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Adrenal Effects and Pharmacokinetics of CFC-free Beclomethasone Dipropionate: a 14-Day Dose–Response Study

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Abstract

Since equivalent efficacy is achieved with lower doses of the reformulated beclomethasone dipropionate in the chlorofluorocarbon (CFC)-free propellant HFA-134a (HFA) than with the original CFC-beclomethasone dipropionate formulation, it is possible the HFA-beclomethasone dipropionate may have less safety concerns than the CFC formulation. Despite its chronic use, the steady-state pharmacokinetics of beclomethasone dipropionate has never been studied before. This double-blind study examined adrenal effects and pharmacokinetics after 14 days of dosing with HFA-beclomethasone dipropionate.

Forty-three steroid-naïve asthmatic patients were randomised into 5 parallel groups and dosed every 12 h for 14 days with: HFA-placebo; 200, 400 or 800 $\mu g\,day^{-1}$ HFA-beclomethasone dipropionate; or 800 $\mu g\,day^{-1}$ CFC-beclomethasone dipropionate. After two weeks of dosing, the 24-h urinary free cortisol of all but one patient remained within the normal range, showing that all doses were well tolerated from a systemic safety perspective. The active HFA-beclomethasone dipropionate treatment groups showed a dose-related fall in 24-h urinary free cortisol. Total-beclomethasone (beclomethasone dipropionate and metabolites) pharmacokinetics after either the first dose of HFA-beclomethasone dipropionate or CFC-beclomethasone dipropionate were not substantially affected by subsequent doses. The extent of drug absorption from 800 $\mu g\,day^{-1}$ HFA-beclomethasone dipropionate and CFC-beclomethasone dipropionate was in the ratio of 1·7 : 1. A non-linear correlation between 24-h urinary free cortisol and the pharmacokinetic parameters was observed, reflecting smaller changes in 24-h urinary free cortisol than in pharmacokinetics as the dose was increased.

No clinically meaningful change in the pharmacokinetics of beclomethasone dipropionate plus metabolites was seen on multiple dosing. The greater systemic availability of HFA-beclomethasone dipropionate was still associated with adrenal effects comparable with that of the CFC formulation at the same dose.

The particle size distribution of chlorofluorocarbon (CFC) beclomethasone dipropionate pressurised metered-dose inhalers suggests that a significant portion of the inhaled dose impacts at the back of the throat of a patient and is swallowed (Keller et al 1997; Leach 1998). The environmental mandate to replace CFCs in pressurised metered-dose inhalers afforded the opportunity to develop an improved beclomethasone dipropionate pressurised metered-dose inhaler utilising the CFC-free propellant HFA-134a. This HFA-beclomethasone dipropionate product (Qvar, 3M Pharmaceuticals) has a greater proportion of fine-particle mass, which is expected to result in less drug impacting in the throat and being swallowed and more drug deposited in the large and small airways than with CFC-beclomethasone dipropionate.

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Deposition studies in humans have confirmed these laboratory predictions. Less impaction on the throat and more deposition in the lungs have been shown with HFA-beclomethasone dipropionate than with CFC-beclomethasone dipropionate (Leach 1998). These findings are clinically relevant because recent studies have shown that airway inflammation involves large and small airways (Hamid et al 1997; Thompson 1998). In efficacy

trials, equivalent efficacy has been obtained between CFC-beclomethasone dipropionate and half the beclomethasone dipropionate dose given as the HFA-beclomethasone dipropionate formulation (Fairfax et al 1997; Gross et al 1997; Davies et al 1998). The observation of comparable efficacy with lower doses of HFA-beclomethasone dipropionate supports the concept that increasing total pulmonary deposition of HFA-beclomethasone dipropionate and distributing HFA-beclomethasone dipropionate to the small airways is beneficial in the treatment of asthma.

Since equivalent efficacy is achieved with lower doses, it is possible that HFA-beclomethasone dipropionate may have less safety concerns than CFC-beclomethasone dipropionate. Therefore, the primary objective of this study was to see if the difference in particle size of the two beclomethasone dipropionate pressurised metered-dose inhalers would affect urinary free cortisol levels to different degrees. Effects on adrenal function are viewed as a paradigm of systemic safety for inhaled steroids (Lipworth & Secki 1997). Although beclomethasone dipropionate is used chronically there have been no published studies on steady-state pharmacokinetics of this drug; a second object of the study was to assess beclomethasone dipropionate pharmacokinetics under multiple-dose conditions and at high dose. The highest recommended dose of HFA-beclomethasone dipropionate ($800\,\mu g\,day^{-1}$) was used in the study.

