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Research Article

A simplified approach for estimating dihydrotestosterone (DHT) reduction when taking finasteride, and/or dutasteride

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Abstract

Dihydrotestosterone (DHT) is associated with benign prostatic hyperplasia, prostate cancer, and androgenetic alopecia (male pattern hair loss). The enzyme 5α-reductase (5a-R) converts testosterone to DHT. Finasteride and dutasteride are the most commonly prescribed 5a-R inhibitors (blockers), approved for the treatment of prostate and/or hair issues. While the dosages are standardised, some persons have concerns for adverse health effects and experiment with lower or less frequent dosages or combinations of the two drugs. In this paper we model the intake of these drugs, separately or simultaneously, at different dosages and frequencies. The model is a simplified approach of previously published models with simplified pharmacokinetics, but expanding the pharmacodynamics to include both drugs simultaneously. The results are compared with the literature and different drug dosages and combination protocols are discussed.

Keywords: finasteride, dutasteride, 5a-reductase, DHT, hair loss, prostate, dosage, half life.

1. Introduction

The enzyme 5α-reductase (5a-R) converts intracellularly testosterone to dihydrotestosterone (DHT). In adult men, DHT is associated with benign prostatic hyperplasia (BPH), prostate cancer, and androgenetic alopecia (male pattern hair loss) [1,2]. The two main iso-enzymes of 5a-R are: (i) type 1, which is predominantly found in the skin and liver; and (ii) type 2, which is primarily found in male genitalia and in hair follicles. Both 5a-R iso-enzymes are expressed in prostate tissue [2]. Data for the type 3 iso-enzyme is limited, but is expressed in prostate basal epithelial cells [3].

Finasteride (FIN) and dutasteride (DUT) are the most commonly prescribed 5a-R inhibitors (blockers). Dutasteride is a more potent inhibitor of type 1 (45-fold) and type 2 5a-R (2.5-fold) than finasteride (a type 2 5a-R inhibitor) in vitro [1]. It has been demonstrated many times in the literature the effectiveness of the two drugs in reducing DHT levels, reducing hair loss and prostate issues [4]. FIN is approved for male androgenic alopecia and both FIN and DUT for treatment of BPH.

No baldness is seen in persons lacking the 5α-R type 2 iso-enzyme [5]. Serum (or plasma, the terms are used interchangeably in this paper) DHT has a direct impact on prostate or scalp. For example, Figure 1 plots the correlation between serum and scalp DHT based on three studies of the literature [6–8]. The best fit of all data is also given in the figure. Although the systemic inhibition of 5a-R activity, which reduces circulating DHT, is believed to be the main mechanism of action of the drugs, the local inhibition plays also a role [2].

The dosages of the drugs are standardised, but quite often people apply different dosages and frequencies, mostly for avoiding side effects [9]. According to our knowledge, there is only one study that combined both drugs with success in avoiding hair loss (0.5 DUT once per week with FIN 1 mg daily) [10].

Models can be used to assess the effectiveness of drugs, but in many cases they are complicated or not applicable to patients or doctors. Simplified approaches can help estimate the impact of a protocol using a few laboratory blood exams [11].

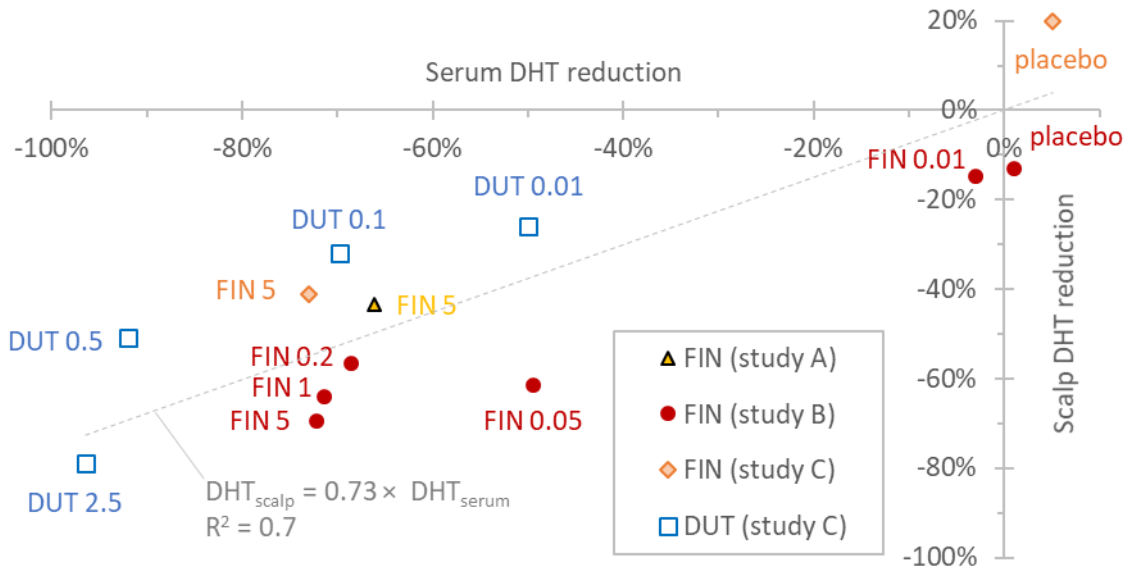


Figure 1: Serum vs. scalp DHT reduction as measured at three studies: A [6], B [7], C [8]. For each point the drug (FIN or DUT) and the dosage (in mg) is given.

