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Saturable Binding of Finasteride to Steroid 5α-reductase as Determinant of Nonlinear Pharmacokinetics

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Summary: Finasteride, a steroid 5α-reductase (5αR) inhibitor, is used to treat benign prostatic hyperplasia and androgenetic alopecia. We aimed to develop a pharmacokinetic/pharmacodynamic model to explain its nonlinear pharmacokinetics and describe the serum concentration profile of dihydrotestosterone (DHT) after finasteride administration. We developed a pharmacokinetic model incorporating a compartment that represents the binding of finasteride to 5αR. We fitted this model to the time-concentration profiles of finasteride after repeated administration of finasteride 0.2 and 1 mg/day. We constructed a pharmacodynamic model considering the inhibition of 5αR type I and type II (5αR1 and 5αR2). This model was fitted to the time profiles of serum DHT. The developed pharmacokinetic model well described nonlinear increase in AUC after repeated administration of finasteride. The association and dissociation rate constants were estimated to be 0.0293/nmol/hr and 0.0185/hr, respectively. Pharmacodynamic model analysis suggested that the 5αR1 inhibition is dose-dependent in the dose range from 0.2 to 100 mg, while the 5αR2 inhibition is almost saturated in the same dose range. Finasteride's saturable binding to 5αR2 is the likely cause of its nonlinear pharmacokinetics. The developed pharmacokinetic/pharmacodynamic model should allow prediction of plasma concentration profiles of finasteride and DHT.

Keywords: finasteride; 5α-reductase; nonlinear pharmacokinetics; dihydrotestosterone; pharmacokinetic/pharmacodynamic modeling

Introduction

The enzyme 5α-reductase (5αR) converts testosterone (TS) into a more potent androgen, dihydrotestosterone (DHT). Two isozymes of 5αR, type I (5αR1) and type II (5αR2), have been identified in humans. 5αR1 is expressed in skin and many organs, including liver and brain, whereas 5αR2 is expressed in prostate gland and seminal vesicles.[1)] Both isozymes are present in the scalp, 5αR1 being predominantly found in sebaceous gland and 5αR2 in connective tissue sheath and dermal papilla.[2)] Because a male genetically deficient in 5αR2 is not affected by male pattern hair baldness, 5αR2 is proposed to be a key enzyme for the treatment of androgenetic alopecia (AGA).[3,4)] Finasteride inhibits 5αR and is used in the treatment of AGA. The concentrations of finasteride producing a 50% reduction in 5αR activity (IC_{50}s) are 500 nM for 5αR1 and 4.2 nM for 5αR2. Thus, finasteride is highly selective for 5αR2, which is associated with AGA.[5)]

The standard dose of finasteride is 1 mg once daily for AGA, and 5 mg once daily for benign prostatic hyperplasia (BPH). In Japan, the recommended dose for treatment of AGA is 0.2 mg once daily and this may be increased up to 1 mg/day. Plasma concentrations of finasteride after single oral administration are proportional to dose over the range from 1 to 100 mg, and the apparent oral clearance (CL_{po}) is almost constant. On the other hand, CL_{po} after single dose of 0.2 mg is considerably larger (**Table 1**).[6,7)] When finasteride 0.2 mg is administered repeatedly, the area under the concentration curve (AUC) on day 17 is about 4.7-fold higher than that on day 1, while the AUC remains constant in the case of repeated doses of 1 mg. A conventional 2-compartment model was applied to explain the pharmacokinetics of finasteride,[8)] but this

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Table 1. Mean pharmacokinetic parameters of finasteride after single oral dosing in healthy volunteers

Dose (mg)	0.2[a] (n=12)	1[a] (n=11)	5[b] (n=6)	10[b] (n=6)	20[b] (n=12)	50[b] (n=6)	100[b] (n=6)
C_{max} (ng/mL)	0.56	9.89	38.1	81.5	147.1	442.0	835.5
AUC_{0-24} (ng·hr/mL)	2.19	49.29	180.6	546.9	997.8	3,359.6	6,712.1
$t_{1/2}$ (hr)	2.76	4.15	4.7	5.3	6.3	7.1	5.4
CL_{po} (L/hr)	91.3	20.3	27.7	18.3	20.0	14.9	14.9