A preliminary report on some of the pharmacokinetic results of this study has been presented (Seale & Harrison 1998).

Materials and Methods

Materials

3M Pharmaceuticals (Northridge, CA) manufactured the HFA-beclomethasone dipropionate and matching HFA placebo inhalers. The CFC-beclomethasone dipropionate (Allen & Hanburys, Research Triangle Park, NC, USA) was obtained from a single commercial lot.

Experimental design

Forty-three non-smoking patients with stable, reversible asthma who had not taken systemic steroids within the previous three months qualified for the study. Eligible patients had a pre-study $FEV_1 \geq 60\%$ of the predicted normal value after a 6-h washout of inhaled beta-agonist, a plasma cortisol concentration in the normal range (≥ 138 nM) and a normal response to an adrenocorticotrophic hormone (ACTH) stimulation test (rapid cosyntropin test). Female patients were not allowed to use oral, parenteral or implanted contraceptives or hormone replacement therapy within three months of the screening visit.

The study was designed as a dose-ranging, placebo-controlled, randomised, parallel group trial. Patients were assigned to one of five study treatments: 200, 400, or $800\,\mu g\,day^{-1}$ HFA-beclomethasone dipropionate; $800\,\mu g\,day^{-1}$ CFC-beclomethasone dipropionate; or HFA-placebo. For the HFA treatments, the investigator and all patients were blinded to the dose level. The protocol was reviewed and approved by an institutional review board and each patient voluntarily signed a written informed consent form.

Dosing began at 0800 h on day 1. Patients were instructed in proper inhalation technique using a 10-s breath hold and took each inhalation 30 s apart. All inhalers delivered $50\,\mu g$ beclomethasone dipropionate/actuation from the valve and were primed before the study. There was no mouth rinse following dosing.

Beginning at 2001 h on day -3 with all patients having an empty bladder, two consecutive 24-h urine collections were used to assess baseline 24-h urinary free cortisol. Additional 24-h urine collections commenced at the same time on days 12 and 13. The urinary free cortisol-to-creatinine ratios were calculated. Plasma samples for cortisol measurement were collected at 0700 and 0900 h on days −2, −1, 13 and 14 and at 0700 h on day 15. Patients remained in the clinic from day −3 to the end of the study. The rapid cosyntropin test was performed as described by the manufacturer (Organon, West Orange, NJ). Serum samples for total-beclomethasone measurement were collected at 0700 h and at 1, 2, 4, 6, 9 and 12 h after the morning dose on days 1 and 14.

Plasma and urine analyses

All analytical methods were validated. Plasma and urine cortisol levels were measured with a radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA). The lower limit of quantitation was $1\,\mu g\,dL^{-1}$ (28 nM). Total beclomethasone, which represented the sum of any beclomethasone dipropionate, monopropionate metabolites and beclomethasone in the serum, was measured by hydrolysing the serum sample and measuring the total beclomethasone released using a liquid chromatograph equipped with triple quadrupole mass spectrometer. This method had a calibration range

of 36–709 pg mL^{-1}. Further details of this method are available elsewhere (Harrison et al 1997).

Data analyses

Eight completers per group for a total of 40 patients were required to give the study a power of 80% to detect a clinically meaningful difference of 25% between the HFA-beclomethasone dipropionate and CFC-beclomethasone dipropionate treatment groups in the primary safety parameter (percent change from baseline 24-h urinary free cortisol). Secondary variables were urinary free cortisol-to-creatinine ratio, plasma cortisol levels, and the rapid cosyntropin test. All analyses presented are based on the intent-to-treat population.

A test for decreasing trend among the groups was performed using Jonckheere's test (Jonckheere 1954). Comparisons of all treatment groups with the 800 μg CFC-beclomethasone dipropionate group were made using 95% confidence intervals. Comparisons of all treatment groups with HFA-placebo were made using Dunnett's test.