The aim of this paper is to present a simplified model for assessing the efficiency of the drugs on reducing serum DHT. The model is expanded taking into account the use of both drugs simultaneously at various frequencies and dosages. The results are expected to help patients and practitioners to apply the appropriate dosages.

2. Materials and methods

The following sections describe the pharmacokinetics (i.e. what the body does to the drug), and pharmacodynamics (i.e. what the drug does to the body) of the simplified model.

2.1. Pharmacokinetic model and pharmacokinetic parameters

There are a few models in the literature of how the ingested FIN or DUT behave in the body. For example, conventional 2-compartment model [12–14] or extensions to low dosages [15]. Here a simple approach was followed. Experimental data from the literature were combined and normalised to derive FIN or DUT serum concentration curves after ingestion of various dosages. Complicated models would not increase more the reliability of the data. Furthermore, measurements of serum FIN or DUT concentration are not typical laboratory tests that one can do in order to fit the model parameters to their situation.

Figure 2 plots FIN serum concentrations after ingestion of 1 mg or 5 mg of FIN. The data were based on studies of the literature for 1 mg [16,17] and 5 mg [18–21]. It should be added that the values reported in the literature are averages with a variability of more than 70% [12]. The curves are in agreement with other studies that reported values, but not in function of time or the data points in graphs were not readable [12,22–24]. The 1 mg and 5 mg normalised curves have small differences during the first 6 h, but after 6 h they tend to be similar. The FIN concentration peaks approximately after 1.5-2 h (1 mg) or 2-2.5 h (5 mg) and drops to half after 6-6.5 h, i.e. 4-4.5 h after reaching the peak. At 24 h the normalised concentration of FIN is mostly between 6% and 9%. The similarity of the normalised graphs justifies the use of common percentages corrected only for the dosage. Typical absolute max concentrations are 5.5 ng/ml after ingestion of 1 mg FIN and 31 ng/ml after ingestion of 5 mg. Much higher values have also been reported in the literature of 9.3-9.9 ng/ml for 1 mg FIN [15] and 38.1 ng/ml for 5 mg FIN [22].

Although it is possible to fit curves and equations to the data, the simplified approach uses only a few points in time: 0 h (ingestion of drug), 2.5 h (peak time), 6.5 h (time that the concentration reaches approximately 50%), 24 h (after one day) etc. Thus, specific percentages (multiplied by the dosage) can be used instead, which will be summarised later at the equations section.

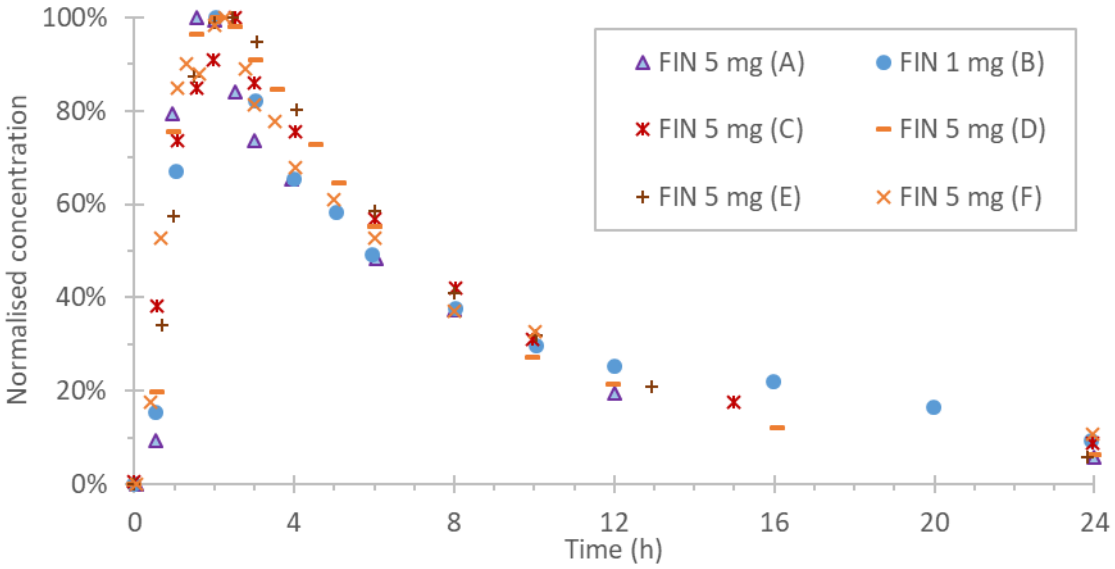


Figure 2: Time plot of normalised serum FIN concentration after receiving 1 mg or 5 mg FIN. The 1 mg data were extracted from the figures of the studies A [17] and B [16]. The 5 mg data were extracted from the figures of the studies C [18], D [19], E [20], F [21].

