ratio; Fh, fractional availability through the liver; Fa, fraction absorbed; Fg, fractional availability through the gut; CLint, intrinsic clearance; Q, hepatic blood flow; CLh, hepatic clearance; CV, coefficient of variation; λz, terminal elimination rate constant.
the major metabolites of tirilazad found in circulation are formed via reduction. In rat and human liver microsomes, 5α-reductase was found to mediate the formation of U-89678 (Wienkers et al., 1995, 1998). This reaction was inhibited by finasteride, an inhibitor specific for this enzyme. Thus, administration of finasteride and tirilazad concomitantly might allow the determination of the relative contribution of 5α-reductase to the elimination of tirilazad in man in vivo.

Our purpose was to determine the relative contribution of 5α-reductase to the clearance of tirilazad in healthy volunteers by administering tirilazad p.o. and i.v. in the presence and absence of the specific 5α-reductase inhibitor, finasteride. Using this approach we hoped to ascertain the relative contribution of 5α-reductase to the clearance of tirilazad after i.v. administration and determine the effect of finasteride on the absolute bioavailability of tirilazad after p.o. administration.

Materials and Methods

Subjects and procedures. The study was conducted at the Upjohn Research Clinics, Kalamazoo, MI. The study was approved by the Bronson Methodist Hospital Institutional Review Board, and each volunteer provided written evidence of informed consent before enrollment.

Nine male volunteers (ages 18–53, weight 55.3–85.3 kg) were enrolled in the study; eight subjects completed all study activities. One subject withdrew from the study for personal reasons. Subjects were determined to be in good health by physical examination and standard clinical laboratory tests. Subjects received no known enzyme inducing agents for 30 days before the study, no medications during the 7 days before the study and no alcohol for 2 days before and throughout the study. During the course of the study, subjects were to receive no medications other than those specified in the protocol.

Subjects received the following treatments according to a randomized four-way crossover design: 1) 5-mg finasteride tablet given p.o. at 06:00 on days 1 to 10 and 2 mg/kg tirilazad mesylate solution (1.5 mg/ml) given orally on day 7 at 08:00, 2) 10 mg/kg tirilazad mesylate solution given orally on day 7 at 08:00, 3) 5-mg finasteride tablet given orally at 06:00 on days 1 to 10 and 2 mg/kg tirilazad mesylate solution given i.v. on day 7 at 08:00 and 4) 2 mg/kg tirilazad mesylate solution given i.v. on day 7 at 08:00. Oral tirilazad was administered via orogastric tube; i.v. tirilazad was administered after 1:2 dilution with normal saline as a 10-min infusion. Tirilazad administration on day 7 occurred after an overnight fast. A 1-wk wash-out period separated study phases.

Clinical assessments. A 12-lead electrocardiogram was recorded pre-dose on day −1, before the tirilazad dose on day 7 and on day 8 (24 hr after the tirilazad dose) in each study phase. A blood sample for the determination of safety laboratories (hematology and chemistry) was collected on day −1 of phase I and day 11 (24 hr after the last finasteride dose) of phase IV. Additional blood samples for the determination of alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, and γ-glutamyl transferase (GGT) were collected on days 1, 7 and 11 of the phases in which subjects received treatments A and C (finasteride + tirilazad treatments). A blood sample was drawn pre-dose on days 1 and 7 of each phase for dihydrotestosterone determinations. Subjects were interviewed before dosing and on the evening of each study day to determine whether they had experienced any medical events.

Blood sampling. Venous blood samples for the determination of tirilazad (7 ml) were collected into heparinized vacutainers immediately prior to drug dosing on day 7 and again at 12, 15, 30 and 40 min and at 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 and 96 hr after the start of tirilazad administration. Plasma was harvested from the samples after centrifugation and frozen at −70°C until analyzed.