Standard pharmacokinetic methods (Gibaldi & Perrier 1982) were used to calculate the following total-beclomethasone parameters: the average steady-state concentration (C_{av}), maximum serum concentration (C_{max}), time of C_{max} (T_{max}) and area under the serum level versus time curve (AUC). Accumulation ratio was calculated as C_{max} at steady state divided by C_{max} on day 1 (Gibaldi & Perrier 1982). Jonckheere's test for increasing trend was used to compare the steady-state concentration and AUC parameters for the HFA-beclomethasone dipropionate treatments. Correlations of 24-h urinary free cortisol with total-beclomethasone steady-state AUC and C_{max} were determined using Pearson correlation coefficients.

Results

Forty patients completed the study, 8 patients per treatment group.

Adrenal effects

The two predose 24-h urine collections were averaged to obtain each patient's baseline 24-h urinary free cortisol value. There was no statistical difference at baseline between the treatment groups in mean 24-h urinary free cortisol values ($P = 0{\cdot}504$).

The two 24-h urinary free cortisol collections at the end of week 2 were combined to give a steady-state 24-h urinary free cortisol. There was a significant trend ($P = 0{\cdot}032$) for progressively greater decreases in the percent change from baseline in steady-state 24-h urinary free cortisol with increasing HFA-beclomethasone dipropionate dose (Figure 1). There was a statistical observation that 400 and 800 μg day^{-1} HFA-beclomethasone dipropionate reduced 24-h urinary free cortisol compared with placebo. The slight fall of 12·2% in 24-h urinary free cortisol following 200 μg day^{-1} HFA-beclomethasone dipropionate was not significantly different from placebo. There was no difference between the 800 μg day^{-1} groups: HFA-beclomethasone dipropionate produced a 37·3% reduction whereas CFC-beclomethasone dipropionate produced a 47·4% reduction in 24-h urinary free cortisol. The same observations were made with regard to the mean absolute change in 24-h urinary free cortisol from baseline.

The reference normal range of 24-h urinary free cortisol was 55–248 nmol $(24\,h)^{-1}$. All patients were within this range at baseline. Despite the observed statistically significant differences between placebo and the three highest dose groups in mean percent change from baseline in 24-h urinary free cortisol, only one patient among all the treatment groups fell below the reference range for this parameter at steady state. That patient entered the study with a 24-h urinary free cortisol level close to the lower end of the normal range and understandably had 24-h urinary free cortisol fall below the normal range after two weeks of dosing with an inhaled steroid.

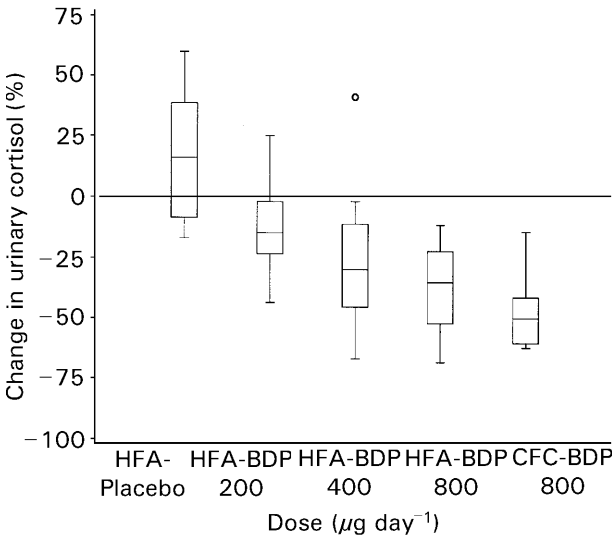

Figure 1. Box plot showing percent change from baseline in 24-h urinary free cortisol with respect to daily dose of beclomethasone dipropionate administered by metered-dose inhaler containing either CFC-free propellant (HFA-BDP) or conventional CFC propellant (CFC-BDP). The central line in each box represents the median value; the upper and lower lines represent the 75th and 25th percentiles. The bars represent the minimum and maximum values; the circle represents the one outlier that was greater than 1·5 times the length of the box.