C_{max}; maximum plasma concentration, AUC_{0-24}; area under plasma concentration-time curve from 0 to 24 hours, $t_{1/2}$; elimination half-life, CL_{po}; apparent oral clearance
[a]reference 6)
[b]reference 7)

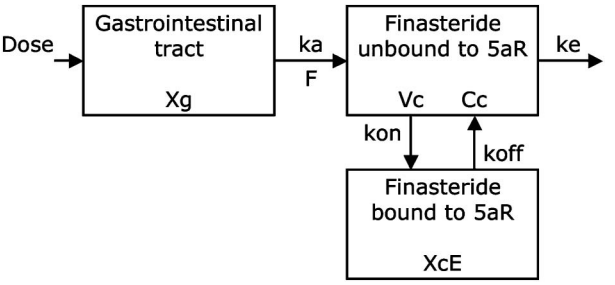

Fig. 1. The developed pharmacokinetic model of finasteride
Xg; the amount of drug in the gastrointestinal tract (nmol), XcE; the amount of enzyme-drug complex (nmol), Cc; plasma concentration of drug (nM), Vc; distribution volume (L), ka; absorption rate constant (/hr), ke; elimination rate constant (/hr), kon; association rate constant (/nmol/hr), koff; dissociation rate constant (/hr)

model failed to describe nonlinear pharmacokinetics at low dose levels. Since finasteride has an extremely high affinity for 5αR,[9,10] which is ubiquitously expressed, the specific binding to 5αR is likely to be responsible for the saturable distribution and increase of AUC during repetitive administrations.

The purpose of this study was to construct a pharmacokinetic model of finasteride to describe nonlinearity at low dose and rise in AUC during repeated administrations, taking into consideration the binding properties of finasteride to 5αR. We also constructed a pharmacodynamic model to predict the time-profile of serum DHT after finasteride administration.

Methods

Pharmacokinetic model and pharmacokinetic parameters for finasteride: **Figure 1** shows the developed pharmacokinetic model based on the following assumptions.

1) Orally administered finasteride is absorbed with a first-order rate constant ka (/hr), and eliminated with a rate constant ke (/hr).
2) Finasteride binds to 5αR reversibly in the stoichiometric ratio of 1:1 at an association rate constant kon (/nmol/hr) and a dissociation rate constant koff (/hr).

Based on these assumptions, the following equations were derived:

$$Xg = Dose \cdot \frac{1 - exp(-n \cdot ka \cdot \tau)}{1 - exp(-ka \cdot \tau)} \cdot \exp[-ka \cdot \{t - \tau \cdot (n-1)\}] \quad (1)$$

$$\frac{dCc}{dt} = \frac{ka \cdot F \cdot Xg}{Vc} + \frac{koff \cdot XcE}{Vc} - ke \cdot Cc - kon \cdot Cc \cdot (Etot - XcE) \quad (2)$$

$$\frac{dXcE}{dt} = kon \cdot Cc \cdot Vc \cdot (Etot - XcE) - koff \cdot XcE \quad (3)$$

where Xg, XcE, Cc, Etot and Vc represent the amount of drug in the gastrointestinal tract (nmol), amount of enzyme-drug complex (nmol), plasma concentration of drug unbound to 5αR (nM), total amount of the enzyme (nmol) and distribution volume (L), respectively. The bioavailability of finasteride, F was set to 0.8.[11] In equation 1, n and τ represent the number of doses and dosing interval, respectively.

To estimate pharmacokinetic parameters, ka, ke, Vc, kon, koff and Etot, equations 1–3 were simultaneously fitted to the time profiles of plasma concentration on day 1 and day 17 after oral administrations of finasteride (molecular weight 372.55) at doses of 0.2 mg and 1 mg once daily for 17 days to healthy male volunteers,[6,10] using a nonlinear least-squares method (MLAB, Civilized Software Inc., MD, USA).

The pharmacodynamic model and pharmacodynamic parameters for finasteride: Based on the following assumptions, we developed a pharmacodynamic model to describe the serum DHT change from the baseline (**Fig. 2**).