Analytical methods. Plasma concentrations of tirilazad, U-89678 and U-87999 were determined by a sensitive and specific LC-MS-MS method. After plasma protein precipitation using acetonitrile containing internal standard (13C3,15N2-U-74006F), the supernatant was injected on an high-performance liquid chromatography system consisting of a mobile phase of methanol:water:5 M ammonium acetate pH 6.0 (85:10:5, v/v/v) flowing at 1.2 ml/min through a Kromasil 100-5C18 column (150 mm × 4.6 mm i.d.). The detector, a Finnegan TSQ-700 triple quadrupole mass spectrometer, was coupled to the LC system via an atmospheric pressure chemical
ionization source. The protonated molecular (M+H) ion for tirilazad at m/z 625 and the stable isotope at m/z 630 were transmitted and the product ion fragments monitored at m/z 260 and 265, respectively. Molecular ions for PNU-87999 at m/z 629, PNU-89678 at m/z 627 and PNU-76824 at m/z 634 were transmitted and product ion fragments at m/z 260 were also monitored.

For tirilazad, the assay was linear over the range of 0.45 to 10490 ng/ml. The precision of the system, expressed as the CV of the slope of the standard curves, was ±3%. The precision of the method, expressed as the mean CV of the back-calculated standard concentrations, was ±5.2%. For the quality control (QC) samples, mean recoveries were 107 ± 9, 112 ± 5 and 105 ± 5% for the low, medium and high concentration controls, respectively.

For U-89678, the assay was linear over the range of 0.47 to 988 ng/ml. The precision of the system, expressed as the CV of the slope of the standard curves, was ±15%. The precision of the method, expressed as the mean CV of the back-calculated standard concentration standards, was ±5.9%. For the QC samples, mean recoveries were 89 ± 6, 93 ± 7 and 97 ± 7% for the low, medium and high concentration controls, respectively.

For U-89678, the assay was linear over the range of 0.47 to 988 ng/ml. The precision of the system, expressed as the CV of the slope of the standard curves, was ±15%. The precision of the method, expressed as the mean CV of the back-calculated standard concentration standards, was ±5.9%. For the QC samples, mean recoveries were 89 ± 6, 93 ± 7 and 97 ± 7% for the low, medium and high concentration controls, respectively.

The assay was linear for U-87999 over the range of 0.51 to 970.5 ng/ml. System precision, expressed as the CV of the slope of the standard curves, was ±11%. The mean CV of the back-calculated standard concentration standards was ±6.8%. For the QC samples, mean recoveries were 88 ± 6, 89 ± 8 and 93 ± 7% for the low, medium and high concentration controls, respectively.

Data analysis. Pharmacokinetic parameters were determined by noncompartmental methods (Gibaldi and Perrier, 1982). The λz was determined by linear regression of the terminal portion of the concentration-time profile. The terminal t1/2 was calculated as 0.693/λz. AU0–∞ was determined by trapezoidal rule up to the last time at which a measurable concentration was observed and extrapolated to infinity. AUMC0–∞ for tirilazad was determined in an analogous manner. MRT after the i.v. administration of tirilazad was calculated as AUMC0–∞/AUC0–∞ – T/2, where T is the infusion duration. CL of tirilazad was calculated as dose i.v./AUC0–∞. CLPO was calculated in an analogous manner. Vss after the i.v. dose of tirilazad was calculated as CL × MRT. Tirilazad Cinf (concentration at the infusion stop), Cmax of U-89678, U-87999 and tirilazad (after oral dosing) and the Tmax at which they occurred were determined by inspection of the plasma concentration-time profile. The F of tirilazad was calculated as (AUC0–∞ PO dose i.v.)/AUC0–∞ i.v. (Dose PO).

Effects of treatment on pharmacokinetic parameters of tirilazad, U-89678, and U-87999 were assessed using ANOVA for a cross-over model. Due to nonhomogeneous variances among treatment groups, ranks rather than the raw data were used for this analysis. The subject number was selected to provide an 88% power to detect a 40% difference in tirilazad AUC0–∞ given a 20% CV from the ANOVA and an α level of 0.05. The actual CV from this study was 19.9%, yielding a power of 90% to detect the above difference in AUC0–∞. Pair-wise comparisons within routes of administration were performed by Waller-Duncan K-ratio t test (Waller and Duncan, 1969).

The method requires equal sample sizes in each treatment group, and the degree of conservatism of the test varies with the heterogeneity of the data (Milliken and Johnson, 1984). This test is thus amenable to the data collected in this study.

