A model for the turnover of dihydrotestosterone in the presence of the irreversible 5α-reductase inhibitors GI198745 and finasteride

Objective: To develop a pharmacokinetic-pharmacodynamic model that characterizes the conversion of testosterone to dihydrotestosterone (DHT) by 5α-reductase types 1 and 2 and the irreversible inhibition of 5α-reductase by finasteride, a 5α-reductase type 2 inhibitor and by GI198745 (dutasteride), a potent and specific dual 5α-reductase inhibitor.

Methods: Healthy men (n = 48) received doses of 0.1 to 40 mg GI198745 (n = 4 subjects per dose), 5 mg finasteride (n = 8), or placebo (n = 8) in a parallel-group study. Plasma concentrations of GI198745, finasteride, and DHT were measured frequently up to 8 weeks after dosing. Models were fitted with mixed-effects modeling with the NONMEM program.

Results: The pharmacodynamics were well described with a model that accounted for the rates of DHT formation and elimination, 5α-reductase turnover, relative capacity of the 2 5α-reductase isozymes, and the rates of irreversible inhibition of one (finasteride) or both (GI198745) types of 5α-reductase. The model indicated that type 2 5α-reductase contributed approximately 80% of plasma DHT. GI198745 was about 3-fold more potent than finasteride on 5α-reductase type 2. Nearly full blockade of both isozymes was achieved at doses of 10 mg or more GI198745, although the potency of this agent on 5α-reductase type 1 was less than on type 2.

Conclusions: A physiologically based model for the turnover and irreversible inhibition of 5α-reductase and for formation and elimination of DHT described the data well. This model helps explain differences in the rates of onset and offset of effect and offers a way to determine the relative potency of the irreversible 5α-reductase inhibitors. (Clin Pharmacol Ther 1998;64:636-47.)

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Pharmacologic intervention to manage benign prostatic hyperplasia (BPH) is desirable because of the high incidence of this disease and its resulting erosion of the quality of life of affected men with the condition.[1] The incidence of prostatic enlargement at autopsy increases from approximately 25% at 50 years of age to more than 80% at 80 years of age.[2] Fifty percent of men older than 60 years have symptoms of bladder outlet obstruction caused by BPH, and 25% to 30% of these ultimately need surgical treatment.[3,4] Dihydrotestosterone (DHT) is believed to be the androgen primarily responsible for the development of BPH. Testosterone is converted to the more potent androgen DHT by 5α-reductase. Two isozymes of 5α-reductase have been identified in humans.[5,6] Type 1 is found predominantly in skin and the liver. Type 2 5α-reductase is the primary isozyme present in the prostate.[5,6] Treatment of patients with finasteride, a selective type 2 5α-reductase inhibitor, reduces circulating DHT concentrations by 60% to 80% of baseline values.[7-10] It has proved efficacious for the management of BPH.[8,9] There is a possibility that lowering circulating DHT

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concentrations beyond those observed with finasteride may lead to faster onset of action and a greater magnitude of clinical effect in the management of symptoms associated with BPH.

GI198745 (17β-*N*-(2,5-bis(trifluoromethyl)phenylcarbamoyl)-4-aza-5α-androst-1-en-3-one; dutasteride) is a potent, specific, and dual 5α-reductase inhibitor. Enzymologic studies have indicated that GI198745 is a potent inhibitor of human cloned type 1 and type 2 5α-reductase.[11] In rats and dogs, GI198745 appears to be more effective than finasteride in lowering DHT levels, a result that likely reflects a greater inherent potency[11] and a longer terminal half-life.[12] Both finasteride and GI198745 are thought to be essentially irreversible inhibitors of 5α-reductase.[11,13] An initial reversible step is followed by the irreversible formation of an enzyme-inhibitor complex.[14]

Inhibition of 5α-reductase has been described by an indirect-response model[15] whereby the drug has a direct inhibiting effect on the formation rate of DHT. In this study a model was developed that also takes into account the turnover of the two 5α-reductase isozymes and the irreversible nature of the enzyme inhibition.

METHODS

Study design and data. This study was a randomized, single-blind, placebo-controlled parallel-group study in which 48 healthy men 20 to 57 years of age (mean age, 39.3 years) who weighed 56.3 to 102 kg (mean weight, 75.7 kg) received single oral doses of GI198745, finasteride, or placebo. Each subject gave informed consent to the study, which was approved by the institutional review board of Besselaar Ltd. The study was conducted in accordance with the provisions of the Declaration of Helsinki (1964) and revisions (Hong Kong, 1989). All subjects were healthy according to physical examination and clinical laboratory data. Four subjects per dose level received doses of 0.01, 0.1, 1, 2.5, 5, 10, 20, and 40 mg GI198745 as an oral solution in a volume of 7.5 mL of PEG400/Tween80 0.01% except for 40 mg, which was administered in 15 mL. Eight subjects received 5 mg finasteride as the marketed tablet formulation, and 8 subjects received placebo. The doses were administered with 240 mL water.

Intake of any medications was prohibited from 1 week before dosing until 1 week after dosing. Alcoholic beverages, caffeine-containing food and beverages, and all tobacco products were prohibited from 24 hours before dosing until 24 hours after dosing. The subjects fasted from 8 hours before dosing until 4 hours after dosing.

Five-milliliter blood samples for assay of GI198745 or finasteride levels were drawn before dosing and ½, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours and 2, 3, 7, 14, 21, and 28 days after dosing. For 6 subjects, 3 of whom received 20 or 40 mg GI198745 and 3 of whom received 5 mg finasteride, an additional sample was obtained 56 days after dosing. The actual time of sampling was recorded and used in all calculations. Samples were allowed to stand and clot for at least 30 minutes and were then centrifuged at a minimum of 3000*g* for 15 minutes. Serum was harvested and stored at –70°C.

