Unique Preclinical Characteristics of GG745, A Potent Dual Inhibitor of 5AR

H. NEAL BRAMSON, DAVID HERMANN, KENNETH W. BATCHELOR, FRANK W. LEE, MICHAEL K. JAMES and STEPHEN V. FRYE

Department of Clinical Pharmacology (D.H.), Divisions of Biochemistry (H.N.B.) and Metabolic Diseases Research (K.W.B.), Bioanalysis and Drug Metabolism (F.W.L.), and Chemistry (S.V.F.), Glaxo Wellcome Research Institute, Research Triangle Park, North Carolina, and Inspire Pharmaceuticals Inc., Durham, North Carolina (M.K.J.)

Accepted for publication May 12, 1997

ABSTRACT

Selective inhibition of type 2 5α-reductase has been shown to be efficacious in the treatment of benign prostatic hyperplasia. Pharmacokinetic and pharmacodynamic results are reported of treatment with a potent inhibitor of both 5α-reductase isozymes, GG745, in rats, dogs and men. In the rat, GG745 has a similar effect on DHT-driven prostatic growth as finasteride, another dual 5α-reductase inhibitor in this species. However, GG745 appears to be more potent in the rat, a result that likely reflects the greater inherent potency and terminal half-life of GG745 (14 hr) compared with that of finasteride (1 hr). These pharmacokinetic differences are also maintained in the dog (65 and 4 hr for GG745 and finasteride, respectively). From these results, the literature, and in vitro studies, we estimated doses of GG745 likely to prove efficacious in reducing DHT levels in man. These estimated values were predictive of single-dose effects of GG745 in man. Results from single-dose evaluations in man indicate that GG745 has a terminal half-life of ~240 hr, and single doses of >10 mg decreased DHT levels significantly more than did single 5-mg doses of finasteride. These data support the hypothesis that a molecule (GG745) that effectively inhibits both 5α-reductases will lower serum DHT levels significantly more than a molecule that inhibits only a single 5α-reductase isozyme (e.g., finasteride, a selective inhibitor of the type 2 enzyme in man).

Pharmacological intervention to treat lower urinary tract symptoms and bladder outlet obstruction secondary to BPH is desirable due to the high incidence of this disease and its resulting erosion in the quality of life for affected men (Geller, 1991). Fifty percent of males over the age of 60 have lower urinary tract symptoms suggestive of bladder outlet obstruction; ultimately, 25% to 30% of them require surgery (Lange, 1992). Although facets of the BPH etiology remain to be explored, the permissive role of DHT for hyperplastic growth of the prostate is well established (Geller, 1991; Lange, 1992; Russell and Wilson, 1994). 5ARs catalyze the transfer of hydride from NADPH to the 5α position of T to produce the more potent androgen DHT, and there has been considerable interest in developing inhibitors for these enzymes. Two 5ARs have been identified; these are referred to as the type 1 and type 2 enzymes on the basis of their order of discovery (Russell and Wilson, 1994). Although the relative physiological roles of these enzymes are not yet understood, the type 2 5AR is the primary isozyme present in human prostates (Russell and Wilson, 1994). Treatment of patients with finasteride, a selective type 2 5AR inhibitor, reduces circulating DHT concentrations to 20% to 40% of base-line values and has been proved to be partially efficacious for the treatment of BPH (Russell and Wilson, 1994; Moore et al. 1995). We previously made the case that drug molecules that inhibit both the type 1 and type 2 enzymes would more effectively reduce circulating DHT levels than would selective inhibitors of a single 5AR isozyme alone (Frye et al., 1993, 1994). Because it is possible that a further reduction in DHT would prove to have clinical advantages, we sought potent dual inhibitors (Frye et al., 1993, 1994, 1995), with our work culminating in GG745 [17β-N-(2,5-bis-(trifluoromethyl) phenylcarbamoyl)-4-aza-5α-androst-1-en-3-one], a potent dual 5AR inhibitor (fig. 1).