### TABLE 1
Mean (± S.D.) pharmacokinetic parameters for tirilazad mesylate (TM) after administration of 2.0 mg/kg tirilazad mesylate i.v. and 10 mg/kg of tirilazad mesylate p.o. in the presence and absence of 5 mg finasteride coadministration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Parameters</th>
<th>10 mg/kg TM p.o. + finasteride</th>
<th>10 mg/kg TM i.v.</th>
<th>2.0 mg/kg TM i.v.</th>
<th>2.0 mg/kg TM i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–∞ (ng hr/ml)</td>
<td>2435 (1113)</td>
<td>1887 (1036)</td>
<td>5324 (1550)</td>
<td>4413 (847)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>382 (79.2)</td>
<td>343 (85.4)</td>
<td>6324 (1490)</td>
<td>5699 (1583)</td>
<td></td>
</tr>
<tr>
<td>CL (L/hr)</td>
<td>0.039 (119)</td>
<td>0.039 (146)</td>
<td>0.259 (7.82)</td>
<td>0.30 (5.37)</td>
<td></td>
</tr>
<tr>
<td>Vss (L)</td>
<td>638 (0.029)</td>
<td>778 (0.029)</td>
<td>193 (0.029)</td>
<td>244 (0.029)</td>
<td></td>
</tr>
</tbody>
</table>

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**a** P < 0.05.

**b** Comparison of i.v. treatments.

**c** Cinf for i.v. doses, Cmax for oral doses.

**d** Systemic clearance for i.v. doses, CLPO for oral doses.

**e** Comparison of oral treatments.
Results

Clinical. Tirilazad administration was well tolerated by both routes of administration in this study. As expected, local injection site discomfort was frequent with i.v. administration. With p.o. tirilazad administration, some reports of nausea and/or dyspepsia were temporally related to dosing. All of these events were transient and mild or moderate in intensity. Finasteride administration was also well tolerated and did not appear to affect the medical event profile of tirilazad. No clinically important alterations in electrocardiogram or laboratory parameters were observed with either drug.

In the treatments in which finasteride was administered, plasma dihydrotestosterone was decreased 36% (p.o. tirilazad) and 40% (i.v. tirilazad) on day 7 of the treatment phase relative to baseline levels. These changes were statistically significant. In the treatments in which tirilazad alone was administered, dihydrotestosterone concentrations increased 14% in both p.o. and i.v. treatments (also statistically significant).

Pharmacokinetics. Plasma concentrations of tirilazad are shown in figure 2. Mean pharmacokinetic parameters for tirilazad are listed in table 1. Individual values for AUC0–∞ and subject weight are provided in table 2. The absolute oral bioavailability of tirilazad was 0.091 ± 0.029. In the presence of finasteride, this value was 0.083 ± 0.029. Mean tirilazad AUC0–∞ was increased 21 and 29% by finasteride administration during i.v. and oral administration of tirilazad, respectively. After p.o. tirilazad, mean tirilazad Cmax was increased 11% by finasteride coadministration. Only the change in tirilazad AUC0–∞ after i.v. tirilazad was statistically significant, but finasteride decreased tirilazad clearance significantly after both i.v. and p.o. tirilazad administration. Tmax after oral tirilazad was not significantly affected by finasteride administration. Neither half-life or volume of distribution after i.v. tirilazad administration was affected by finasteride administration. For p.o. tirilazad, terminal half-life was unaffected by finasteride coadministration.

Plasma concentrations of U-89678 are depicted in figure 3; mean pharmacokinetic parameters for this metabolite are shown in table 3. Coadministration of finasteride resulted in 92 and 75% decreases in the apparent AUC0–∞ of U-89678 after i.v. and p.o. administration of tirilazad, respectively. Cmax was decreased 95 and 91% after i.v. and p.o. tirilazad, respectively, during finasteride administration. All of these differences were statistically significant. Mean U-89678 Tmax values after p.o. and i.v. tirilazad were significantly longer when finasteride was coadministered.

Plasma concentrations of U-87999 are depicted in figure 4; mean pharmacokinetic parameters are listed in table 4. Due to the fact that terminal half-life for this metabolite could not be determined in the majority of subjects in the finasteride treatments, AUC0–96 was calculated instead of AUC0–∞. As with U-89678, administration of finasteride significantly decreased AUC0–96 and Cmax of U-87999 after p.o. and i.v. tirilazad administration.

