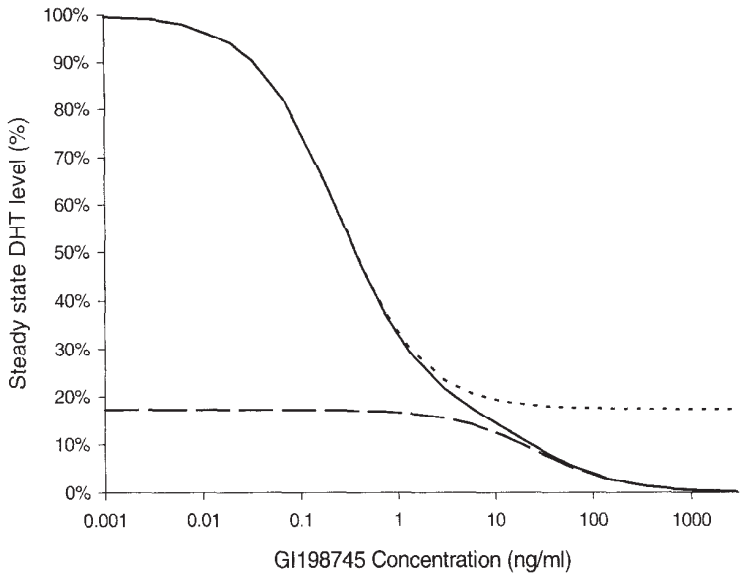

Figure 5. Population mean steady-state concentration-effect curve shows dihydrotestosterone (DHT; *solid line*) suppression as a function of GI198745 concentration and the relative contributions of 5α-reductase type 1 (*dashed line*) and 5α-reductase type 2 (*dotted line*).

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.

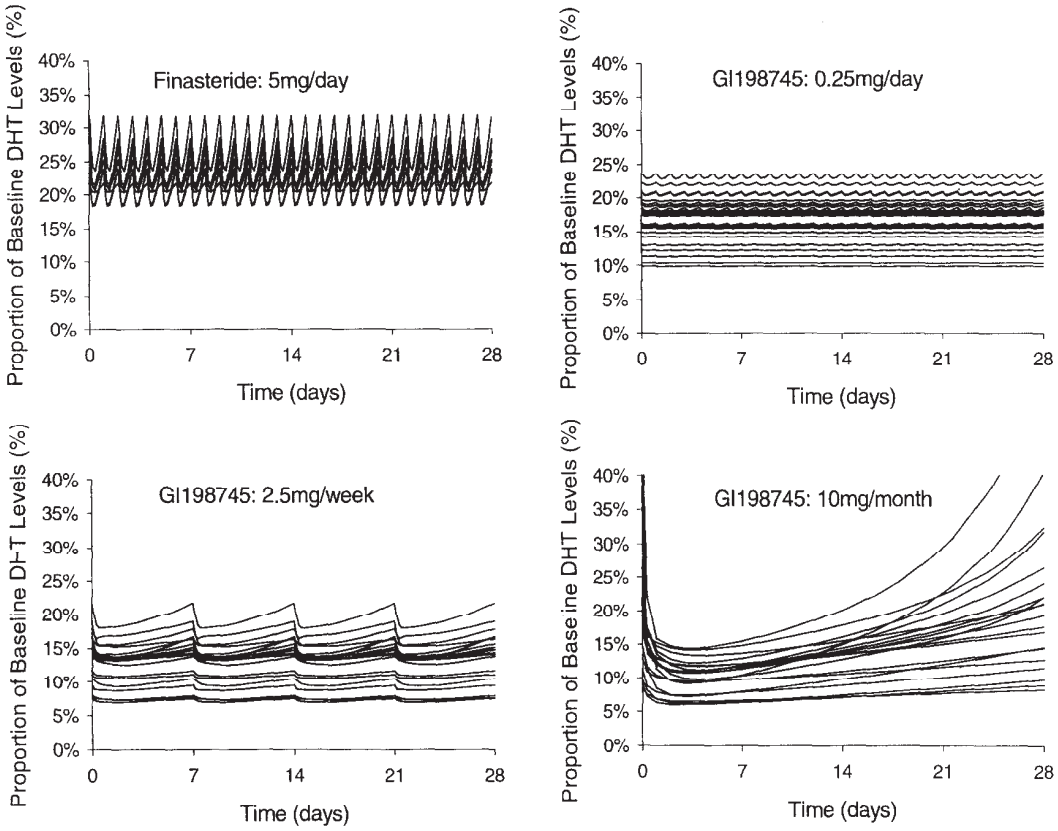

Figure 7. Individually predicted steady-state concentrations of dihydrotestosterone (DHT) after dosing of 5 mg finasteride once a day, 0.25 mg GI198745 once a day, 2.5 mg GI198745 once a week, and 10 mg GI198745 once a month.

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.