Levels of GI198745 were analyzed by means of liquid chromatography–atmospheric pressure chemical ionization–mass spectrometry assay with a detection limit of 0.1 ng/mL.[16] All doses except 0.01 mg gave detectable levels, and all available data were included in the analysis. Finasteride levels were analyzed by means of a liquid chromatography–atmospheric pressure chemical ionization–tandem mass spectrometry assay with a detection limit of 0.5 ng/mL. Five-milliliter blood samples for assay of DHT concentration were drawn before dosing, at 2, 4, 8, 12, and 24 hours, and at 2, 3, 7, 14, 21, and 28 days after dosing. For the 12 subjects receiving doses of ≥10 mg GI198745 and for the 3 subjects receiving finasteride, additional DHT samples were obtained 56 and 84 days after dosing. DHT levels were analyzed by means of a gas chromatography–mass spectrometry assay with a detection limit of 10 pg/mL.

Pharmacokinetic models. The pharmacokinetics of GI198745 were modeled with a 2-compartment, first-order oral-absorption model with parallel linear and saturable elimination, as described previously.[17] Finasteride was modeled with a 2-compartment oral-absorption model with linear elimination parameterized in terms of clearance and volume. GI198745 or finasteride concentrations at entrance into the pharmacodynamic model were calculated for each subject from the individually predicted (Bayesian) pharmacokinetic parameters. To shorten computational time while retaining information about the rapid absorption and distribution and slow elimination phase, we predicted concentrations from the pharmacokinetic model at 60 to 80 prespecified times, compared with the 6 to 17 observed concentrations. Values between these times were calculated by means of linear interpolation.

Pharmacodynamic model. On the basis of current knowledge about the formation of DHT, a physiologically plausible model was suggested for the changes in DHT levels during administration of a 5α-reductase inhibitor (Figure 1). The two 5α-reductase isozymes transform testosterone into DHT, which is further transformed into inactive components. The isozymes are formed at zero-order rates and eliminated by means of

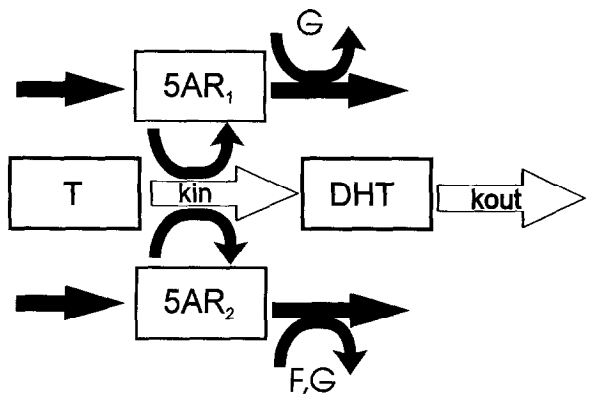

Figure 1. Testosterone (T) is transformed to dihydrotestosterone (DHT) by the 5α-reductase type 1 ($5AR_1$) and 5α-reductase type 2 ($5AR_2$) isozymes at a formation rate (k_{in}). DHT is eliminated at a first-order rate (k_{out}). The 5α-reductase isozymes are subject to physiologic turnover. The 2 5α-reductase inhibitors GI198745 (G) and finasteride (F) act by irreversibly blocking 5α-reductase type 1 (G) and 5α-reductase type 2 (F,G) and increasing the rate of 5α-reductase inactivation.

first-order processes. When an inhibitor is added, the isozymes are irreversibly removed from the system at rates proportional to enzyme and inhibitor concentrations. This model can be described with a system of differential equations. If it is assumed that testosterone concentrations are constant, changes in DHT concentration can be described by the following differential equation:

$$(dDHT/dt) = k_{in} \cdot FAR_2 \cdot 5AR_2 + k_{in} \cdot (1 - FAR_2) \cdot 5AR_1 - k_{out} \cdot DHT \quad (1)$$

in which k_{in} is the formation rate of DHT, FAR_2 is the proportion formed by 5α-reductase type 2, $5AR_1$ and $5AR_2$ are proportions of baseline 5α-reductase type 1 and 2 activities, and k_{out} is the first-order elimination rate of DHT. This equation can be reparametized in terms of the steady-state (baseline) DHT concentration, DHT_{ss} ($DHT_{ss} = [k_{in}/k_{out}]$), as follows:

$$(dDHT/dt) = k_{out} \cdot DHT_{ss} \cdot FAR_2 \cdot 5AR_2 + k_{out} \cdot DHT_{ss} \cdot (1 - FAR_2) \cdot 5AR_1 - k_{out} \cdot DHT \quad (2)$$

At steady state, this model can be simplified as $(dDHT/dt) = 0$. Substituting into equation 2 and solving for DHT:

$$DHT = DHT_{ss} \cdot FAR_2 \cdot 5AR_2 + DHT_{ss} \cdot (1 - FAR_2) \cdot 5AR_1 \quad (3)$$

The proportional decrease from baseline can be described as follows:

$$(DHT/DHT_{ss}) = FAR_2 \cdot 5AR_2 + (1 - FAR_2) \cdot 5AR_1 \quad (4)$$

In the absence of any drug, the turnover of the two 5α-reductase isozymes can be described as follows:

$$(d5AR_i/dt) = k_i - k_i \cdot 5AR_i \quad (5)$$

in which i is the isozyme, k_i is the turnover rate of 5α-reductase type i, and $5AR_i$ is the enzyme concentration relative to baseline.

GI198745 and finasteride both work by irreversibly blocking 5α-reductase. This can be modeled with a second-order rate constant as follows:

$$(d5AR_i/dt) = k_i - k_i \cdot 5AR_i - ko_{ij} \cdot C_j \cdot 5AR_i \quad (6)$$

in which j corresponds to the drug, which will later be indicated by G for GI198745 and F for finasteride; ko_{ij} is the second-order rate constant of the irreversible binding of drug to the enzyme, and C_j is the plasma concentration of the drug. For finasteride, which has no appreciable inhibitory activity on 5α-reductase type 1, equation 5 was used for 5α-reductase type 1 and equation 6 for 5α-reductase type 2. For GI198745, which inhibits both 5α-reductase isozymes, equation 6 was used for both enzymes. The resulting 5AR values were substituted into equation 2, and the parameters of the system of differential equations were estimated simultaneously.