1) In the absence of finasteride, DHT is released into serum with a rate constant Kin (% of baseline/hr), and eliminated with a rate constant kout (/hr). Therefore, Kin is equal to kout × 100.
2) DHT is formed by 5αR1 and 5αR2, and the proportion of DHT formed by 5αR2 is represented as F2 under physiological conditions.
3) The inhibition rate of 5αR2 by finasteride, $\Phi 2$, is parallel to the ratio of the amount of drug-bound enzyme to the total amount of 5αR2.

$$\Phi 2 = \frac{XcE}{Etot} \quad (4)$$

The binding of finasteride to 5αR1 is thought be sufficiently small to be negligible in pharmacokinetic analysis at low doses (0.2 mg and 1 mg). Thus, we assumed that the Etot estimated in pharmacokinetic analysis is the total amount of 5αR2.

4) The inhibition rate of 5αR1 by finasteride, $\Phi 1$, is determined using the inhibition constant, Ki1 (nM).

$$\Phi 1 = \frac{Cc}{Cc + Ki1} \quad (5)$$

Based on these assumptions, the mass balance equation for DHT is given by equation 6:

$$\frac{d[DHT]}{dt} = Kin \cdot F2 \cdot (1 - \Phi 2) + Kin \cdot (1 - F2) \cdot (1 - \Phi 1) - kout \cdot [DHT] \quad (6)$$

where [DHT] represents serum DHT (% of baseline). We used equation 7 to calculate the amount of drug in the gastrointestinal tract after single oral administration (nmol), Xg.

$$Xg(t) = Dose \cdot exp(-ka \cdot t) \quad (7)$$

To estimate pharmacodynamic parameters, F2, kout and Ki1, we used the time profiles of serum DHT changes after single administrations of finasteride at 5, 10, 20, 50 or 100 mg to healthy male volunteers.[7] First, we simulated the time profiles of plasma concentration of finasteride after single oral administration of 5, 10, 20, 50 and 100 mg using the pharmacokinetic model with the estimated parameters (ka, ke, Vc, kon, koff and Etot), and then compared the simulated profiles with reported data.[7] Next, equations 2–7 were simultaneously fitted to the time profile of serum DHT change after single oral administrations of finasteride,[7] using a nonlinear least-squares method (MLAB), to obtain pharmacodynamic parameters, F2, kout and Ki1.

Simulation of serum DHT change and inhibition rate of 5αR: We simulated the time profiles of serum DHT change and inhibition rate of 5αR after single oral administrations of 0.2 and 1 mg finasteride. We also simulated the time profile of serum DHT change after repeated oral administrations of 5 mg or less once daily for 14 days.

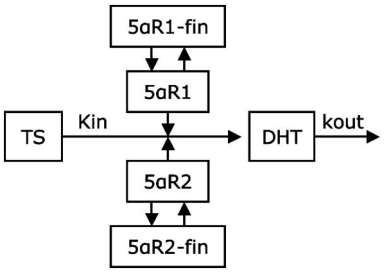

Fig. 2. The developed pharmacodynamic model of finasteride
TS; testosterone, DHT; dihydrotestosterone, 5αR1; free 5α-reductase type I isoenzyme, 5αR1-fin; 5αR1-finasteride complex, 5αR2; free 5α-reductase type II isoenzyme, 5αR2-fin; 5αR2-finasteride complex, Kin; formation rate of DHT (%/hr), kout; elimination rate of DHT (/hr)

Results

Pharmacokinetic model analysis: The plasma finasteride profiles after repeated oral administration of 0.2 and 1 mg were successfully described by the developed pharmacokinetic model (**Fig. 3**). In particular, this pharmacokinetic model well described the increase in AUC after repeated oral doses of 0.2 mg. The values of kon and koff were estimated to be 0.0293/nmol/hr and 0.0185/hr, respectively (**Table 2**).

Pharmacodynamic model analysis: The time profiles of plasma concentration of finasteride after single oral administration of 5, 10, 20, 50 and 100 mg were well predicted by this pharmacokinetic model with the estimated parameters (**Fig. 4**). The predicted values were within the range of standard derivative of the observed values. With this profile as an input function, the serum DHT profile was well described by the developed pharmacodynamic model (**Fig. 5a, Table 3**).