Figure 3 plots DUT serum concentrations after ingestion of 0.5 mg of DUT. The DUT concentration peaks after 1 h [13] to 4 h [25] with most studies reporting 2-3 h [26,27]. After peaking, the time to drop to half is 3.1 [13] to 12.5 h [25], but most studies found somewhere in between; around 5 h [26,27]. After 1 day (24 h) the concentration drops to one forth (22-25%) [13,26], with some studies measuring higher percentages (30% to 40%) [25,27]. After 2 days (48 h) the DUT concentration is 18-24% [13,26,27], but higher percentage (33%) has also been measured. At the 3rd day (72 h) the DUT concentration is 15-25% of the peak concentration.

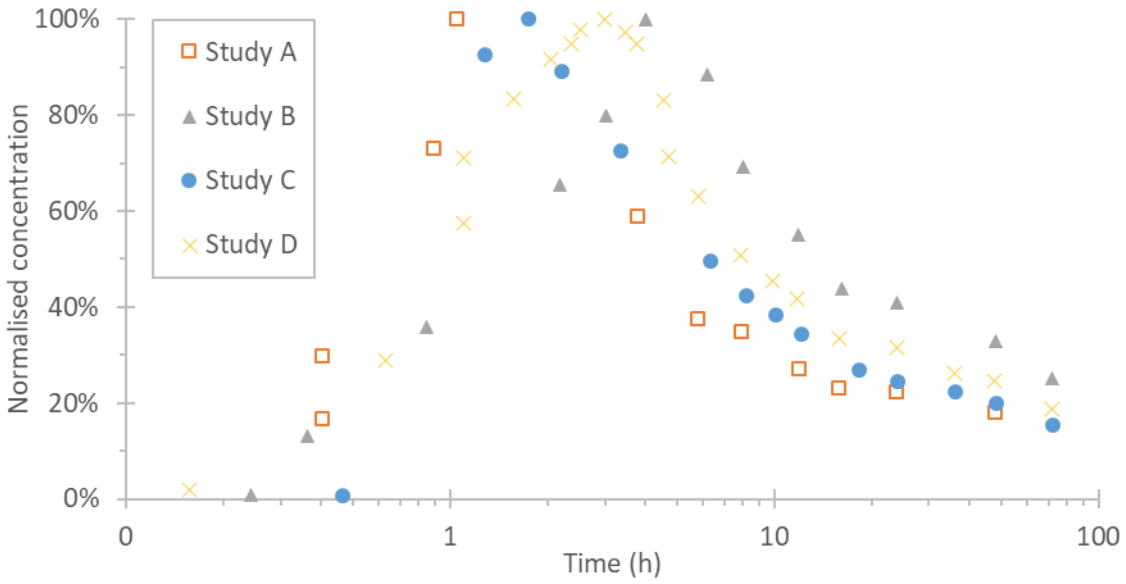


Figure 3: Time plot of normalised serum DUT concentration after receiving 0.5 mg FIN. The data were extracted from the figures of the studies of A [13], B [25], C [26], D [27]. Note the logarithmic time scale (x-axis).

The following equations were used to calculate the peak serum concentration $C_{peak,j}$ of a drug (j is FIN or DUT) (ng/ml) after ingestion of some *Dosage* (mg):

$$C_{peak,DUT} = 5.5 \times Dosage_{DUT}$$

$$C_{peak,FIN} = 7.0 \times Dosage_{FIN}$$

Table 1 Summarises the normalised concentrations of the drugs over time, as applied in the simplified model.
Table 1: Approximated values for the serum concentrations of drug j (FIN or DUT) over time. Values are based on Figure 2 (FIN) and Figure 3 (DUT). The percentages refer to the $C_{peak,j}$.

Time (h)	0	2.5	6.5	24	48	72
C_{FIN}	0%	100%	63%	27%	19%	15%
C_{DUT}	0%	100%	50%	8%	2%	-

It is important to note that these times should not be confused with the terminal plasma half-life, which is the time required to divide the plasma concentration by two after reaching pseudo-equilibrium, and not the time required to eliminate half of the administered dose [28]. In the figures above, the terminal half-life would be calculated from the tail, after the concentration has dropped to half. According to the literature, the half-life of FIN is 4-7 h [29,30], while of DUT from 1 week [2,31] up to 5 weeks [12]. However, DUT at low dosage (0.01 mg) has half-life of only 3 h [12]. In this paper the minimum DUT dosage that is examined is 0.1 mg and it is assumed that it behaves as the higher concentrations. Nevertheless, the conclusions at this 0.1 mg dosage should be treated with care.

The graphs above plotted concentrations after a single dose of the drug. The time to reach the steady state concentration is obtained after a delay of 3–5 times the half-life and is not influenced by the dosing interval [28]. This is not an issue for FIN with short half-life, but it is for DUT. Studies demonstrated that it can take at least one month or even longer [13] to reach steady state. For the simplified approach of this paper a correction factor is applied for the long term concentrations of DUT.

It should be noted that the average plasma concentration at steady state is the same taking the drug once or splitting the dose. However, dividing the daily dose is associated with a reduction of the amplitude of fluctuations at steady state, which usually represents an increase of safety for drugs. The analysis in this paper is done mainly assuming daily dosages. The conclusions should be similar with similar total dosage in less frequent intervals (e.g. every other day), but the fluctuations would be different and in some cases the concentrations might be too low for long period to have any meaningful impact.