Both GG745 and finasteride are time-dependent inhibitors of the human type 1 and 2 5α-reductases (Faller et al., 1993; Tian et al., 1994, 1995). Finasteride has been suggested to be an irreversible inhibitor of both 5ARs (Faller et al., 1993;
Tian et al., 1994, 1995), but recent studies have indicated that this inhibition process instead results from the enzyme-catalyzed formation of the potent disubstrate inhibitor NADP-dihydrofinasteride (Bull et al. 1996). Just as 5ARs catalyze the reduction of the C5 position of testosterone by NADPH, these enzymes also catalyze the NADPH-dependent reduction of the C1 position of finasteride. In the case of the 1,2-ene-containing finasteride, reduction of C1 enables the nucleophilic attack of C2 on the nicotinamide C4, resulting in the formation of NADP-dihydrofinasteride, which has a half-life for dissociation from the type 2 5AR of ≥1 month (Bull et al. 1996). Thus, finasteride effectively is an irreversible inhibitor of the type 2 5AR in vivo. We presume that the structurally related GG745, which also appears to irreversibly inhibit the 5ARs (Tian et al. 1995), does so by a similar mechanism.

The kinetics of types 1 and 2 5AR inhibition by GG745 and finasteride fit well to a mechanism in which inhibitor binds to enzyme in a fast equilibrium ($K_i$), which is followed by an irreversible rate-determining inactivation step ($k_{ir}$) (Faller et al., 1993; Tian et al., 1994, 1995). At pH 7.0 and 37°C, values for $k_{ir}/K_i$ describing the interactions of the type 1 5AR with GG745 and finasteride are $1.8 \pm 0.3 \times 10^5$ and $4.0 \pm 0.6 \times 10^3$ M/sec, respectively (Tian et al., 1995). Under equivalent conditions, values for $k_{ir}/K_i$ obtained from the inhibition of the type 2 5AR by GG745 and finasteride are $6.8 \pm 2.9 \times 10^5$ and $3.2 \pm 0.4 \times 10^5$ M/sec, respectively (Tian et al., 1995).

These data indicate that both GG745 and finasteride are potent inhibitors of the human type 2 5AR but that finasteride is a 50-fold weaker inhibitor of the human type 1 5AR. The degree to which slow inhibition of type 1 5AR by finasteride influences the efficacy of this drug in man was predicted by a modeling study that considered the above $k_{ir}/K_i$ values, drug tissue distribution, and pharmacokinetics of finasteride disposition in man (Tian, 1996). The conclusion of this study was that the rate of type 1 5AR inhibition by finasteride was sufficient at the predicted tissue drug concentrations and rates of enzyme synthesis to only partially inhibit this enzyme (Tian, 1996). Thus, finasteride fails to suppress circulating DHT levels by >60% to 80%. Interestingly, the $k_{ir}/K_i$ describing GG745 inactivation of the type 1 5AR is nearly as fast as the $k_{ir}/K_i$ describing finasteride interactions with the type 2 5AR (Faller et al., 1993; Tian et al., 1994, 1995). These data provided an indication that GG745 would be more effective than finasteride at reducing serum DHT concentrations in man.

We report initial preclinical pharmacokinetic and pharmacodynamic results of the potent dual 5AR inhibitor GG745 and how these results were used to estimate effective exposures in humans. These results include (1) initial studies to explore the efficacy of GG745 performed in an intact rat model of 5AR-dependent prostatic growth and (2) the pharmacokinetics of GG745 in rats and dogs.

On the basis of these preclinical data, we estimated probable therapeutic doses of GG745 in man. These estimates are compared with results obtained from the first evaluation of GG745 in humans.

**Experimental Procedures**

**Materials.** Tween-80 and Cremophor EL were purchased from Sigma Chemical (St. Louis, MO). Finasteride and 4-MA were synthesized according to Rasmusson et al. (1986), and GG745 was synthesized as previously described.1


**In vitro determinations of GG745 selectivity.** The inhibition of human adrenal 3β-hydroxy-Δ^4-steroid dehydrogenase/3-keto-Δ^4-steroid isomerase was measured according to Frye et al. (1995). Androgen receptor binding assays were performed by Novascreen (Hanover, MD) as described in their catalog.2 Inhibitors were tested in duplicate for potency at three concentrations: $10^{-5}$, $10^{-7}$ and $10^{-9}$ M. For the androgen receptor assays, T, DHT and 4-MA (Fig. 1), a Merck inhibitor known to be a low-affinity inhibitor of androgen binding to the androgen receptor (Russell and Wilson, 1994), were used as controls. All inhibitors and controls were coded by Glaxo Wellcome, so their identities were unknown by Novascreen. DHT and T were found to be potent inhibitors of [3H]methyltrienolone binding to the androgen receptor, whereas 4-MA was intermediate and of the magnitude expected (Brooks et al., 1982).