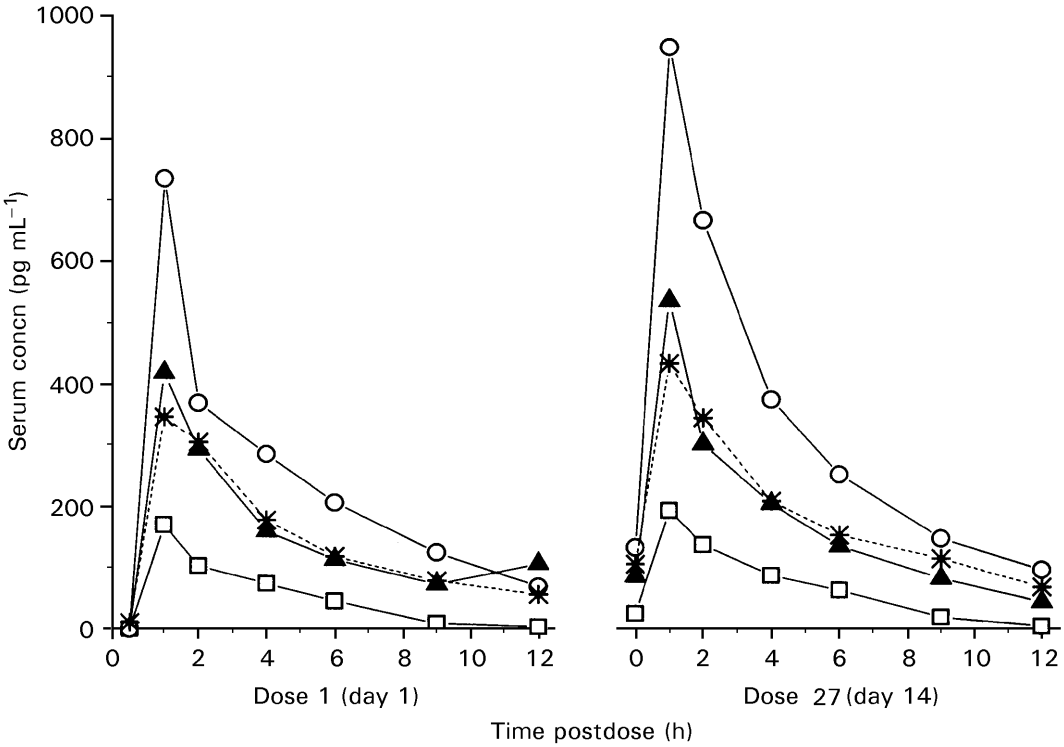

Figure 2. Mean total-beclomethasone concentrations; beclomethasone dipropionate administered dose was half the daily dose. □, 100 μg HFA (beclomethasone dipropionate in CFC-free propellant); ▲, 200 μg HFA; ○, 400 μg HFA; *, 400 μg CFC (beclomethasone dipropionate in CFC propellant).

Comparison of the urinary free cortisol-to-creatinine ratios, plasma cortisol levels at 0700 and 0900 h and mean change from pre-injection plasma cortisol at 30 and 60 min after stimulation with cosyntropin were not as sensitive to dose variations. No significant differences with any of these tests were detected between placebo and any of the active treatments.

Serum levels of total beclomethasone

Mean total-beclomethasone serum profiles are presented in Figure 2 for the groups that received drug. The highest concentrations of total beclomethasone were seen at the first blood sampling time (1 h) in almost all patients in the active treatment groups. The derived pharmacokinetic parameters (Table 1) showed that the rate and extent of total-beclomethasone absorption increased with increasing doses of HFA-beclomethasone dipropionate ($P < 0{\cdot}0001$). The extent of drug absorption (steady-state AUC values) from 800 μg day^{-1} HFA-beclomethasone dipropionate and CFC-beclomethasone dipropionate was in the ratio of 1·7 : 1.

Table 1. Total-beclomethasone pharmacokinetic parameters.