2.2. Pharmacodynamic model and pharmacodynamic parameters

The model described in [12] was selected because it includes equations for both FIN and DUT. Here the equations are extended for cases using both FIN and DUT.

In brief, the basis is that the two 5a-R iso-enzymes transform testosterone into DHT. The 5a-R inhibitors irreversibly remove the iso-enzymes from the system at rates proportional to iso-enzymes and inhibitors concentrations. It is also assumed that the testosterone concentration remains on average constant. At steady state:

$$DHT/_{DHT_S} = F_{5AR,2} \times 5AR_2 + (1 - F_{5AR,2}) \times 5AR_1$$

where DHT_S is the steady-state DHT concentration; $F_{5AR,2}$ is the fraction of DHT formed by 5a-R type 2; $5AR_1$ and $5AR_2$ are proportions of the baseline 5a-R type 1 and 2 activities. They are given from the following equations, which are based on [12] and expanded to include both FIN and DUT.

$$d5AR_1/_{dt} = k_1 - k_1 \times 5AR_1 - k_{O,1,FIN} \times 5AR_1 \times C_{FIN} - k_{O,1,DUT} \times 5AR_1 \times C_{DUT}$$

where k_1 is the fractional turnover rate of 5a-R type 1 (h^{-1}), $k_{O,i,j}$ is the second order rate constant for the irreversible binding of drug j (where j is FIN or DUT) to 5a-R type i (where i is type 1 or 2) (ml/ng/h), C_j is the serum concentration of the drug (ng/ml). At steady state $d5AR_1/dt$ is zero, thus:

$$5AR_1 = k_1/(k_1 + k_{O,1,FIN} \times C_{FIN} + k_{O,1,DUT} \times C_{DUT})$$

Similarly,

$$5AR_2 = k_2/(k_2 + k_{O,2,FIN} \times C_{FIN} + k_{O,2,DUT} \times C_{DUT})$$

where k_2 is the fractional turnover rate of 5a-R type 2 (h^{-1}).

For details and how the equations are derived the interested reader is referred to [12]. The values of the constants are taken from [12], based also on the potency of DUT vs. FIN (DUT is 45 times more potent inhibitor than FIN for 5a-R

type 1 and 2.5 times for type 2) [1] (Table 2). $F_{5AR,2}$ is set to 0.827 [12], but lower values have also been reported in the literature.

Table 2: Values for the model of this study [12].

Type *i* (1 or 2)	k_i (h^{-1})	$k_{O,i,FIN}$ (ml/ng/h)	$k_{O,i,DUT}$ (ml/ng/h)
Type 1	0.0153	2% $k_{O,1,DUT}$	0.000594
Type 2	0.00871	30% $k_{O,2,DUT}$	0.0357

The previous equations apply for single doses (or 1-2 weeks). For long term (i.e. >1 month of use) the following corrections are applied for DUT (dosages 0.1 to 10 mg):

$$k_{O,1,DUT,long} = k_{O,1,DUT} \times 0.749 * ln(C_{DUT}) + 3.77$$

$$k_{O,2,DUT,long} = k_{O,2,DUT} \times 0.695 * ln(C_{DUT}) + 2.93$$

These corrections were based on fittings of 5a-R activities presented in graph 6 of [12] based on the values after 4 weeks compared to after one week.

3. Results and Discussion

3.1. DHT changes

Figure 4 plots the DHT ratio (DHT / DHT_S) using FIN 1 mg or 5 mg daily. The contribution of the 5a-R type 1 iso-enzyme is given separately, and it is the same for both cases, because FIN has practically no effect on 5a-R type 1 and the DHT reduction is due to 5a-R type 2 inhibition. With a high dose of 5 mg, DHT is reduced to 20% of the initial levels after 2 h, and then increases to 35% until the next dose. With 5 mg the DHT reduction is almost maximum for a few hours after drug ingestion and cannot go lower, as FIN has no impact on 5a-R type 1, which contributes around 17% (1 - $F_{5AR,2}$) of the DHT in the values of the pharmacodynamics model of this study.

With a dose of 1 mg, DHT is reduced to 25% of the initial levels after 2 h, and then increases to 32% after 4 h and 65% after 24 h. The 32% level is indicated with the 'low' line and is the expected DHT level if one measures their DHT within 8 h from the drug ingestion. The 'mean' day DHT ratio can be calculated from the area under the curve and is estimated to be around 45% for the 1 mg case. The value is a rough approximation due to the limited number of points of the curve and the linear interpolation between them, as no model was developed for the FIN serum concentration.