**Pharmacodynamics of GG745 and finasteride in intact adult male rats.** This study was designed to compare the efficacy of new 5AR inhibitors with the approved 5AR inhibitor finasteride. GG745 and finasteride were evaluated in experiments performed on different days. For each inhibitor to be evaluated, male Sprague-Dawley rats ($n = 32$, ranging from 200 to 225 g) were divided into four groups of eight on the basis of body weight. Rats in each group ($n = 8$) were dosed (5 ml/kg) for 14 days by oral gavage with either inhibitor or vehicle alone (1 part cremophor/2 parts saline/0.5% Tween 80). On day 15, each rat was killed by asphyxiation. After

---

determination of total body weight, the adrenal glands, liver, ventral prostate, seminal vesicles and right testicle were removed, cleared of adherent tissue and weighed. The data in table 1 were obtained using GG745 doses of 1, 10 or 100 mg/kg/day and equimolar amounts of finasteride (0.7, 7.2 or 72 mg/kg/day).

Values are reported as mean ± S.E.M. for actual weights and percentage of vehicle control and were obtained by using the analysis of variance feature in Excel 5.0 for Windows (Microsoft, Redmond, WA). Pairwise comparisons between treatment groups were made using t test with the Bonferroni adjustment for multiple comparisons (Kleinbaum et al., 1988).

Pharmacokinetics of GG745 and finasteride in the dog. The pharmacokinetics of GG745 was determined in a total of six male beagle dogs weighing −10 kg (Marshall Farms, North Rose, NY; Hazleton Laboratories, Cumberland, VA). Dog 1 was prepared with two venous canullae and received an i.v. infusion dose of 5 mg/kg GG745 over a 10-min period, whereas dogs 2 to 5 were prepared similarly but received a i.v. bolus dose of 0.1 mg/kg. Dog 6 was prepared with a single venous cannula and dosed by oral gavage at a dose level of 5 mg/kg. The dogs were fasted overnight before administration. The doses for dogs 1 and 6 were prepared by dissolving GG745 in propylene glycol, and doses for dogs 2 to 5 were prepared in 40% Molecusol (PharmaTech, Alachua, FL). After dose administration, blood samples (2 ml) were withdrawn from dogs 1 and 6 via the cephalic vein cannula into a heparinized syringe at 0 (predose), 5, 15, 30 and 45 min and 1, 1.5, 2.5, 4, 6, 8, and 24 hr after the start of the infusion or oral bolus dosing. Samples were removed from dogs 2 to 5 similarly at 0 (predose), 5, 15 and 30 min and 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, 192, 240, 312, 360, 408, 456, 504, 576, 744, 912, 1080, 1248 and 1416 hr. All samples were stored at −70°C in a freezer before analysis.

For comparison, the pharmacokinetic characteristics of finasteride were studied (n = 3). These dogs received finasteride through i.v. dose administration (10 mg/kg). The finasteride dose solution was prepared in a 40% Molecusol water solution (pH 6). Blood samples were collected in a similar fashion as described for dog 1 in the GG745 dog study.

Pharmacokinetics of GG745 and finasteride in the rat. A total of four male wu/Wistar rats (Harlan, Indianapolis, IN) with body weight ranging from 320 to 350 g were used in the study of GG745 pharmacokinetics. Rats were randomly divided into two groups. Jugular vein cannulation was performed the day before study drug administration. Femoral vein cannulation was also performed in the two rats that received an i.v. dose. The first group of dogs received an i.v. dose of GG745 (1 mg/kg), and the second group of rats received an oral dose of GG745 (1 mg/kg). GG745 was dissolved in a 40% Molecusol water solution (pH 6) to give a concentration of 0.33 mg/ml. Blood samples were withdrawn via the jugular cannula at 0 (predose), 15, 30 and 45 min and 1, 1.5, 2.5, 4, 6, 8, 24 and 96 hr after dose administration and transferred into heparinized microfuge tubes. The blood samples were stored at −70°C in a freezer until analysis.