For a comprehensive description of the steady-state situation, elaborations of the model were made. At steady state, $(d5AR_i/dt) = 0$. Substituting into equation 6 and solving for $5AR_i$:

$$5AR_i = k_i/(k_i + ko_{ij} \cdot C_j) \quad (7)$$

which can be rearranged as follows:

$$5AR_i = 1 - \frac{C_j}{(k_i/ko_{ij}) + C_j} \quad (8)$$

Substituting equation 8 into equation 4:

$$\frac{DHT}{DHT_{ss}} = FAR_2\left(1 - \frac{C_j}{(k_2/ko_{2j}) + C_j}\right) + (1 - FAR_2)\left(1 - \frac{C_j}{(k_1/ko_{1j}) + C_j}\right) \quad (9)$$

This equation describes a dual inhibitory E_{max} model in which the contribution of each part of the model is decided according to the proportion of DHT formed by each enzyme without drug present (FAR_2 and

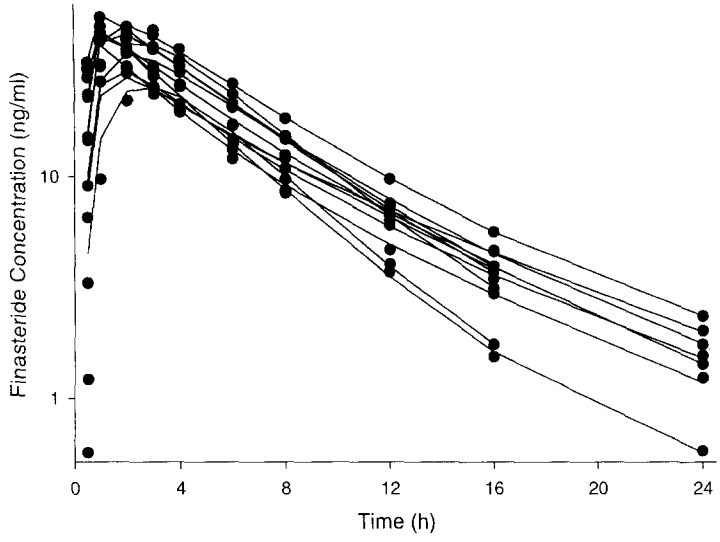

Figure 2. Time course of finasteride concentration after oral administration of 5 mg tablets. *Lines* show the fit of a 2-compartment, first-order absorption, pharmacokinetic model and represent the individually predicted concentration–time profiles.

$1 - FAR_2$). Drug concentrations corresponding to 50% suppression of the concerned isozyme activity (EC_{50}) can be calculated from the ratio k_i/ko_{ij}. At EC_{50}, the rate of elimination of 5α-reductase caused by the drug, $ko_{ij} \cdot C_j \cdot 5AR_i$, equals the baseline endogenous elimination rate. At steady state, only FAR_2 and the ratio k_i/ko_{ij} influence the shape of the concentration-effect curve. All pharmacokinetic and pharmacodynamic modeling was performed with nonlinear mixed-effects models. All pharmacokinetic and pharmacodynamic data were used in the analysis.

Interindividual variability in pharmacokinetic and pharmacodynamic parameters is modeled according to an exponential variance model:

$$P_k = \tilde{P}\exp(\eta_k) \quad (10)$$

in which P_k is the parameter value for the kth subject, $\tilde{P}$ the population mean parameter value, and η_k the deviation for the individual from the population mean. The value η_k is assumed to be normally distributed with a mean value of zero and a variance (ω^2) to be estimated.

The model was evaluated with interindividual variabilities (η) initially applied to all parameters. Reduction from this full variability model was made when indicated by high standard errors or small values of ω. Because this study was performed with a relatively small group of healthy volunteers, no attempts were made to examine the effects of covariates on the model parameters.

Residual variability (ε), corresponds to the deviation of observed serum concentration (C) from the concentration ($\hat{C}$) predicted with the subject-specific parameters. The value ε is assumed to be normally distributed with a mean value of zero and a variance (σ^2) to be estimated in the analysis according to the following equation:

$$C = \hat{C} \cdot (1 + \varepsilon) \quad (11)$$

Data analysis and simulations were performed with NONMEM IV, level 1.1, first-order method, and PREDPP version 3, level 1.0, running on a DEC alphaserver 200 4/275 computer. Model adequacy was evaluated by graphical means. The Xpose 1.14 program[18] running under Splus3.3 for Windows software (MathSoft, Seattle, Wash) and SAS 6.11 (SAS Institute, Cary, NC) were used for production of graphs and visual evaluation of the fits.

Predictions. Simulations were performed to illustrate the consequences of different loading and maintenance dosing regimens over a range of dose levels and to illustrate the interindividual variability in pharmacokinetics and pharmacodynamics. The population estimates of the parameters were used to calculate the degree of DHT suppression and the degree of inhibition of the two 5α-reductase isozymes for a variety of doses and dosing regimens. Individual predicted parameters (P_k) from all subjects who received 5 mg finasteride or doses of at least 2.5 mg GI198745 were used to simulate time-effect profiles for a variety of dosing regimens. Pharmacokinetic

Table I. Population mean pharmacokinetic parameters and associated intersubject variability for GI198745 (2-compartment parallel nonlinear and linear elimination model) and finasteride (2-compartment model)

	GI198745		*Finasteride*	
Parameter	*Population mean*	*Intersubject variability (η) (CV%)*	*Population mean*	*Intersubject variability (η) (CV%)*
k_a (h^{-1})	2.4	70	3.2	68
t_{lag} (h)	0.32	38	0.34	
CL_l/F (L/h)	0.58	69	23	42
K_m (ng/mL)	0.96		NA	
V_{max}/F (μg/h)	5.9	43	NA	
Q/F (L/h)	33	62	3.2	105
V_c/F (L)	173	32	97	17
V_p/F (L)	338	41	37	
V_{ss}/F (L)	511		134	
Residual variability (σ)	0.13		0.079	

CV, coefficient of variation; K_a, absorption rate constant; t_{lag}, absorption lag time; CL_l/F, apparent linear clearance; K_m, concentration at which the saturable elimination pathway operates at half maximal rate; NA, not applicable; V_{max}/F, apparent maximal elimination rate of the saturable pathway; Q/F, apparent intercompartmental clearance; V_c/F and V_p/F, apparent volumes of the central and peripheral compartments; V_{ss}/F, apparent steady-state volume of distribution ($V_{ss} = V_c + V_p$).

and pharmacodynamic parameters for subjects who received lower doses were not used, because their individual parameters were not likely to be as precisely estimated as those of the subjects who received higher doses.