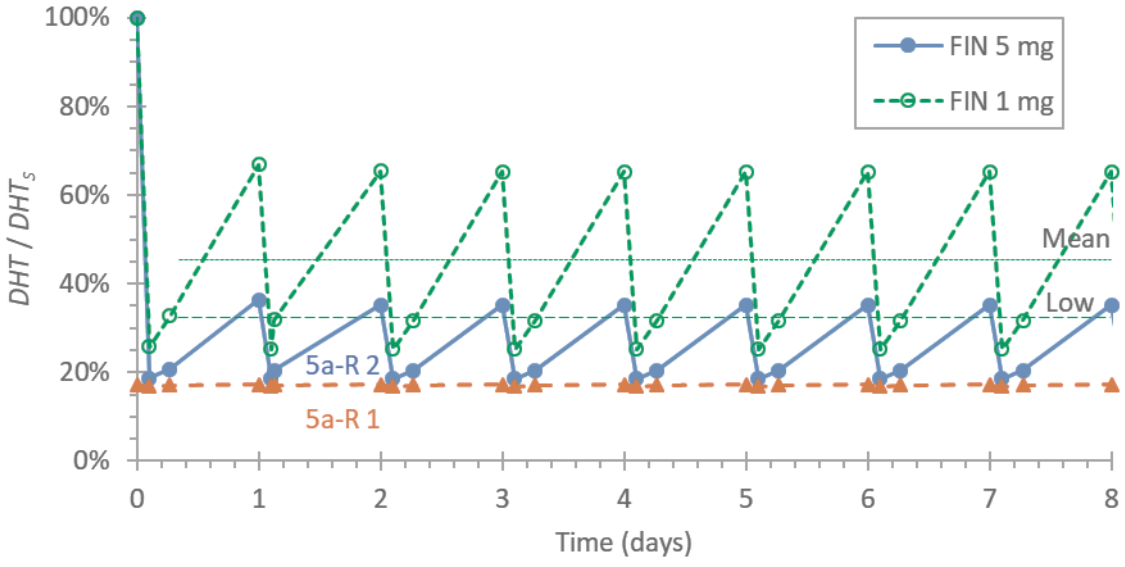


Figure 4: Simulated DHT ratio using FIN 5 mg (solid circles) and 1 mg (open circles) daily. Dashed line with triangles shows the DHT due to 5a-R type 1. The two green lines show the low (i.e. within 8 h after ingestion) and mean daily levels of DHT ratio for the 1 mg case.

Figure 5 plots the DHT ratio using 0.5 mg DUT every day or every other day. Initially the level drops to around 20% and then increases to 40% (after 24 h) or 45% (48 h). The reduction is mainly due to 5a-R type 2 inhibition, because the DHT

reduction due to 5a-R type 1 inhibition is small (<2%). In the long term, the suppression of DHT due to 5a-R type 2 inhibition is around 80%, and due to 5a-R type 1 inhibition another 6%. Due to the long half-time of DUT, the increase of DHT the second day is relatively small.

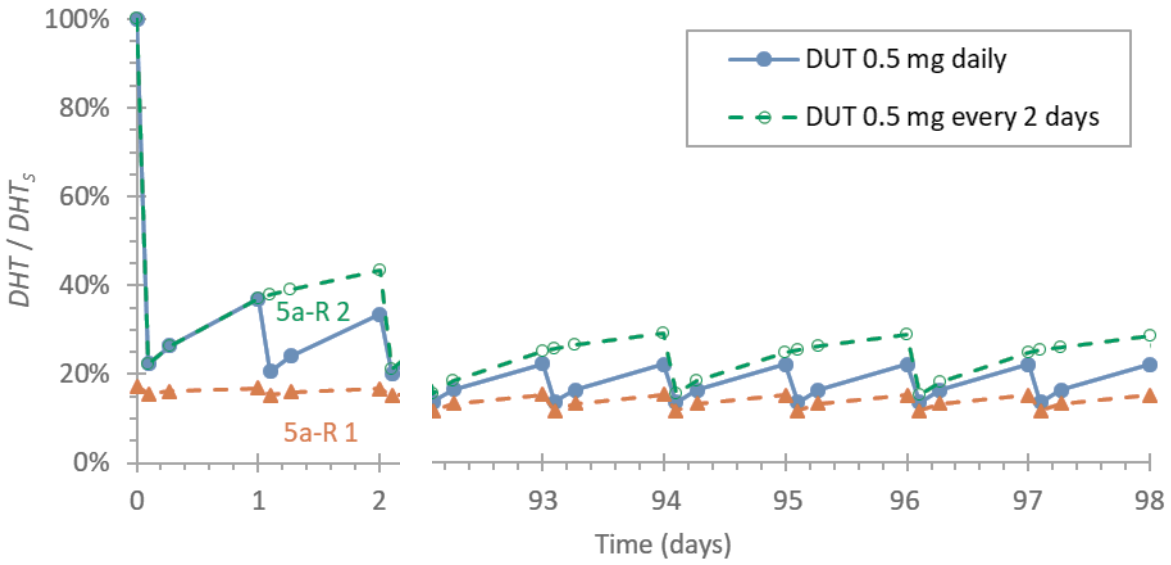
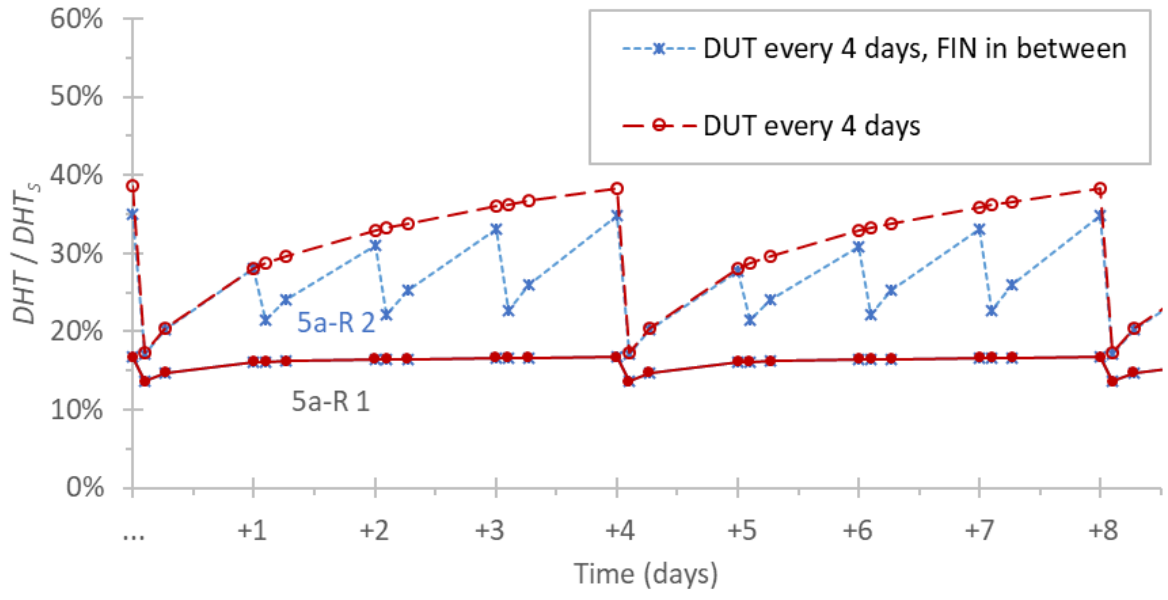