For the pharmacokinetic study of finasteride, a total of 10 Sprague-Dawley rats (250–300 g) were purchased from the Charles River Laboratory (Raleigh, NC). An i.v. bolus dose was administered to rats in one of the lateral tail veins at 15 mg/kg. Two rats were killed with carbon dioxide at each time point (1, 2, 4, 6 and 24 hr after administration), and blood samples were collected. Blood was allowed to clot and centrifuged to obtain serum.

HPLC assay. For the analysis of GG745 blood samples, blood (100 μl) was first mixed with 300 μl of acetonitrile to precipitate protein. After centrifugation at 3500 rpm for 10 min, the supernatant was decanted into a fresh vial and evaporated to dryness under a gentle stream of nitrogen at 45°C. The residue was reconstituted into 100 μl of HPLC mobile phase. HPLC analysis was performed using a 5 micron Hypersil BDS C8 (25 × 0.46 cm) HPLC column. GG745 was eluted with acetonitrile and 50 μM ammonium acetate buffer (pH 4.2) over a 10-min linear gradient from 50% to 80% acetonitrile at a flow rate of 1 ml/min.

Estimation of pharmacokinetic parameters in rat and dog. Area under the GG745 or finasteride concentration in blood or serum vs. time curve and half-life were determined with RSTRIP (MicroMath Scientific Software, Salt Lake City, UT). Pharmacokinetic parameters were determined using a model-independent method.

Pharmacokinetics of GG745 and effects on DHT concentration in man. Single doses of GG745 in 7.5 ml of PEG400 were administered orally to healthy male subjects at doses ranging from 0 to 40 mg. Serum samples were collected and analyzed by gas chromatography-mass spectrometry to quantify DHT and GG745 levels. These gas chromatography-mass spectrometry measurements and the following extraction were performed at Pharmaco International (Richmond, VA). Briefly, DHT and GG745 were extracted from serum with an organic solvent mixture, purified by solid phase extraction, and stored at −20°C before analysis. Samples were evaporated under nitrogen when solvent changes were necessary. DHT-d3 was included as an internal standard in samples used for DHT determinations, and all steroids in these samples were derivatized before purification. Samples for DHT determinations were collected at 2, 4, 8, 12 and 24 hr and 2, 3, 7, 14, 21 and 28 days after dosing. GG745 determinations were made using samples collected at 0.5, 1, 2, 3, 4,

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Treatment dose</th>
<th>Prostate</th>
<th>Seminal vesicles</th>
<th>Adrenals</th>
<th>Body weight</th>
<th>Liver</th>
<th>Testis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg/day</td>
<td>mg</td>
<td>mg</td>
<td>g</td>
<td>g</td>
<td>g</td>
<td></td>
</tr>
<tr>
<td>Finasteride</td>
<td>0.7</td>
<td>154.1 ± 7.6</td>
<td>216.7 ± 13.0</td>
<td>38.0 ± 1.8</td>
<td>259.9 ± 10.1</td>
<td>14.7 ± 0.5</td>
<td>1.04 ± 0.03</td>
</tr>
<tr>
<td>Finasteride</td>
<td>7</td>
<td>107.0 ± 4.7a</td>
<td>151.9 ± 18.0a</td>
<td>34.1 ± 0.09</td>
<td>232.4 ± 4.6</td>
<td>13.3 ± 0.4</td>
<td>1.04 ± 0.01</td>
</tr>
<tr>
<td>Finasteride</td>
<td>70</td>
<td>96.2 ± 6.1a</td>
<td>121.4 ± 8.5a</td>
<td>33.3 ± 1.2</td>
<td>234.7 ± 2.1</td>
<td>13.3 ± 0.3</td>
<td>1.11 ± 0.03</td>
</tr>
<tr>
<td>GG745</td>
<td>1</td>
<td>65.8 ± 3.7a</td>
<td>83.8 ± 12.8a</td>
<td>35.9 ± 1.3</td>
<td>210.6 ± 4.3</td>
<td>12.3 ± 0.3</td>
<td>1.01 ± 0.03</td>
</tr>
<tr>
<td>GG745</td>
<td>10</td>
<td>120.0 ± 6.9a</td>
<td>165.4 ± 22.1a</td>
<td>41.6 ± 1.5</td>
<td>275.3 ± 3.3</td>
<td>14.1 ± 0.4</td>
<td>1.32 ± 0.05</td>
</tr>
<tr>
<td>GG745</td>
<td>100</td>
<td>115.6 ± 20.7a</td>
<td>132.8 ± 15.9a</td>
<td>42.0 ± 1.0</td>
<td>265.5 ± 3.4</td>
<td>14.1 ± 0.4</td>
<td>1.27 ± 0.03</td>
</tr>
</tbody>
</table>