RESULTS

Pharmacokinetics. In this study, the pharmacokinetics of GI198745 have been described with a 2-compartment model with 2 parallel elimination pathways—a linear and a nonlinear pathway.[17] At high concentrations the linear pathway dominates as the route of elimination, giving a clearance of 0.58 L/h, which combined with the large volume of distribution (511 L) gives a terminal half-life of up to 5 weeks. As concentrations declined toward the concentration at which the saturable elimination pathway operates at half maximal rate (K_m) (0.96 ng/mL), the proportion eliminated through the relatively rapid saturable elimination pathway increased, and the half-life decreased to about 3 days. This marked decrease in half-life was a consequence of the relatively high clearance (6.2 L/h) of the saturable pathway at low concentrations.

The pharmacokinetics of finasteride were well described with a 2-compartment linear model whereby interindividual variability was applied to absorption rate, apparent clearance, apparent intercompartmental clearance, and apparent volume of the central compartment. Absorption of finasteride was relatively rapid. Peak concentrations appeared within 1 to 2 hours after administration and were followed by a biexponential decline in which the terminal phase has a half-life of approximately 10 hours. Figure 2 shows the fit of the pharmacokinetic model to the data. The parameters of the pharmacokinetic models are listed in Table I.

Pharmacodynamics. The DHT data are presented in Figure 3. After administration of placebo and 0.01 and 0.1 mg GI198745, DHT concentrations remained unchanged, except for a slight average reduction of 30% during the first day after dosing. For higher GI198745 doses, DHT concentrations rapidly decreased by 70% to 95% of predosing levels and remained suppressed for 3 to 8 weeks after dosing. The extent and duration of suppression increased with dose. After administration of 5 mg finasteride, DHT levels were suppressed by approximately 80%, and the duration of the suppression was short, about 1 to 2 weeks.

The results of the pharmacodynamic modeling are presented in Table II. There was good agreement between actual and predicted concentrations, and there were no trends in weighted residuals versus time. There was no apparent dependence of weighted residuals on predicted concentrations, indicating that the applied residual variance model was appropriate. Individually predicted values closely followed the observed concentrations (Figure 4). A model with interindividual variability (η) applied to the parameters DHT_{ss}, k_{out}, FAR_2, k_2, and k_{1G} was used as the final model, because only these η values could be reliably estimated and adding further η values did not substantially improve the fit. The model was robust to the choice of η structure, and the parameter estimates did not change substantially when the number of estimated η values was varied. All model parameters and associated η values were well estimated; the relative standard error in the estimation ranged from 7% to 44%.

The baseline DHT level, DHT_{ss}, was estimated to be 488 pg/mL. The fraction of DHT formed by 5α-reduc-

