A New Solution-Based Intranasal Triamcinolone Acetonide Formulation in Patients with Perennial Allergic Rhinitis: How Does the Pharmacokinetic/Pharmacodynamic Profile for Cortisol Suppression Compare with an Aqueous Suspension-Based Formulation?

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The present study was undertaken to describe the pharmacokinetics of a new solution-based intranasal triamcinolone acetonide formulation (Tri-Nasal®) in patients with perennial allergic rhinitis and to use a pharmacokinetic/pharmacodynamic (PK/PD) simulation approach to compare the potential effects on plasma cortisol with that of an aqueous suspension-based nasal triamcinolone acetonide formulation (Nasacort® AQ). Data from an open-label, randomized, three-way crossover study in patients with perennial allergic rhinitis receiving three doses (100, 200, and 400 μg) of a nasal solution-based triamcinolone acetonide formulation (Tri-Nasal®) over 7 days were used to describe the pharmacokinetics of this formulation. Available literature data for a suspension-based aqueous triamcinolone acetonide formulation (Nasacort® AQ) were used to describe its pharmacokinetic profile after similar single doses of 110, 220, and 440 μg. A PK/PD simulation approach was used to predict the anticipated cumulative cortisol suppression (CCS) of these two formulations. These simulations suggested a cortisol suppression of 8% to 16% for the single and steady-state doses of the solution-based product. Similar CCS estimates were predicted for equivalent doses of the aqueous suspension-based triamcinolone acetonide formulation with no difference between both formulations. Post hoc power analysis suggested that the predicted cortisol suppression is not likely to be significant for either preparation, including the clinically recommended doses of 200 and 220 μg of the solution-based and suspension-based formulations, respectively. In summary, based on the results of this PK/PD simulation, the plasma levels observed after nasal administration of the solution or the aqueous suspension are unlikely to induce a clinically relevant cortisol suppression, especially for the recommended dosing regimens of 200 and 220 μg/day.

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According to the American Academy of Allergy, Asthma, and Immunology, approximately 40 million persons in the United States suffer from allergic rhinitis. The typical symptoms of itching, sneezing, nasal congestion, and runny nose are unpleasant and significantly affect the patient's quality of life. Because of their effectiveness and high safety profile, intranasal glucocorticoids are the first-line treatment in the management of seasonal and perennial allergic rhinitis.[1,2]

A new aqueous, solution-based triamcinolone acetonide formulation (Tri-Nasal®) has recently been approved by the Food and Drug Administration (FDA) for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis. The formulation delivers 50 μg of triamcinolone acetonide (TAA) via a metered-dose manual spray pump and has a recommended daily dose of 200 μg (100 μg per nostril) given once a day. The efficacy of this solution-based formulation has been studied in patients with seasonal and perennial allergic rhinitis.[3] Comparable with studies for other nasal triamcinolone acetonide formulations, the solution-based formulation at daily doses of 100 to 400 μg significantly reduced nasal symptoms, including sneezing, congestion, stuffiness, rhinorrhea, and itching, when compared to placebo.[3]

Despite the favorable safety profile of intranasal glucocorticoids, some systemic side effects, such as growth retardation and changes in bone density, may be possible. Suppression of serum cortisol is currently judged as a good surrogate marker for such systemic effects. Pharmacokinetic/pharmacodynamic (PK/PD) models of serum cortisol suppression have been shown to be predictive in evaluating the degree of these effects. The aim of this study was to evaluate the pharmacokinetics of Tri-Nasal® in patients with perennial rhinitis after single dosing and at steady state and to apply the generated PK profiles for a PK/PD-based simulative assessment of potential cortisol suppression. For comparison, the same approach was used to evaluate a suspension-based triamcinolone acetonide formulation.

MATERIALS AND METHODS

Pharmacokinetics after Administration of Triamcinolone Acetonide (TAA) in Solution

The pharmacokinetic profiles of the solution-based product were evaluated in 28 patients with a history of perennial allergic rhinitis (10 females). This three-way crossover study, which was approved by an institutional review board, included subjects with a mean age of 28.3 years (range: 19-40 years), mean height of 175 cm (range: 163-191 cm), and a mean weight of 75.4 kg (range: 51.3-100.7 kg). Patients received each of the following treatments in a randomized crossover fashion. Treatment 1 consisted of 100 μg Tri-Nasal® (triamcinolone acetonide, 0.5 mg/ml nasal solution, 50 μg/actuation) dosed as 1 spray per nostril daily for 7 days. Treatment 2 consisted of 200 μg TAA dosed as two sprays per nostril daily for 7 days. Treatment 3 consisted of 400 μg TAA dosed as four sprays per nostril daily for 7 days. There was a 16-day washout period between treatments.

On each treatment day, the patients received their assigned drug treatment in the morning following an 8-hour fast. No food or beverages, with the exception of water, were consumed until the 2-hour blood sample was taken, after which a light breakfast was served; lunch was provided 5 to 6 hours after dosing, while dinner was supplied 10 to 12 hours after dosing. A light snack was also offered in the evenings. All meals were of low fat content, and the same menu was served on corresponding days of each study period. Skim milk was available, as well as beverages without caffeine and alcohol.