Eight rats per group were treated with vehicle or test compound by the oral route for 14 days. Finasteride and GG745 data were obtained from studies performed on different days. Organ weights for the drug-treated animals are compared vs. the vehicle-treated animals within the same study.

* Significantly different (p < .05) from the vehicle controls.
GG745 is an extremely potent and selective inhibitor of human 5α-reductases. This inhibitor appears to irreversibly inhibit 5α-reductases but is a weak and competitive inhibitor of the human adrenal 3β-hydroxy-Δ5-steroid dehydrogenase/3-keto-Δ5-steroid isomerase (Kᵢ = 11 μM) and does not inhibit androgen binding to the androgen receptor, even at a concentration of 10⁻⁵ M. The inhibition of the isomerase is ~3 orders of magnitude weaker than the initial Kᵢ that describes the interactions of GG745 with either of the human 5α-reductases (Tian et al., 1995).

We performed studies in the rat both to select the most potent dual 5AR inhibitor (e.g., Frye et al., 1993, 1994, 1995) and to assess the relative potency of GG745 and finasteride in an animal model. Rats were a good choice because finasteride is a potent dual inhibitor of the rat 5ARs (Russell and Williams 1994) just as GG745 is of the rat³ and human enzymes (Tian et al., 1995). Because the potency of the effect of finasteride on DHT levels in man is known (Ohtawa et al., 1991; Vermeulen et al. 1989), the relative potencies of GG745 and finasteride in rats together with our in vitro enzymological data formed a good basis for estimating the potency of GG745 in man. Similarly, to estimate the half-life and suitable doses of GG745 in man, we compared the pharmacokinetics of GG745 and finasteride in the rat and the dog.

**Pharmacokinetics of GG745 and finasteride in intact adult male rats.** As in man, androgens stimulate the proliferation of prostatic tissue in the rat (Frye et al., 1994; Russell and Wilson, 1994). 5AR inhibitors prevent the conversion of testosterone to the more potent androgen DHT; therefore, animals treated (2 weeks) with either finasteride or GG745 were expected to have prostate volumes significantly smaller than those of control animals. Consistent with these expectations, finasteride produced a dose-related change in prostate volume. The highest dose of finasteride (72 mg/kg/day, which is equimolar to the 100 mg/kg/day doses of GG745) produced similar effects on prostatic volume as those observed in the GG745 groups. Rats treated daily with GG745 at 1, 10 or 100 mg/kg/day for 2 weeks had prostates approximately half as large as those in rats treated with vehicle alone (table 1). There was no significant difference between the GG745 dose groups, suggesting that the maximum effect of GG745 in this model had been achieved at much lower doses than those necessary to produce similar effects with finasteride. Because rats were treated with GG745 and finasteride on different days and the size of the prostates in the different control groups for each experiment were different (table 1), it is difficult to directly compare the potencies of GG745 and finasteride. Effects of GG745 and finasteride on seminal vesicle weights were similar to those on prostate weights (i.e., 50% decrease; see table 1). There were no significant differences between treatment groups in adrenal weight, body weight, liver weight, or testicular weights of rats at the conclusion of these studies. In addition, no significant histological changes were found in the tissues of any of the treatment groups.

**GG745 and finasteride in the dog.** The half-life, total body clearance, volume of distribution at steady state and oral bioavailability of GG745 in the dog were 65 hr, 0.5 ml/min/kg, 3 liters/kg and 43%, respectively. The GG745 blood level reached the peak (745 ng/ml) at 2.5 hr after oral dosing. The GG745 blood concentration at the end of iv. infusion (10 min) was 3430 ng/ml. The half-life, total body clearance and volume of distribution at steady state of finasteride in the dog were 3.9 hr, 4.9 ml/min/kg and 1.6 liters/kg, respectively. These data are summarized in table 2.