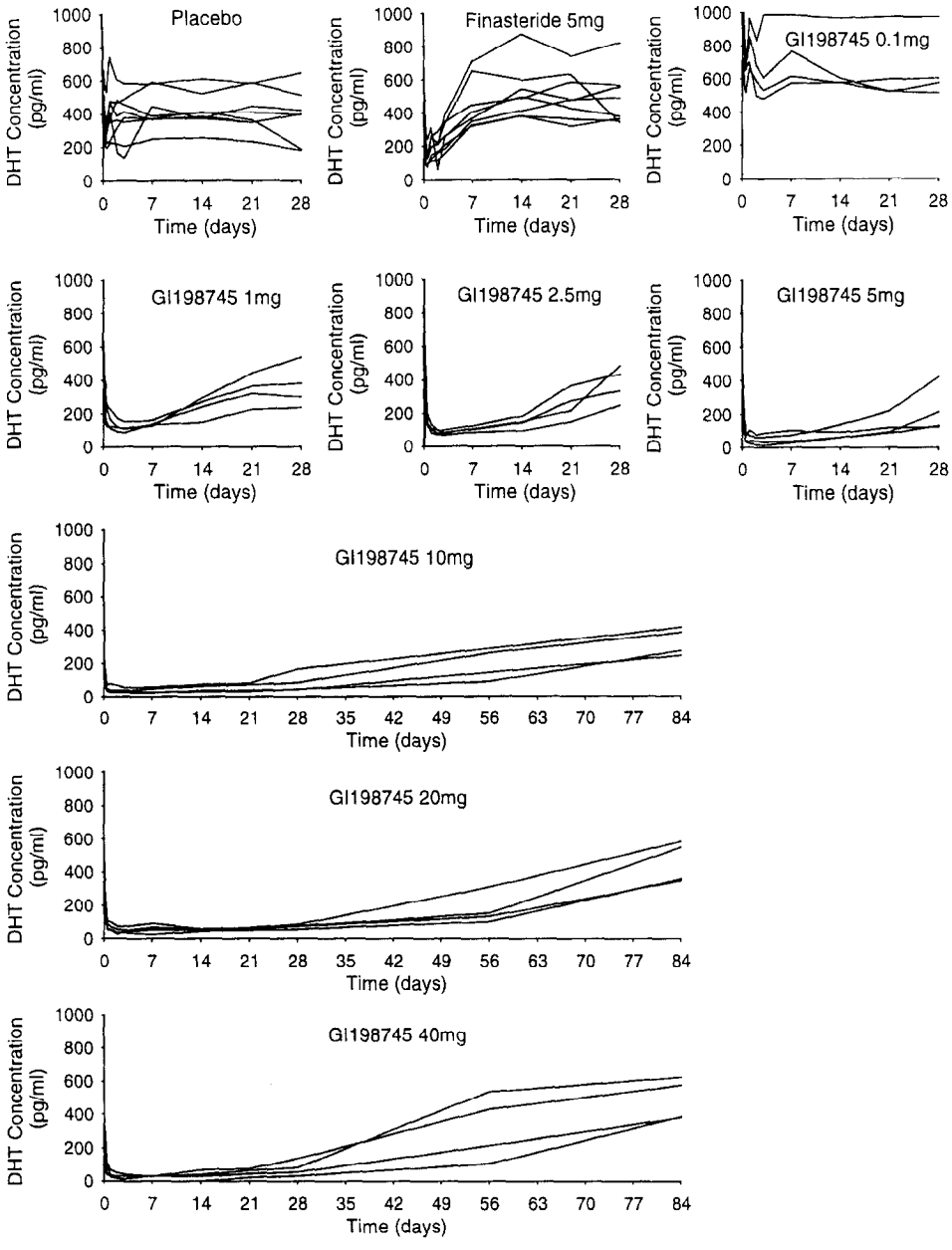

Figure 3. Dihydrotestosterone (DHT) concentrations according to treatment group.

tase type 2 was estimated to be 83%. The elimination rate of DHT, k_{out}, was relatively high, corresponding to an elimination half-life of about 2 hours. The endogenous elimination rates for the two 5α-reductase isozymes, k_1 and k_2, were lower, corresponding to half-lives of 45 and 80 hours for 5α-reductase types 1 and 2, respectively.

GI198745 was more potent at inhibiting 5α-reductase type 1 than type 2; the second-order rate constant for the irreversible binding to the enzyme was 60-fold higher. GI198745 was about 3-fold more potent in inhibiting 5α-reductase type 2 than was finasteride. Figure 5 shows the population mean GI198745 steady-state concentration–effect curve with the separate contributions of the two 5α-reductase isozymes. The estimated interindividual variability was low for FAR_2. It corresponded to a coefficient of variation of only 5%. Variability in DHT_{ss} and in the rate constants k_{out}, k_2, and ko_{2G} was higher, ranging from 37% to 64%.

To validate the use of linear interpolation in calculating drug concentrations for use in the pharmacodynamic

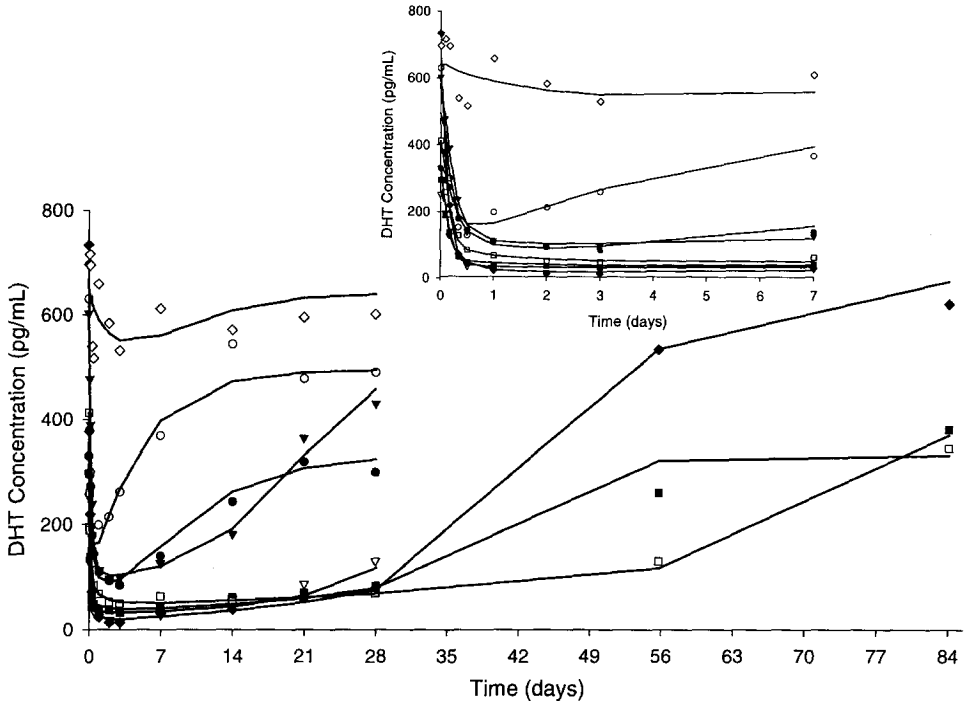

Figure 4. Time course of dihydrotestosterone (DHT) concentrations for 1 subject per dose group receiving doses of 0.1 mg *(open diamonds)*, 1 mg *(solid circles)*, 2.5 mg *(solid triangles)*, 5 mg *(open triangles)*, 10 mg *(solid diamonds)*, 20 mg *(solid squares)*, or 40 mg *(open squares)* GI198745 or 5 mg finasteride *(open circles)*. *Lines* show the fit of the pharmacodynamic model and represent the individually predicted concentration–time profiles. **Inset,** first 7 days after dosing.

Table II. Population mean pharmacodynamic parameters and associated intersubject variability

Parameter	*Population mean*	*SE of estimate (%)*	*Intersubject variability (η) (CV%)*	*SE of variability estimate (%)*
DHT_{ss} (pg/mL)	488	7	37	12
k_{out} (h^{-1})	0.393	10	64	22
FAR_2	0.827	4	5	37
k_1 (h^{-1})	0.0153	20		
k_2 (h^{-1})	0.00871	44	66	35
ko_{1G} (mL . ng^{-1} . h^{-1})	0.000594	33	45	38
ko_{2G} (mL . ng^{-1} . h^{-1})	0.0357	14		
ko_{2F} (mL . ng^{-1} . h^{-1})	0.0108	34		
$EC_{50,1G}$ (ng/mL)	26			
$EC_{50,2G}$ (ng/mL)	0.24			
$EC_{50,2F}$ (ng/mL)	0.81			
Residual variability (σ)	0.18	14		

CV, Coefficient of variation; DHT_{ss}, steady-state dihydrotestosterone concentration; k_{out}, first-order elimination rate of DHT; FAR_2, proportion of DHT formed by 5α-reductase type 2; k_1 and k_2, elimination rates for 5α-reductase type 1 and type 2; G, GI198745; F, finasteride; ko_1 and ko_2, rates of elimination caused by binding to 5α-reductase type 1 and type 2; $EC_{50,1}$ and $EC_{50,2}$, drug concentration suppressing 5α-reductase type 1 and type 2 activity by 50%.

modeling, the final model was refitted with the exact pharmacokinetic solution. All parameters and their associated variabilities were within ±3% of those of the final model, except for ko_{2F}, which was 8% lower, and the variability associated with k_{out}, which was 5% higher.