We simulated the inhibition rates of 5αR1 and 5αR2 after single oral administrations of 5–100 mg finasteride. The inhibition rate of 5αR1 was found dose-dependent

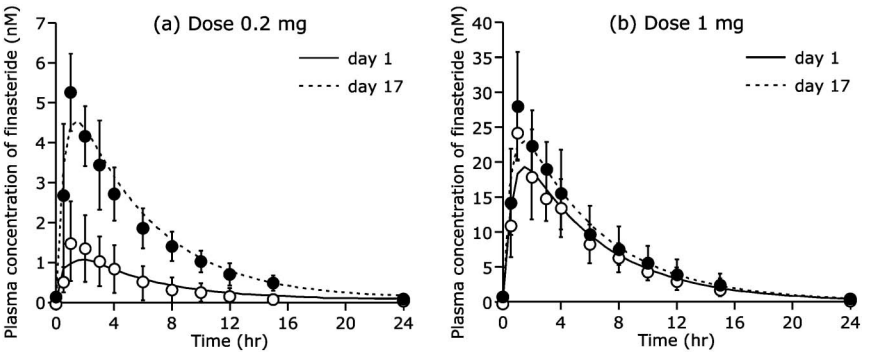

Fig. 3. Pharmacokinetic analysis of the plasma concentration-time profiles of finasteride
Finasteride at a dose of 0.2 mg (a) or 1 mg (b) was administered once daily for 17 days.[6] Open symbols represent the observed mean values ± SD on day 1 (n = 12), and closed symbols represent those on day 17 (n = 11). For the data on day 17, the dosing time (384 hr) was represented as time 0. The solid lines are the model-fit values based on the pharmacokinetic model on day 1, and dotted lines are those on day 17.

Table 2. Pharmacokinetic parameters estimated from the model analysis

Parameter	Estimate	−SD ~ +SD
ka (/hr)	1.87	1.64 ~ 2.10
ke (/hr)	0.177	0.167 ~ 0.186
Vc (L)	73.7	69.8 ~ 77.6
kon (/nmol/hr)	0.0293	0.0182 ~ 0.0471
koff (/hr)	0.0185	0.0046 ~ 0.0737
Etot (nmol)	320	292 ~ 347

ka; absorption rate constant, ke; elimination rate constant, Vc; distribution volume, kon; association rate constant, koff; dissociation rate constant, Etot; total amount of the enzyme

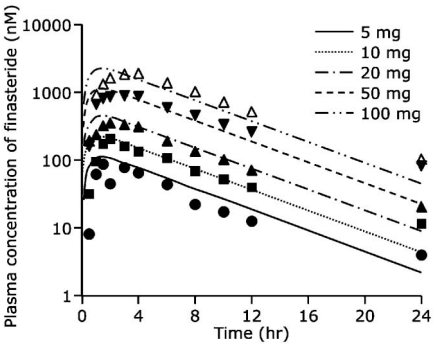

Fig. 4. Pharmacokinetic analysis of plasma concentration-time profiles of finasteride after single oral dosing of finasteride (5–100 mg)
The closed circles, closed squares, closed triangles, closed inverted triangles and open triangles represent the observed mean values in the cases of 5 mg, 10 mg, 20 mg, 50 mg and 100 mg finasteride oral administration.[7] The lines are model-fit values based on the pharmacokinetic model.