**GG745 and finasteride in the rat.** The half-life, total body clearance, volume of distribution at steady state and oral bioavailability of GG745 in the rat were 13.7 hr, 4.1 ml/min/kg, 4 liters/kg and 100%, respectively. The GG745 blood level reached peak (139 ng/ml) at 7 hr after oral dosing. The GG745 blood concentration was 200 ng/ml at 15 min after i.v. dosing. The half-life, total body clearance and volume of distribution at steady state of finasteride in the rat...
were 0.9 hr, 13.4 ml/min/kg and 0.6 liters/kg, respectively. These data are summarized in table 2.

**Dose selection and first human exposure.** With the data generated in these preclinical pharmacokinetic studies (table 2), estimates of human pharmacokinetic parameters were obtained using basic allometric principles (Boxenbaum, 1982; Ings, 1990; Mordenti, 1986). Volume of distribution (log) and systemic clearance (log) were plotted against weight (log) (fig. 2). Estimates of clearance and volume of distribution were predicted for humans based on the relationship between body weight/size and pharmacokinetic parameters. Estimates of 0.7 liters/hr and 180 liters were predicted for clearance and steady-state volume of distribution for a 70-kg human. These estimates indicated that GG745 would have a long terminal half-life of ~180 hr. This compares with the 6- to 8-hr half-life of finasteride in man (Rittmaster, 1994).

Second, a target GG745 concentration was estimated for humans through analysis of data from the rat pharmacodynamic study and indexing of the result to published clinical literature on finasteride. Although it is difficult to directly compare the potencies of GG745 and finasteride on the basis of table 1, both GG745 and finasteride are orally bioavailable steroidal inhibitors of the types 1 and 2 rat 5α-reductase and can be assumed to achieve equivalent inhibition of prostatic growth at maximally effective doses. Because GG745 achieves a maximal effect at 1 mg/kg/day and a peak blood level at 140 ng/ml, whereas finasteride achieves a maximal effect at 70 mg/kg/day and a peak blood level at 7840 ng/ml, an estimated potency ratio of 56 based on the peak blood levels was used in the prediction of GG745 human dose. In humans, the relationship between single doses of finasteride and maximal DHT suppression appeared to become asymptotic (approaching maximum effective exposure) at doses of 50 to 100 mg (De Schepper et al., 1991). The mean peak plasma concentration (C_max) observed after a single 100-mg dose of finasteride was ~836 ng/ml (Ohtawa et al., 1991). Using the in vivo potency of 56:1, a target GG745 concentration of ~15 ng/ml was estimated to be needed to reach the top of the GG745 dose-response (DHT reduction) curve.

Pharmacokinetic simulations were performed using the parameters determined from interspecies scaling. Absorption was considered to be rapid and complete. Based on these assumptions, a dose of 3 mg was estimated to provide peak concentrations of ~15 ng/ml and provide significant DHT suppression.

Because GG745 was expected to have a long terminal half-life, a conservative starting dose of 0.01 mg was selected. This dose was ~2 orders of magnitude lower than the proposed clinically effective dose of 3 mg and was well below doses found to produce no toxicologically significant findings in long-term toxicology studies.

Subsequently, 48 healthy male subjects received single oral doses of GG745, placebo or finasteride (5 mg) in a randomized, blinded, sequential-cohort dose-escalation study. GG745 doses of 0.01 to 40 mg were studied in cohorts consisting of four GG745, one placebo and one finasteride subject. Doses were escalated in subsequent groups after an evaluation of safety. Serial serum samples were collected for determination of circulating DHT and GG745 concentrations. DHT samples were assayed via GC-MS with a limit of detection of 10 pg/ml and interday coefficient of variation of ±9.5%. These data are shown in table 3. GG745 samples were assayed via a liquid chromatography-MS method with a limit of detection of 0.1 ng/ml and interday coefficient of variation of ±11.6% (Morris et al., 1995).

**Pharmacokinetics.** Pharmacokinetic parameters were determined using standard noncompartmental methods. The parameters determined in humans were consistent with estimates obtained from interspecies scaling (see fig. 2 and table 3). For doses in which the pharmacokinetic profile was fully described, the clearance, steady-state volume of distribution and terminal half-life were 1.3 liters/hr, 385 liters and 247 hr, respectively. The model predicted (based on interspecies scaling) peak concentration after the 2.5-mg dose was 12.5 ng/ml, which compared well with the observed mean peak of 14.3 ng/ml.