Simulated population mean DHT levels and 5α-reductase activities for different daily GI198745 doses are shown in Figure 6. Results of simulations of monthly, weekly, and daily doses of GI198745 and daily doses of finasteride with individually predicted

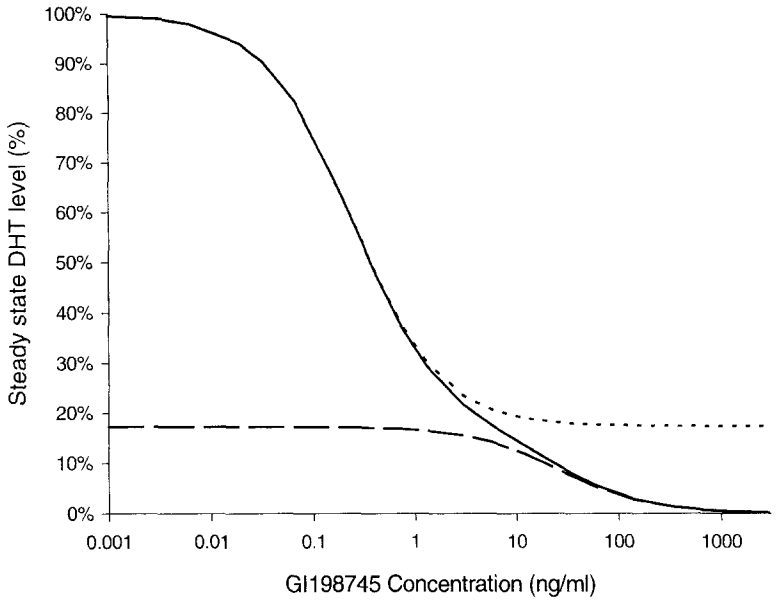

Figure 5. Population mean steady-state concentration-effect curve shows dihydrotestosterone (DHT; *solid line*) suppression as a function of GI198745 concentration and the relative contributions of 5α-reductase type 1 (*dashed line*) and 5α-reductase type 2 (*dotted line*).

parameters from 20 subjects who received GI198745 at doses of at least 2.5 mg and subjects who received 5 mg finasteride are displayed in Figure 7.

DISCUSSION

A population indirect-response model was developed for the conversion of testosterone to DHT by 5α-reductase types 1 and 2, for the endogenous turnover of 5α-reductase, and for the irreversible inhibition of 5α-reductase by finasteride and GI198745. The pharmacokinetics of finasteride were well described with a 2-compartment model with first-order absorption. After adjustment for previously reported bioavailability,[19] the estimated values of total body clearance and steady-state volume of distribution were close to the values previously published.[10,19] The pharmacokinetics of GI198745 were well described with a pharmacokinetic model with parallel linear and nonlinear elimination, as reported previously.[17] Individually predicted concentrations of both GI198745 and finasteride (Figure 2) closely followed the observed data. Thus the use of individually predicted drug concentrations as input into the pharmacodynamic model was justified.

One of the assumptions used in developing this model is that testosterone levels are not affected by 5α-reductase blockade. Most testosterone is eliminated by other routes than conversion to DHT. However, a minor effect of 5α-reductase blockade, which results in an approximate increase of testosterone levels by 8% to 10%, has been observed after long-term administration of finasteride.[8] This change was not taken into account in the current model, which may lead to slight underestimation of the degree of 5α-reductase suppression. The diurnal variability of testosterone also has not been incorporated into this model.

After administration of placebo and the 2 lowest doses of GI198745, DHT concentrations decreased intermittently, with an average maximum decrease of 30% 12 hours after dosing. This might indicate that DHT levels show diurnal variation. Because most of the samples throughout the study were taken in the morning, there are not sufficient data in this study to explore this possibility further. The estimated value of DHT_{ss}, 488 pg/mL, is close to the mean predosing DHT value, 515 pg/mL, and the estimated intersubject variability in this parameter, 37% coefficient of variation, is close to the coefficient of variation of the predose values, 43%. The fraction of DHT formed by 5α-reductase type 2, FAR_2, was 83%. This is close to the 60% to 80% maximum suppression that has been observed after repeated dosing of finasteride.[7-10] Among persons with male pseudohermaphroditism, who have a mutation in the 5α-reductase type 2 isozyme but normal function of the 5α-reductase type 1 isozyme, DHT production is approximately 30% of normal,[20] slightly higher than the 17% estimated to be produced by 5α-reductase type 1 in our study.