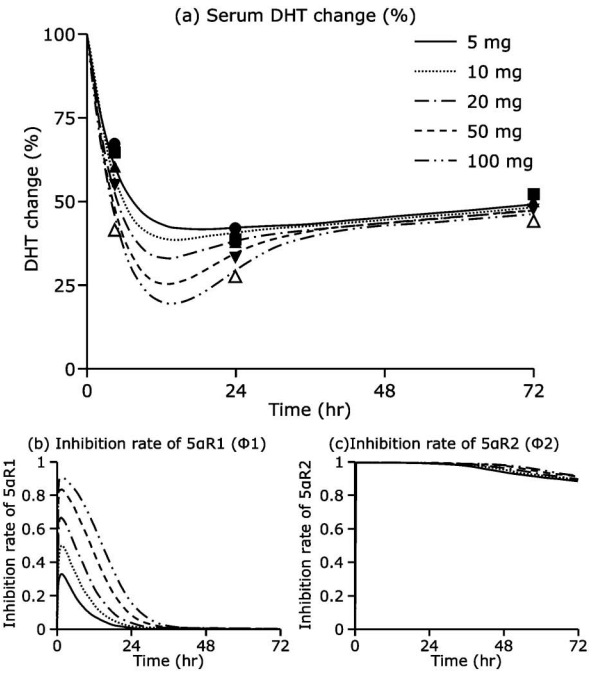

Fig. 5. Serum DHT change (%) and inhibition rate of 5αR after single oral dosing
(a) The closed circles, closed squares, closed triangles, closed inverted triangles and open triangles represent the observed mean values after oral administration of 5 mg, 10 mg, 20 mg, 50 mg and 100 mg finasteride.[7] The lines are model-fit values based on the pharmacodynamic model. (b, c) The lines are the simulated inhibition rates of 5αR1 (*Φ*1) and 5αR2 (*Φ*2) based on the pharmacodynamic model.

Table 3. Pharmacodynamic parameters estimated from the model analysis

Parameter	Estimate	SD
F2	0.574	0.0196
kout (/hr)	0.188	0.0160
Ki1 (nM)	220	13.0

F2; proportion of DHT formed by 5αR2, kout; elimination rate constant of DHT, Ki1; inhibition constant of 5αR1

(**Fig. 5b**), while that of 5αR2 remained almost saturated (**Fig. 5c**).

Simulation of serum DHT change and inhibition rate of 5αR: We simulated the time profile of serum DHT change and inhibition rates of 5αRs after single oral administration of finasteride. The effect on DHT level was estimated to be almost equivalent within the dose range from 0.2 to 5 mg (**Fig. 6**).

Repeated oral administrations of 0.01 or 0.05 mg finasteride decreased serum DHT by only 10 and 30%, respectively (**Fig. 7**). In contrast, repeated oral administrations of 0.2 or 5 mg finasteride to decreased serum DHT concentration by about 60% (**Fig. 7**).

Discussion

In this study, we developed a pharmacokinetic model for finasteride, and obtained pharmacokinetic parameters by fitting it to the time profiles of plasma concentration after oral administration of finasteride 0.2 and 1 mg/day at day 1 and day 17. This pharmacokinetic model successfully described the nonlinear kinetics observed after a single dose and the rise in AUC observed during repeated oral administrations of 0.2 mg (**Fig. 3**). Banyu Pharmaceutical Co., Ltd. also suggests that nonlinear pharmacokinetics of finasteride may be explained with the model considering the binding to 5αR, which is consistent with our study.[10] The values of distribution volume (Vc) and total clearance ($CL_{tot} = ke \cdot Vc$) were calculated to be 74 L and 13 L/hr, respectively. These values are similar to the reported model-independent values, 76 L (range 44–96) and 9.9 L/hr (range 4.2–16.9), respectively.[11]

In the pharmacokinetic analysis, we assumed that the binding of finasteride to 5αR1 is sufficiently small that

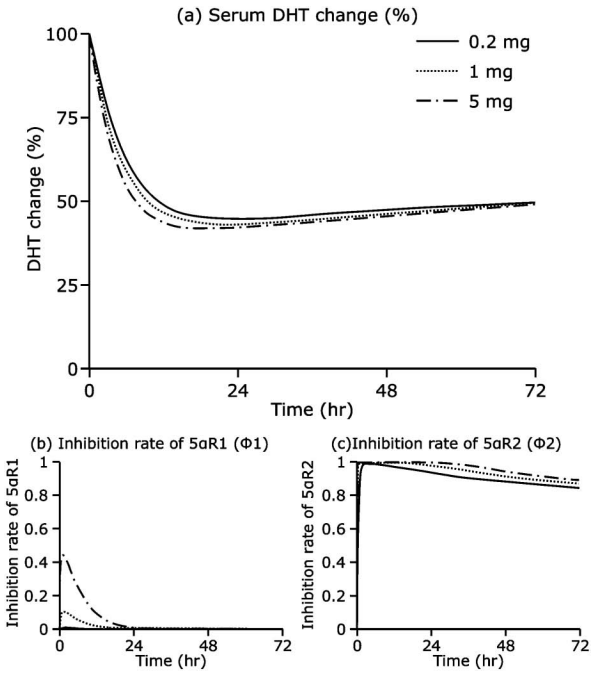

Fig. 6. Changs in serum DHT (%) and inhibition rate of 5αR after single oral dosing of finasteride (0.2–5 mg)
The lines are simulated DHT change (%) (a), inhibition rate of 5αR1 (b), inhibition rate of 5αR2 (c) based on the pharmacodynamic model.