On the designated pharmacokinetic evaluation day (day 1 and day 7 of a given study period), 7 ml venous blood samples were drawn into evacuated tubes containing EDTA at the following time points: 0 (predose); 5, 10, and 30 minutes; and after 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours. In addition, a trough blood sample was taken on the morning of day 6. Blood samples were centrifuged to obtain plasma and stored at –70°C until they were shipped on dry ice to the analytical facility. A validated high-performance liquid chromatography (HPLC)/radioimmunoassay (RIA) procedure was used to determine TAA in human plasma with a lower limit of quantification (LOQ) of 100 pg/ml. Aliquots of plasma sample were extracted with ethyl acetate, and the organic layer was evaporated to dryness under vacuum. The reconstituted samples were injected onto a reverse-phase HPLC system using a C18 reversed phase column (Sperisorb ODSII, Aldrich) and mixture of water and acetonitrile (62.5:37.5, v:v) as mobile phase. The TAA-containing fraction was collected, concentrated under vacuum, and assayed by RIA using an antiserum previously characterized by Haack and Vecsei.[4] The LOQ was set as 0.1 ng/ml. Intraday variability, assessed on three different occasions, was between 4.7% and 24.9% (mean = 11%) for 0.1, 0.15, 0.35, 0.75, and 1.5 ng/ml quality control samples. Accuracy was between 85.6% and 121.6%. Average interday variability was 18.8, 16.8, 18.7, 12.5, and 8.8 (mean = 15.1%) for 0.1, 0.15, 0.35, 0.75, and 1.5 ng/ml quality controls, respectively. Accuracy for these samples was between 100.9% and 109.6% (mean = 106.7%).

Data obtained for the solution-based formulation on day 1 and day 7 were analyzed by noncompartmental pharmacokinetic analysis. CL/f was calculated from dose and $AUC_{0-\infty}$. Analysis of variance (ANOVA) for the pharmacokinetic variables was performed using a stan-

dard three-period crossover design with effects for sequence, period, and dose. A Tukey multiple comparisons procedure was used to compare pairs of doses. Two one-sided tests of equivalence (TOST) were also used to compare the different doses. Twenty percent was taken as equivalence criteria. This statistical analysis was conducted by Dr. Alan Bostrom (Crunch Software Corporation, San Francisco).

The average kinetic data after administration of the three doses of Tri-Nasal® were also fitted to a one-compartment body model with first-order absorption. These fits were subsequently used within the PK/PD simulations.

Pharmacokinetics of the Suspension-Based Formulation

Pharmacokinetic profiles after administration of 110, 220, and 440 µg Nasacort® AQ were constructed from literature data using published t_{max}, C_{max}, and k_e values in a one-compartment body model with first-order absorption.[3,5] This was necessary as these were the only data available for this preparation, and detailed concentration-time profiles have not yet been published for Nasacort® AQ. The correctness of the fits (Figure 1) was verified by comparing the resulting AUC estimates with the published literature values. Differences between simulated and published AUC estimates were less than 2%. The pharmacokinetic parameters were subsequently used within the PK/PD-based simulations.

Evaluation of Pharmacodynamic Effects on Cortisol

A previously published indirect response model was applied to predict the potential pharmacodynamic effects on cortisol suppression induced by Tri-Nasal® and Nasacort® AQ.[6]

For the PK/PD modeling of both preparations, the concentration-time profiles for total drug generated by the compartmental model (see above) were transformed into the free TAA concentration (C_f^{TAA}) using a fraction unbound of 0.29.[7]

In the absence of exogenous stimuli, a linear release model can adequately describe the circadian rhythm of endogenous cortisol release, with a maximum in the morning and a minimum around midnight.[6] This approach describes the increase and decrease of daily cortisol release R_C with two straight lines, characterized by the maximum cortisol release R_{max} at time t_{max} and no cortisol release at time t_{min}. The resulting change in total cortisol serum concentration C_{tot}^{Cort} is described by equation (1), where k_e^{Cort} is the first-order elimination rate constant for cortisol.

$$\frac{dC_{tot}^{Cort}}{dt} = R_C - k_e^{Cort} \bullet C_{tot}^{Cort}. \quad (1)$$

Cortisol release after triamcinolone acetonide was described by

$$\frac{dC_{tot}^{Cort}}{dt} = R_C \bullet \left(1 - \frac{C_f^{TAA}}{EC_{50} + C_f^{TAA}}\right) - k_e^{Cort} \bullet C_{tot}^{Cort}, \quad (2)$$

where C_f^{TAA} is the free triamcinolone acetonide concentration in plasma, EC_{50} is the free TAA concentration that reduces R_C to 50% of the baseline value, C_{tot}^{Cort} is total cortisol concentration, and k_e^{Cort} is the elimination rate of cortisol. As the maximum suppression of cortisol release (I_{max}) had been set to 1 (100%), this term is not shown in equation (2). Simulations were performed with Scientist 2.0 (Micromath, Salt Lake City, UT, 1995).