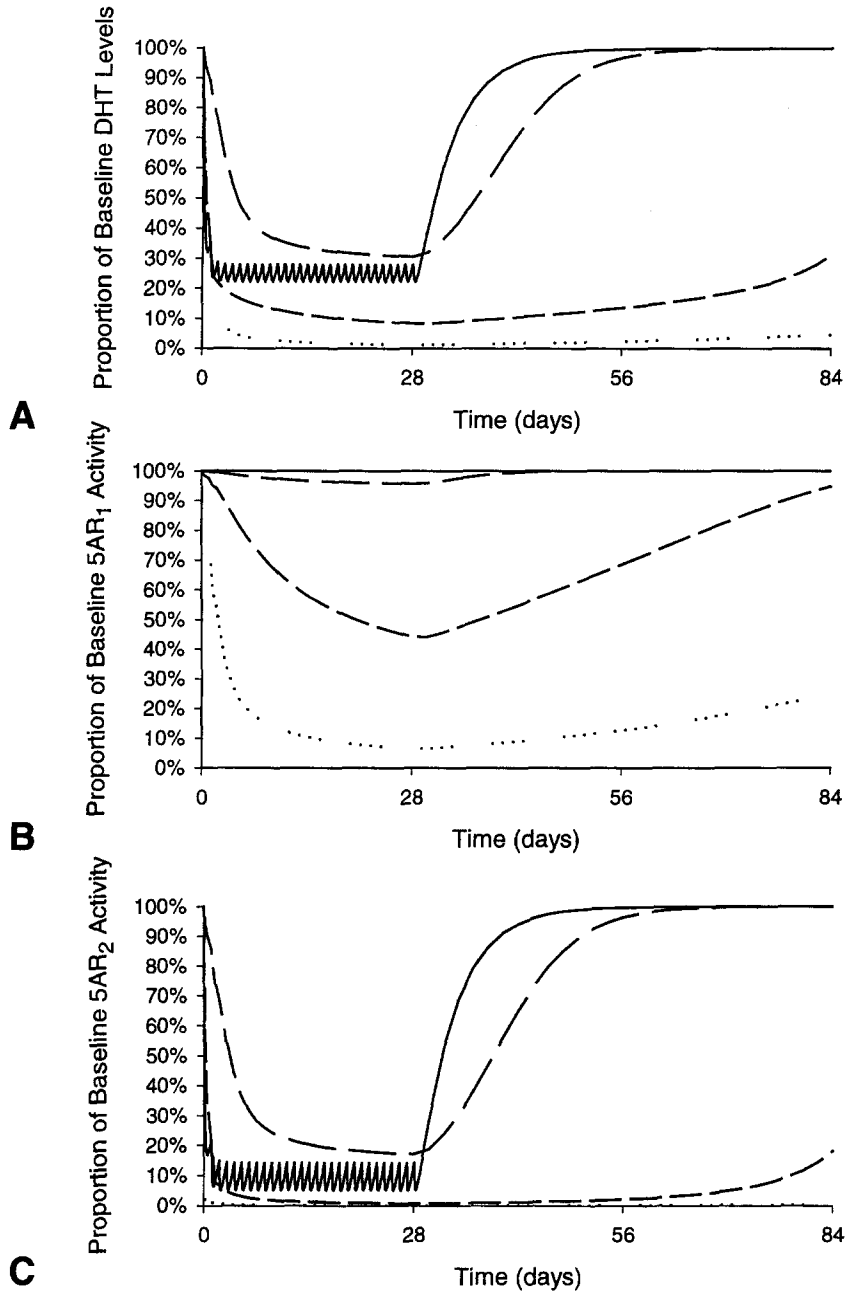

Figure 6. Predicted mean levels of dihydrotestosterone (DHT) **(A)**, 5α-reductase type 1 **(B)**, and 5α-reductase type 2 **(C)** suppression after daily doses of 5 mg finasteride (*solid line*) and 0.1 mg (*long-dashed line*), 1 mg (*short-dashed line*), and 10 mg (*dotted line*) GI198745 for 28 days.

In this model, interaction between 5α-reductase and the inhibitor is described by a single, irreversible step. Data from in vitro experiments[11,13,21] suggest that the interaction between the inhibitor and 5α-reductase involves 2 steps, as follows:

$$5AR + I \underset{}{\overset{K_i}{\rightleftarrows}} 5ARI \xrightarrow{k_3} EI^* \qquad (12)$$

in which K_i is the initial inhibition constant, which corresponds to the 50% inhibitory concentration (IC_{50}) for the initial inhibition step, and k_3 is the rate constant for the second, irreversible step, which for finasteride has been attributed to a covalent modification of 5α-reductase.[14] This 2-step association process can be characterized by a hybrid second-order rate constant, $K_{on} = k_3/K_i$.