Discussion

Tirilazad administration was well tolerated in male volunteers by both routes of administration in this study. As expected, local injection site discomfort was frequent with i.v. administration. With p.o. tirilazad administration, some reports of nausea and/or dyspepsia were temporally related to
dosing. Finasteride administration did not appear to affect
the medical event profile of tirilazad.

The purpose of this trial was to assess the effect of finas-
teride on the pharmacokinetics of tirilazad after i.v. and p.o.
administration of tirilazad mesylate. These data were to help
in assessing the relative clearance of tirilazad by oxidative
and reductive routes. According to the well-stirred model of
hepatic clearance (Wilkinson and Shand, 1975), hepatic
clearance can be described as:

$$CL_h = QE$$  \hspace{1cm} (1)

where Q is hepatic blood flow and E is the extraction ratio.
Because tirilazad does not partition into erythrocytes, CLh
and Q will refer to plasma clearance and hepatic plasma flow,
respectively, throughout the remainder of the discussion. The
fractional availability through the liver (Fh) is described as:

$$Fh = 1 - E$$ \hspace{1cm} (2)

TABLE 3
Mean (±S.D.) pharmacokinetic parameters for U-89678 after
administration of 2.0 mg/kg tirilazad mesylate (TM) i.v. and 10 mg/kg
tirilazad mesylate p.o. in the presence and absence of 5 mg
finasteride

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment</th>
<th>10 mg/kg TM p.o.</th>
<th>10 mg/kg TM p.o. + finasteride</th>
<th>2.0 mg/kg TM i.v.</th>
<th>2.0 mg/kg TM i.v. + finasteride</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–∞ (ng hr/ml)</td>
<td>237 b</td>
<td>953</td>
<td>99.1 ac</td>
<td>1213</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>(155)</td>
<td>(758)</td>
<td>(90.4) (585)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>3.38 b</td>
<td>2.25</td>
<td>0.625 ab</td>
<td>0.521</td>
<td></td>
</tr>
<tr>
<td>λz (hr⁻¹)</td>
<td>(1.77)</td>
<td>(1.58)</td>
<td>(0.173) (0.059)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apparent t½ (hr)</td>
<td>41.6</td>
<td>41.6</td>
<td>26.3 ab</td>
<td>59.7</td>
<td></td>
</tr>
</tbody>
</table>

a P < .05.
b Comparison of oral treatments.
c Comparison of i.v. treatments.

where CLh is the intrinsic clearance.

Previous results indicate that tirilazad is metabolized pre-
dominantly by CYP3A to various hydroxy metabolites (Wien-
kers et al., 1996), but that U-89678, the major circulating
metabolite is formed by 5α-reductase (Wienkers et al., 1995,
1998). Rearranging equation 1 and using a value of 54 li-
ter/hr for hepatic plasma flow (liver blood flow ×0.6), the
extraction ratio of tirilazad is calculated from the systemic
clearance of tirilazad after i.v. administration to be 0.56 and
0.48 in the absence and presence of finasteride administra-
tion, respectively. By rearranging equation 3 and substitut-
ing the above values for the extraction ratio, it is apparent
that intrinsic clearance of tirilazad in the liver decreased
from 68.7 to 49.8 liter/hr, or decreased by approximately 28%.

Mean AUC0–∞ of the two reduced metabolites were re-
duced much more substantially by finasteride coadministra-
tion. Therefore, the results of this study confirm that 5α-
reductase is responsible for the formation of U-89678 in vivo
in man.