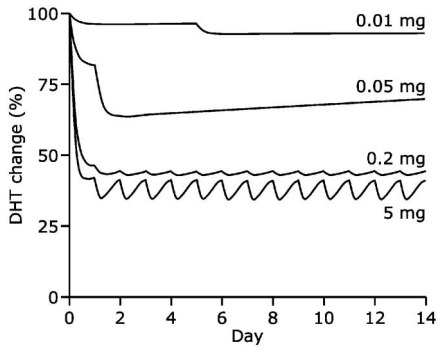

Fig. 7. Changes in serum DHT (%) after 14-day repeated oral administrations of finasteride (0.01–5 mg)
The lines represent the simulated serum DHT change (%) based on the pharmacodynamic model after 0.01 mg, 0.05 mg, 0.2 mg and 5 mg finasteride oral administration once daily for 14 days.

Etot, obtained from the pharmacokinetic analysis, may be taken to reflect the total amount of 5αR2. The results of simulation support the view that inhibition of 5αR1 is negligible in the dose range up to 1 mg (**Fig. 6b**). Etot was estimated to be 320 nmol, but we have no further physiological or biochemical information about the amount of 5αR.

It seems likely that increase in AUC after repeated administration of 0.2 mg finasteride results from the saturation of finasteride binding to 5αR2. At a dose of 1 or 5 mg, 5αR2 was estimated to be almost completely inhibited for 24 hours (**Fig. 6c**), indicating that binding of the inhibitor to the enzyme is saturated. On the other hand, after single administration of finasteride at a dose of 0.2 mg, 5αR2 was estimated to be not fully inhibited (**Fig. 6c**). However, during repeated administration at a dose of 0.2 mg, the binding of finasteride to 5αR2 was estimated to increase gradually to saturation, accompanied by time-dependent increase in AUC.

We assumed that finasteride reversibly inhibits 5αR because it has been reported that finasteride is a competitive inhibitor.[12] Although a possible mechanism-based inhibition has also been proposed,[9,13] the pharmacokinetic model based on irreversible inhibition (koff = 0) failed to converge.

When estimated Ki was corrected for the plasma free fraction of finasteride (15%[6]), the Ki value for 5αR1 (Ki1, f) was calculated to be 33.1 nM. This value was reasonable compared with previously reported Ki1, f (about 300 nM) obtained by in vitro experiment.[5,14,15] Ki2, f was determined by koff/kon/Vc and corrected for plasma protein binding, then calculated to be 0.00129 nM. Ki2, f has been reported to be 2–7 nM using 5αR-expressing cell lines.[5,14,15] This discrepancy may be due to the differences of experimental conditions; *e.g.*, the nonspecific binding of finasteride to cells was not taken into consideration. The proportion of DHT formed by 5αR2 (F2) was estimated to be 0.574. DHT production by male pseudohermaphrodites with inherited 5αR2 deficiency was reported to be 30% of the normal.[16] This is consistent with our result.

We simulated serum DHT profiles after administration of finasteride at a variety of dosages, using the developed pharmacodynamic model and estimated parameters. The simulation indicated that the serum DHT concentration would be reduced by about 10, 30, 60 and 60% after administration of 0.01, 0.05, 0.2 and 5 mg of finasteride, respectively (**Fig. 7**). This implies that the serum DHT-reducing effect of finasteride would reach the maximum at a dose of 0.2 mg in the case of repeated administration. In a clinical study, serum DHT was reduced by 49.5% after administration of finasteride at 0.05 mg/day for 42 days, and by about 70% after 0.2–5 mg/day.[17] These clinical observations are consistent with our simulation results.

In conclusion, the time-dependent increase in AUC during repeated administration of finasteride in the low dose range was well described by the developed pharmacokinetic model. We also constructed a pharmacodynamic model to explain the time profile of serum DHT under various dosage regimens of finasteride. The developed pharmacokinetic/pharmacodynamic model of finasteride is expected to be useful in dosage optimization by predicting plasma concentrations of finasteride and DHT.

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