Figure 5: Simulated DHT ratio using DUT 0.5 mg every day (solid circles) or every other day 1 mg (open circles). Dashed line with triangles shows the DHT due to 5a-R type 1. The first days (left panel) and the long term ratios (right panel) are given separately.

Figure 6 plots the DHT ratios following various protocols: Figure 6a plots DUT (0.5 mg) every four days and DUT (0.5 mg) every four days with FIN (1 mg) the three days in between. Note that for the long-term corrections the daily equivalent was used, i.e. the dosage (0.5 mg) was divided with the frequency (every 4 days). Starting with the DUT every 4 days protocol (red line with circles), the DHT ratio varies between 15% and 38%. The 5a-R type 1 converted DHT is reduced only a few percent (from 16% to 13%) the first hours after DUT ingestion. When FIN is added in the days in between, the DHT ratio varies between 22% and 33%. The 5a-R type 1 converted DHT is identical with the DUT every four days protocol, because FIN has no impact on 5a-R type 2.

Figure 6b plots DUT (0.5 mg) every two days and DUT (0.5 mg) every two days with FIN (1 mg) the one day in between. At the DUT every 2 days protocol (red line with circles), the DHT ratio varies between 15% and 29%. Addition of FIN only slightly reduces the range to 15% and 28%. Thus, the additive effect is relatively small, and much smaller compared to the protocol where DUT was taken every four days.



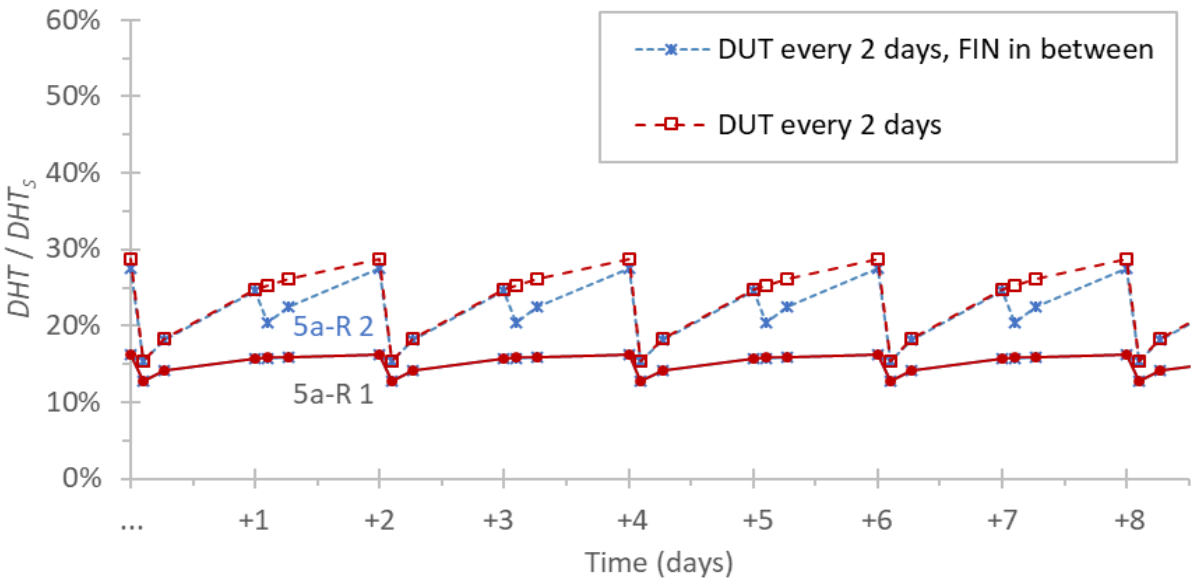


Figure 6: Various protocols indicated with different symbols: (**a**) DUT every four days; (**b**) DUT every two days. Dotted lines and open symbols plot DHT ratio, while continuous lines with solid symbols the DHT 5a-R type 1 derived.