By considering our results in light of the results of the
previous tirilazad, ketoconazole interaction trial (Fleishaker
et al., 1996), it is possible to address the relative importance
of 5α-reductase in the clearance of tirilazad. Ketoconazole, a
specific 3A inhibitor, has no effect on 5α-reductase activity.
Finasteride, although it is metabolized by CYP3A4 (Huskey
et al., 1995), appears to have little effect on cytochrome P-450
activity (Winchell et al., 1993). Therefore, by considering the
residual intrinsic clearance of tirilazad in the presence of
these specific inhibitors, we may assess the relative impor-
tance of these routes of metabolism. In the presence of keto-
conazole, the intrinsic clearance of tirilazad is reduced from
68.7 to 28.4 liter/hr. Therefore, if one assumes that metabo-

Fig. 4. Mean plasma concentrations of
U-87999 after the administration of p.o.
and i.v. tirilazad in the presence and ab-
sence of finasteride coadministration.
intrinsic clearance by non CYP3A pathways would be 28.4 liter/hr. In our study, the intrinsic clearance of tirilazad was reduced by approximately 18.9 liter/hr by finasteride administration. The evidence from this study suggests that 5α-reductase may not have been completely blocked by finasteride, because dihydrotestosterone levels were reduced by a maximum of 40% compared to the 61 to 63% reported after 7 days of administration of finasteride at doses of 1 and 10 mg/day, respectively, to healthy volunteers (Ohtawa et al., 1991). Thus, it is not possible to determine exactly the relative contributions of CYP3A and 5α-reductase to the metabolic clearance of tirilazad. However, the results of these two studies confirm the results of in vitro work that shows that tirilazad is predominantly metabolized by CYP3A. Although the major circulating metabolites of tirilazad are formed via 5α-reductase, this represents a minor route of tirilazad metabolism in man. These conclusions are represented schematically in figure 5, which outlines the most important pathways for tirilazad metabolism in man.

The results after oral administration show that the absolute bioavailability of tirilazad is unaffected by finasteride administration; however, to consider this further, one should take into account those factors that can affect oral bioavailability. The factors that affect F have been described by the following equation (Hebert et al., 1992):

\[ F = F_a F_g F_h \]  

(10)

where \( F_a \) is the fraction absorbed and \( F_g \) is the fractional availability through the gut. Because the fractional absorp-

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**TABLE 4**

Mean (±S.D.) pharmacokinetic parameters for U-87999 after administration of 2.0 mg/kg tirilazad mesylate (TM) i.v. and 10 mg/kg of tirilazad mesylate PO in the presence and absence of 5 mg finasteride

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment</th>
<th>10 mg/kg TM p.o.</th>
<th>10 mg/kg TM p.o.</th>
<th>2.0 mg/kg TM i.v.</th>
<th>2.0 mg/kg TM i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–96 (ng hr/ml)</td>
<td>24.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>165</td>
<td>11.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(28.2)</td>
<td>(193)</td>
<td>(27.4)</td>
<td>(137)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>0.940&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.9</td>
<td>0.286&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.727)</td>
<td>(10.8)</td>
<td>(0.533)</td>
<td>(11.9)</td>
<td></td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.13</td>
<td>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.89)</td>
<td></td>
<td>(0.502)</td>
<td></td>
</tr>
<tr>
<td>λz (hr&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.0646</td>
<td>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.0288</td>
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<tr>
<td></td>
<td></td>
<td>(0.0720)</td>
<td></td>
<td>(0.0246)</td>
<td></td>
</tr>
<tr>
<td>Apparent t½ (hr)</td>
<td>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>31.3</td>
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<td>36.5</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(30.0)</td>
<td></td>
<td>(19.3)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> P < .05.
<sup>b</sup> Comparison of oral treatments.
<sup>c</sup> Comparison of i.v. treatments.
<sup>d</sup> The majority of observed values was below the limit of quantitation, so Tmax values were not determined.
<sup>e</sup> Terminal rate constant and half-life could not be determined in % (oral tirilazad).

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**Fig. 5.** Metabolic scheme for tirilazad bio-transformation in man.
tion of tirilazad in man is not known, we can only determine the product of Fa and Fg in this study. Previous results suggest that tirilazad undergoes substantial gut wall metabolism (Fleishaker et al., 1996). Using the values described above for Fh and for F from table 1, the product of Fa and Fg is calculated to be 0.18 and 0.17 in the absence and presence of finasteride, respectively. If one assumes that finasteride does not affect tirilazad absorption, this result indicates 5α-reductase does not substantially contribute to the presystemic metabolism of tirilazad in the gut.

Subarachnoid hemorrhage is an event that occurs most commonly in the middle-age population. Males in this age group are also at risk to develop prostatic hypertrophy; thus, the total exposure to active

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