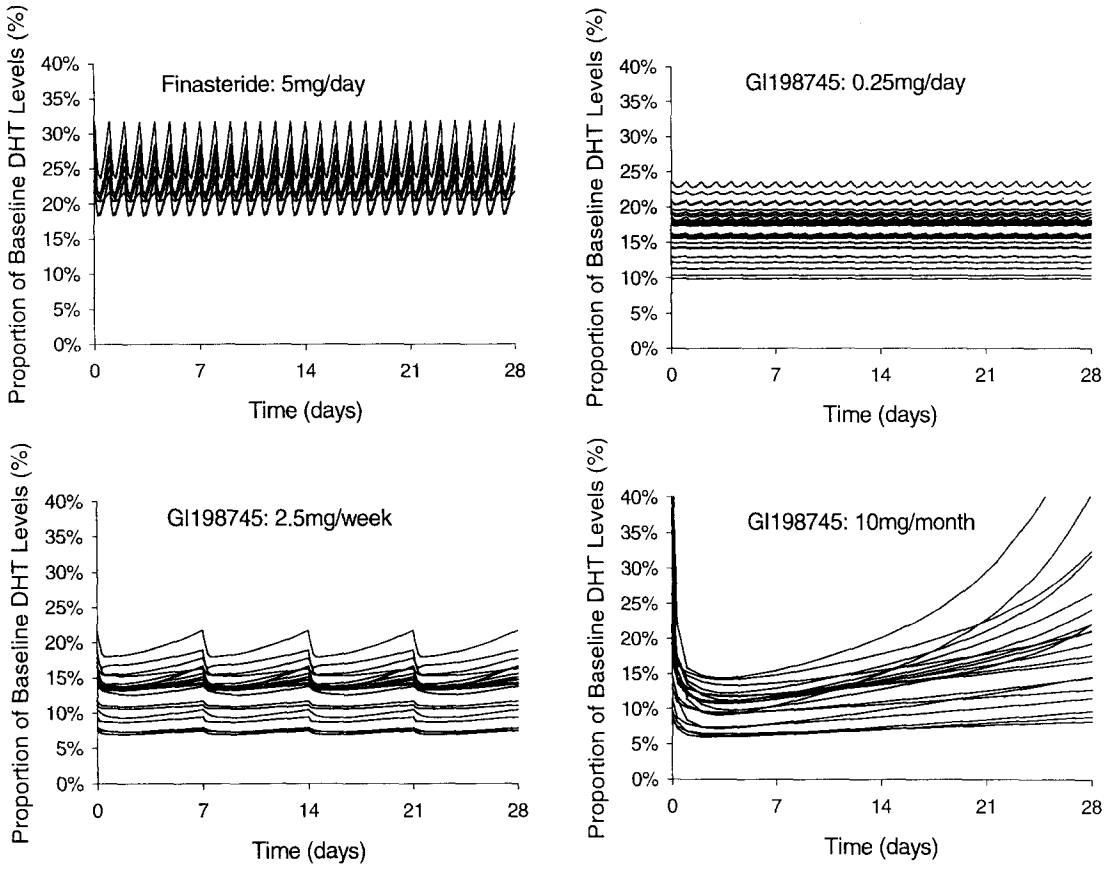

Figure 7. Individually predicted steady-state concentrations of dihydrotestosterone (DHT) after dosing of 5 mg finasteride once a day, 0.25 mg GI198745 once a day, 2.5 mg GI198745 once a week, and 10 mg GI198745 once a month.

If the remainder of the system were constant, irreversible binding of an inhibitor to a receptor would eventually lead to full blockade of the receptor irrespective of the rate of binding. In the current model, 2 factors influences the ability of the drug to fully inhibit the receptors: the pharmacokinetics of the inhibitor and the turnover of the receptor. The pharmacokinetics determine inhibitor concentration at the receptor, which drives the rate of inhibition. The production of new 5α-reductase competes with the rate of drug–5α-reductase interaction so that if the rate of drug–5α-reductase interaction is relatively slow, only a minor part of the available 5α-reductase will be inhibited.

Levels of 5α-reductase during drug treatment are determined by a balance between endogenous turnover rate, k_i, and the rate of elimination caused by binding to drug, ko_{ij}. At steady state the effect of GI198745 on DHT levels can be described as the sum of 2 inhibitory E_{max} models in which the EC_{50} values are calculated as the ratio k_i/ko_{ij}. Because the estimated turnover rate for 5α-reductase type 1 is almost double that of type 2 and the relative potency of GI198745 is 60-fold higher for 5α-reductase type 2 than for type 1, about 100-fold higher GI198745 concentrations are needed to affect 5α-reductase type 1 activity compared with 5α-reductase type 2 activity. This is illustrated in Figure 5. At GI198745 concentrations up to 1 ng/mL suppression of 5α-reductase type 2 governs the overall level of DHT suppression. At concentrations higher than 1 ng/mL suppression of both isozymes plays a role. Simulations show that in doses of about 0.1 mg/day, 5α-reductase type 2 can be blocked by 80%, whereas 5α-reductase type 1 is virtually unaffected, giving a degree of DHT suppression similar to that from 5 mg finasteride a day (Figure 6). By increasing to 10 mg/day GI198745, near full blockade of both isozymes can be achieved, and DHT levels can be reduced 99% from baseline. At these levels of blockade, DHT plasma concentrations would be about 1 order of magnitude lower than can be achieved with full finasteride blockade of 5α-reductase type 2 alone.

No effect of finasteride on 5α-reductase type 1 was included in the current model. However, finasteride has been shown to interact with 5α-reductase type 1 in vitro with a second-order rate about 2.2% of the rate constant for the GI198745–5α-reductase type 1 interaction. If the same relation between the rate constants of the 5α-reductase type 1 interaction with finasteride and GI198745 is true in vivo, a steady-state finasteride concentration of about 1200 ng/mL ($EC_{50,1G}$/0.022) would be needed to suppress 5α-reductase type 1 by 50%. Assuming linear pharmacokinetics, daily doses of about 270 mg finasteride would be required to achieve average concentrations of this magnitude. Because this is more than 50-fold higher than the dose used clinically, exclusion of the finasteride–5α-reductase type 1 interaction should not affect predictions with the current model.

Because the rate of DHT elimination, k_{out}, is high and the rate of drug absorption is rapid for both drugs, the rate of onset of effect depends on the rate of drug-dependent 5α-reductase elimination and increases with dose. It is ultimately limited only by k_{out}. For finasteride, which has an apparent terminal elimination half-life of approximately 10 hours, the rate of return to baseline DHT levels is governed mainly by the rate of 5α-reductase type 2 turnover, which has a half-life of 80 hours. This half-life agrees with the 1 to 2 weeks needed for DHT levels to return to baseline after finasteride treatment.[22] At higher doses, the half-life of GI198745 is long, approximately 5 weeks, and the rate of GI198745 elimination determines the rate of return to baseline DHT levels. Thus the difference in duration of effect between GI198745 and finasteride observed in this study can be explained from the difference in half-life between the 2 compounds. Given the pharmacokinetic and pharmacodynamic characteristics of GI198745, a variety of long-term dosing regimens are possible, as shown in Figure 7.

It is worth bearing in mind that all our predictions were made with parameter values derived from data for young, healthy subjects. It is likely that the values of both pharmacokinetic and pharmacodynamic parameters and the associated variabilities will be different for the target population, which is typically persons older than 60 years. The structural models used here are based on the physiologic mechanisms of the 5α-reductase system and the mode of action of the 5α-reductase inhibitors. The models therefore are likely to be valid for the patient population, and although the effects will appear at slightly different doses, the overall pattern of these simulations should hold. Predictions with these models give a good picture of the expected pharmacodynamic effects of different long-term dosing regimens.

In summary, a physiologically based model of the turnover and irreversible inhibition of 5α-reductase and the formation and elimination of DHT described the data well. Use of this model helped explain the differences in rates of onset and offset of effect of the 5α-reductase inhibitors and offered a way to determine the relative potency of these irreversible inhibitors.

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