Dose[a] (μg)	Single dose (dose 1)[b]		Steady state (dose 27)[b]			Accumulation ratio[c]
	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	C_{av} (pg mL^{-1})	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	
200 HFA	170 (100·5)	571 (302·7)	66 (15·0)	197 (83·9)	792 (179·7)	1·4 (0·8)
400 HFA	455 (159·3)	1958 (799·3)	176 (67·0)	539 (237·9)	2113 (804·4)	1·1 (0·4)
800 HFA	736 (252·1)	2854 (897·8)	333 (130·1)	953 (358·8)	3999 (1561·6)	1·3 (0·4)
800 CFC	374 (196·3)	1782 (867·3)	188 (58·4)	439 (187·5)	2256 (700·7)	1·7 (1·5)

Results are means(s.d. in brackets). [a]Dose, daily dose of beclomethasone dipropionate administered by metered-dose inhaler with either chlorofluorocarbon-free propellant (HFA) or CFC propellant (CFC). [b]Morning dose, half the daily dose. [c]Accumulation ratio = C_{max} steady state/C_{max} single dose.

In most cases, the predose samples drawn on day 1 had no quantifiable total beclomethasone ($<36\,pg\,mL^{-1}$); however, the samples drawn on day 14 did, indicating some accumulation upon multiple dosing. There was no statistical difference among the accumulation ratios for the active treatment groups (Table 1).

Relationship between 24-h urinary free cortisol and serum total beclomethasone

Correlation coefficients were computed between the change from baseline of the different indicators of adrenal function and the steady-state pharmacokinetic parameters of total beclomethasone. The highest correlation was obtained between the percent change from baseline in 24-h urinary free cortisol and steady-state total beclomethasone AUC (Figure 3). A moderate correlation ($r = -0{\cdot}56$) was found, indicating that as the AUC increased, the percent change from baseline in 24-h urinary free cortisol decreased, although not in a linear manner. For example, doubling of the AUC from 2000 pg hour mL^{-1} to 4000 pg hour mL^{-1} resulted in only about a 10% change in the 24-h urinary free cortisol. A similar correlation was seen between 24-h urinary free cortisol and C_{max}.

Adverse events

Four patients reported an adverse event. Three patients were withdrawn because of fever that was not related to the study treatment. The fourth patient, receiving $400\,\mu g\,day^{-1}$ HFA-beclomethasone dipropionate, reported nausea following dosing that was considered probably or possibly related to study medication. One of the patients who reported fever and was withdrawn (in the placebo group) also reported pharyngitis.

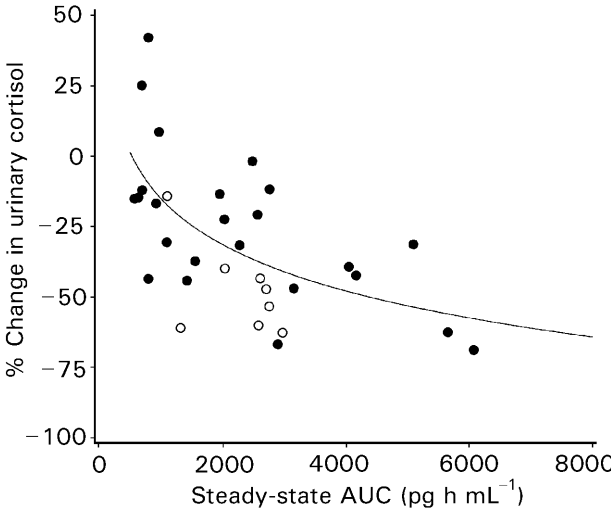

Figure 3. Correlation of total-beclomethasone AUC and percent change from baseline in 24-h urinary free cortisol on day 14 for each treatment in each patient. ○, CFC-beclomethasone diproprionate; ●, HFA-beclomethasone dipropionate (CFC-free preparation).

Discussion

Dosing for two weeks with up to $800\,\mu g\,day^{-1}$ HFA-beclomethasone dipropionate did not result in decreases in 24-h urinary free cortisol outside of the normal range, demonstrating that all doses were well tolerated from a systemic safety perspective. As expected, there was a significant trend for progressively greater decreases in the percent change from baseline in 24-h urinary free cortisol with increasing HFA-beclomethasone dipropionate dose.

The novel finding of this study was the lack of relevance of serum levels of total beclomethasone to drug effect on adrenal function. Despite there being a large and significant difference in the systemic availability of beclomethasone dipropionate plus metabolites resulting from dosing with $800\,\mu g\,day^{-1}$ HFA-beclomethasone dipropionate and CFC-beclomethasone dipropionate, no statistically significant difference was observed in 24-h urinary free cortisol. The correlation between 24-h urinary free cortisol and pharmacokinetics was non-linear, reflecting smaller changes in urinary free cortisol than in pharmacokinetics as the dose was increased.