**Pharmacodynamics.** GG745 produced dose-related decreases in DHT (table 3). DHT reduction across GG745 dose groups were compared with finasteride using a general linear model with pairwise comparisons. Responses to GG745 increased sharply at doses of 0.1 to 2.5 mg and started to asymptote at doses of >5 to 10 mg. This agrees well with the 3 mg that was predicted based on the preclinical data for GG745 obtained in rat and dog.

**Discussion**

The goal of our discovery program was to identify a molecule that was a potent inhibitor of both human isozymes with suitable selectivity and drug properties for administration to patients. This goal was based on the postulate that finasteride is potent in the rat because it inhibits both rat isozymes (Russell and Wilson, 1994) but is only partially effective in man (Moore et al., 1995) due to its inability to effectively inhibit the type 1 5AR (Tian et al., 1994; Tian,
1996). Although the type 1 5AR is expressed primarily in skin and the liver (Thigpen et al., 1993), the virilization at puberty of pseudohermaphrodites lacking type 2 5AR correlates with increasing type 1 5AR expression in skin (Thigpen et al., 1993). This suggests that DHT can have paracrine effects and that effective control of DHT actions requires the inhibition of both the type 1 and 2 5ARs.

Because finasteride is potent against both rat isozymes, a drug molecule that is a potent inhibitor of all human and rat isozymes was expected to be equally effective in the rat as finasteride. The identification of such molecules justified pharmacokinetic studies of these candidates in the rat and dog to evaluate their drug properties. On the basis of these studies, GG745 was chosen to test the hypothesis that a potent inhibitor of both human 5α-reductases would be more effective than finasteride at reducing serum DHT levels in man and, ultimately, the symptoms of BPH.

In vitro, GG745 was shown to be a potent and selective inhibitor of both human 5α-reductases; in fact, GG745 is nearly as potent against the type 1 5AR as finasteride is against the type 2 enzyme (Tian et al., 1995). Both finasteride and GG745 were effective at reducing prostate weights when administered to rats, with GG745 appearing to be more potent than finasteride (table 1). This increased potency likely results largely from the longer half-life and decreased total body clearance of GG745 compared with finasteride in the rat (table 2).

GG745 showed a longer terminal half-life than finasteride in both dog and rat. The long terminal half-life of GG745 (65 hr) in the dog was the result of low total body clearance (0.5 ml/min/kg) and high volume of distribution (3 liters/kg) compared with finasteride. The half-life of GG745 in the rat was shorter (14 hr) than that in the dog; this is due to the higher total body clearance of GG745 in the rat. A similar pharmacokinetic pattern in the dog and rat was also observed for finasteride. The half-life of finasteride in the dog (4 hr) was longer than that in the rat (1 hr). The terminal half-life of finasteride in humans (6–8 hr) was longer than that observed in the dog (Carlin et al., 1992; Rittmaster, 1994). These information provided added confidence in the estimates of human GG745 pharmacokinetic parameters from interspecies scaling.

Single oral doses of GG745 of >10 mg decreased DHT significantly more than finasteride. The level of DHT reduction attained by administration of GG745 was >90% at the maximal doses used in this study. Finasteride, in contrast, decreased DHT levels by ~70% at single doses of 40 mg (Vermeulen et al., 1989) and 100 mg (Ohtawa et al., 1991). Increasing the dose of finasteride from 5 to 100 mg achieved negligible further reduction in serum DHT (Ohtawa et al., 1991; Vermeulen et al., 1989), which is consistent with an interpretation that finasteride effectively inhibits the type 2 but not type 1 5α-reductase. From the results of these studies, we conclude that GG745, a potent dual inhibitor of human 5α-reductases, is more effective than finasteride, a type 2 5AR selective inhibitor, in reducing serum DHT levels in man. Further studies will determine whether this greater reduction in serum DHT concentrations offers clinical advantages.

Acknowledgments

The hard work and dedication of the 5AR project team are gratefully acknowledged.

References


Send reprint requests to: H. Neal Bramson, Glaxo Wellcome Research Institute, 5 Moore Drive, Research Triangle Park, NC 27709.