3.2. DHT ratios

Figure 7 plots the model predictions of DHT ratios using various dosages of FIN and DUT. For DUT the short-term and long-term ratios are plotted. The simulated curves are based on the 'low' percentages (i.e. values within 8 h of drug intake). The daily mean values would be somewhat higher, and the minimum values (i.e. after 2 hours from ingestion) somewhat lower. It should be recalled that for non-daily intakes, the daily equivalent can be used. Measured values from studies in the literature are also plotted in the figure. Table 3 summaries these studies.

In general, simulated and measured data are in good agreement considering the experimental and individual variabilities. For example, in one study the DUT concentration was nearly zero after one week in one subject, but dropped to zero after two weeks for another subject [13]. In the modelling studies the inter-subjects variability was on the order of 70%.

The conclusions that can be drawn from the figure are:

- The improvement from 1 mg to 5 mg FIN is very small, not even evident from the experimental data.
- FIN 1 mg and DUT 0.1 mg seem equivalent. This low DUT dosage would be equivalent to 1-2 DUT 0.5 mg capsules per week.
- DUT 0.5 mg is significantly better than DUT 0.1 mg. The improvements at higher dosages are smaller and are mainly due to 5a-R type 1 inhibition.

Although out of the scope of this paper, there is an interesting case report [32], where after one year of DUT 0.5 mg, the average DHT of thirty patients with benign prostate hyperplasia was reduced only 38% (see the 0.5 mg DUT star symbol at 62% in Figure 7). Some anecdotal claims in forums also have reported small DHT reduction with FIN or DUT. Although there are no clear explanations for these claims, as it was discussed before, the time of DHT measurement (compared to the drug ingestion) and individual variabilities can partly explain such claims.

Finally, it should be reminded that DHT reduction does not result in prostate or hair issues improvements to all subjects [2].

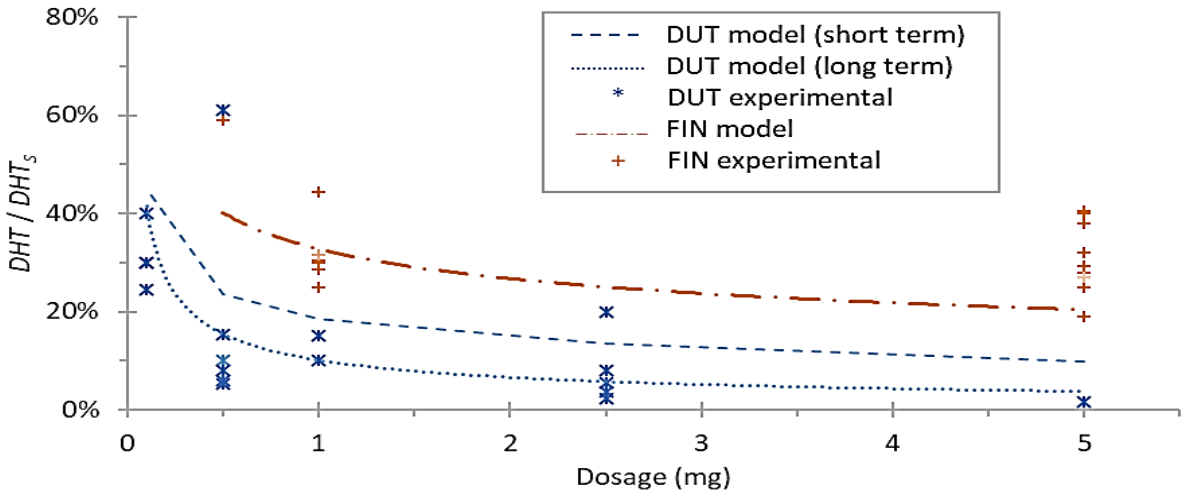


Figure 7: DHT ratio using daily DUT or FIN at various dosages. Lines are based on the simplified model of this paper for short-term (i.e. without the *5AR* correction for DUT) and long-term (i.e. with the *5AR* correction for DUT) usage. Values are based on DHT ratios within 8 h of drug ingestion (i.e. 'low' levels). Asterisks and crosses are experimental data based on the literature for DUT and FIN, respectively. Details about the experiments can be found in Table 3. For protocols with less frequency divide the dosage with the frequency. For example 1 mg FIN every other day is (almost) equivalent to 0.5 mg daily.

Table 3: Overview of studies in chronological order that measured serum DHT before and after taking FIN or DUT at various dosages.