Morning plasma cortisol levels were variable among the patients and we were not able to detect differences among the treatments studied. Measurement of the reserve cortisol pool rather than unbound cortisol following a bolus injection of cosyntropin also did not show any differences or trends among the treatments studied.

Twenty-four-hour urinary free cortisol was selected as the primary parameter to assess adrenal effects (Lipworth & Secki 1997). To make the results more relevant to long-term safety, a 14-day dosing interval was used, which is longer than in most other dose–response studies of adrenal effects. To reduce variability of this parameter, two 24-h urine collections were performed and averaged at predose and at steady state. Patients remained in the clinic throughout the study, so that all dosings could be monitored for compliance and good inhalation technique, and all urine collections could be assured to be complete. To further reduce bias, all HFA doses were administered blinded and both a placebo and a CFC-beclomethasone dipropionate reference were included as negative and positive controls, respectively.

Total beclomethasone was an appropriate measure of beclomethasone dipropionate pharmacokinetics since greater than 75 percent of the total-beclomethasone concentration in serum at all times consisted of beclomethasone 17-monopropionate (Falcoz et al 1996). This component is the most pharmacologically active moiety and is associated with most of the efficacy (Würthwein & Rohdewald 1990). The remaining components of the total-beclomethasone fraction, namely beclomethasone dipropionate, beclomethasone 21-monopropionate and beclomethasone free base, all have pharmacological activity and are presumed to contribute to the activity of the drug. Thus, the total-beclomethasone analysis summed all the active components derived from beclomethasone dipropionate.

The pharmacokinetics of total beclomethasone after administration of the first dose of either HFA-beclomethasone dipropionate or CFC-beclomethasone dipropionate was not substantially altered by the administration of subsequent doses. Good proportionality was observed among the inhaled HFA-beclomethasone dipropionate doses. Our additional clinical experience with HFA-beclomethasone dipropionate has been that pharmacokinetic linearity is maintained with inhaled single doses of HFA-beclomethasone dipropionate as high as 1600 μg (equivalent to 3200 $\mu g\,day^{-1}$) (Harrison et al 1997).

A previous single-dose study predicted an accumulation ratio of 1·33 with twice-daily dosing based on the estimated 6-h half-life of beclomethasone dipropionate metabolites (Harrison et al 1996). In the present study, the total-beclomethasone accumulation ratio in serum at steady state was the same as that predicted from the single-dose study and was without clinical consequence, having no significant effect on the serum profiles of any dose group. This is in contrast to fluticasone propionate, which has been shown to have a significant drug accumulation in the plasma upon multiple dosing (Thorsson et al 1997), which, in turn, results in increased systemic safety risk (Lönnebo et al 1996; Clark & Lipworth 1997). The longer plasma elimination half-life, extensive tissue binding and prolonged receptor binding of fluticasone were likely causes of this result (Clark & Lipworth 1997).

Because the objective of this study was to maximise the changes in adrenal function to better assess safety with respect to the new HFA-beclomethasone dipropionate formulation, steroid naïve patients were enrolled. It is recognised that this patient group is the most sensitive population of asthmatics to steroid-induced changes in adrenal function (Barnes 1998). It is likely that less change in adrenocortical function in response to inhaled corticosteroids would be seen in patients with moderate to severe or steroid-resistant asthma.

In conclusion, results of all analyses were consistent in demonstrating that 200–800 $\mu g\,day^{-1}$ HFA-beclomethasone dipropionate is at least as favourable as 800 $\mu g\,day^{-1}$ CFC-beclomethasone dipropionate, with regard to adrenal suppression, as measured by 24-h urinary free cortisol. No clinically significant accumulation of beclomethasone dipropionate and metabolites was seen with multiple doses of HFA-beclomethasone dipropionate. The increased total-beclomethasone serum levels observed with HFA-beclomethasone dipropionate compared with the same dose of CFC-beclomethasone dipropionate were not associated with systemic safety concerns.

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