Drug	**FIN**			**DUT**				
Dose	**0.5**	**1.0**	**5.0**	**0.1**	**0.5**	**1.0**	**2.5**	**5.0**
Model	42%	32%	21%	45%	18%	12%	7%	4%
[22]		30%	41%					
[33]	59%		25-38%					
[34]		32%						
[12]			19-32%	30-40%		10-15%	8-20%	
[14]				24%	15%		6%	
[7]		29%	28%					
[35]			29%		5%		2%	2%
[8]			27%	30%	8%		4%	
[36]			27%		6%			
[37]					10%			
[15]			40%					
[16]		25-30%						
[32]					62%			
[38]		44%						

For higher dosages, the interested reader is referred to older [12,22] and newer studies [39].

For completeness, the DHT ratios are presented for various protocols of FIN only, DUT only, or combinations of the two drugs in Figure 8. To compare different frequencies the mean daily ratio calculated from four days is given and not the minimum or low level, which would not be representative of the impact of the protocol. Thus, the values are higher compared to Figure 7 for the same dosage. For all protocols 0.5 mg DUT and/or 1 mg FIN was assumed, at the frequencies indicated in the figure. For example, the first bar is the 1 mg FIN daily protocol, the second is the DUT 0.5 mg every four days, etc. The last column is a combination of DUT every four days and FIN the three days in between. The contribution of 5a-R type 1 and type 2 iso-enzymes is also given in the figure. As expected, the inhibition of 5a-R type 1 is negligible or very low with the 0.5 mg DUT protocols. As discussed before, addition of FIN at a DUT protocol decreases DHT, but the impact is meaningful for low DUT frequencies (e.g. every three or four days).

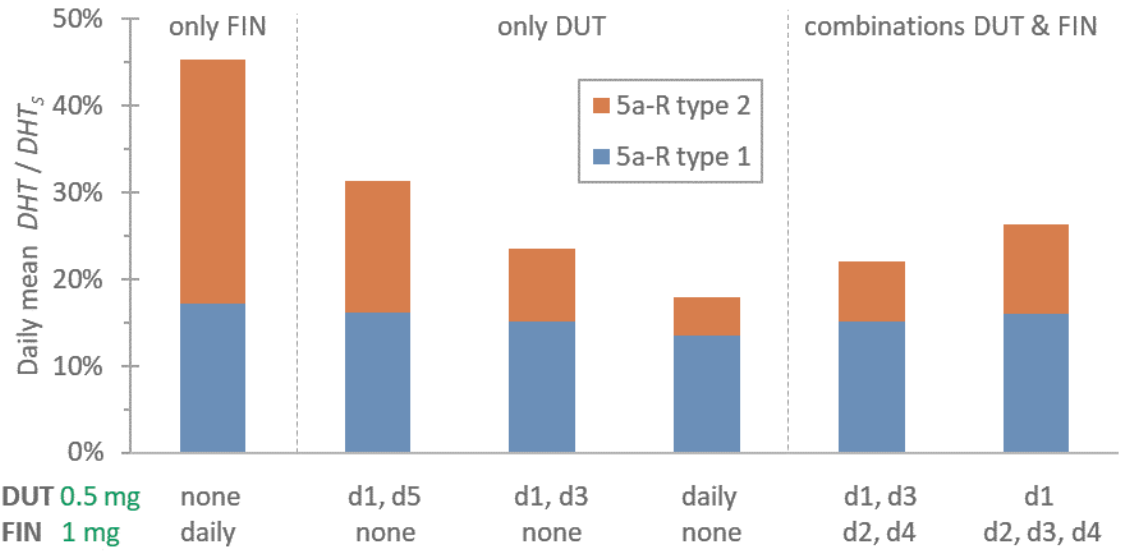


Figure 8: Daily mean DHT ratios following various protocols of FIN only, DUT only, or DUT and FIN combinations. The dosage was 0.5 mg DUT and/or 1 mg FIN at the frequency indicated in the graph (d stands for day).

4. Conclusions

In this paper we modelled the effect of 5a-R inhibitors (blockers) on DHT. The model was based on previous studies, but here we simplified the pharmacokinetics and combined the pharmacodynamics for the two commonly prescribed drugs (finasteride and dutasteride). The pharmacokinetics were based on normalised experimental data from the literature, while the long-term accumulation was taken into account with correction factors. The model results were in good agreement with the experimental data of the literature. Nevertheless, validation of the model with serum DHT exams is suggested, and most importantly, confirmation that the DHT reductions based on different combinations translate to different hair or prostate improvements. For the more enthusiastic practitioners, personal (individual) DHT measurements can be used to adjust the model or predict the impact of changing the dosages or frequencies of the drugs or any combinations of them.s

The key conclusions of the simplified approach were:

- The time after drug ingestion is important for the DHT measured value;
- DUT 0.5 mg once or twice per week is equivalent to 1 mg FIN;
- Daily intake of drugs keeps DHT concentration variation in a smaller range compared to less often;
- DUT keeps the DHT variation range smaller compared to FIN;
- DUT dosages higher than 0.5 mg have significant impact on 5a-R type 2 inhibition.
- Combination of DUT every few days with FIN at the days in between is a possible combination that keeps 5a-R type 2 inhibition low. However, the addition of FIN when DUT is taken frequently (e.g. every other day) has small additive effect.

Disclosure of conflict of interest: No conflict of interest to be disclosed.
Disclaimer: Mention of trade or commercial products does not constitute endorsement or recommendation by the authors or their employers. Before beginning any drug protocol, always consult with your doctor.

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