The area under the simulated cortisol concentration-time curve (AUC) was calculated using the trapezoidal rule for a 24-hour period. The cumulative cortisol suppression (CCS) was calculated from simulated data for placebo (equation (1)) and treatment data (equation (2)) according to

$$CCS = 100 \bullet \frac{AUC_{placebo} - AUC_{treat}}{AUC_{placebo}}, \quad (3)$$

where $AUC_{placebo}$ is the AUC for placebo data and AUC_{treat} is the AUC after triamcinolone acetonide administration. Estimates for R_{max} (2966 µg/ml), t_{min} (16.2 h), t_{max} (20.7 h), k_e^{Cort} (0.64 h^{-1}), V_c (33.7 L), and EC_{50} (0.21 ng/ml) were taken from the literature.[7,8] A one-sided power analysis was performed by SAS (version 6.12, SAS Institute, Cary NC) to statistically assess the predicted cortisol suppression (power: 0.8, p = 0.05, n = 28, 25% variability of placebo and active treatment AUC estimates for the 24-h cortisol concentration-time profile).

RESULTS

Figures 1A-C show the mean plasma TAA concentration-time profiles for day 1 and day 7 for the 100 µg, 200 µg, and 400 µg doses of Tri-Nasal®. The noncompartmental pharmacokinetic parameters are summarized in Table I. Although plasma samples were collected over a 24-hour period, the limit of detection was approached for the majority of patients after 4 to 8 hours, and data are shown here only for this time period. Trough values on day 6, day 7, and day 8 (24-h value of day 7) were be-

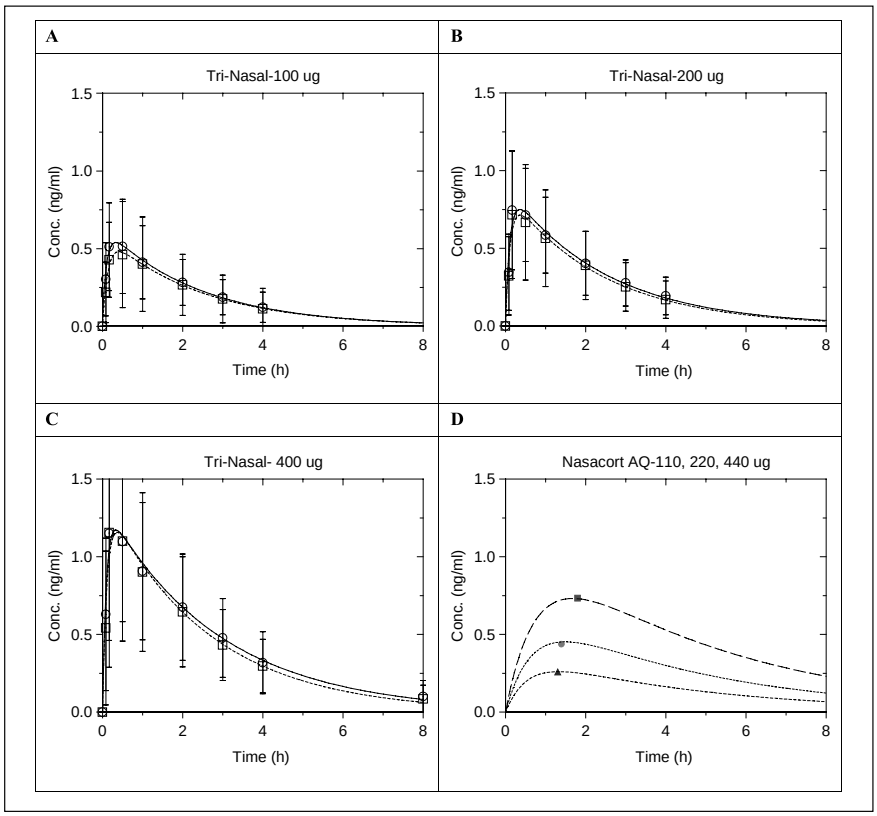

Figure 1. Triamcinolone acetonide (TAA) plasma concentration-time profiles after administration of 100 µg (A), 200 µg (B), and 400 µg (C) of TAA (Tri-Nasal®). Squares in A-C represent data for the first dosing (day 1, ---); circles represent profiles of the last dosing day (day 7, —). Figure 1D illustrates fits obtained from literature estimates on C_{max}, t_{max}, and k_{term} for the application of 110 µg TAA (▲), 220 µg TAA (●), and 440 µg TAA (■) as Nasacort® AQ in patients with perennial rhinitis.[5] Fits (based on a one-compartment body model with first-order absorption) were used to predict 24-hour cortisol suppression.

low the limit of detection for all of the patients for all the doses tested, indicating the lack of any accumulation of the drug. There were no statistically significant differences in C_{max} and $AUC_{0-\infty}$ between day 1 and day 7. The lack of TAA accumulation suggests that steady state was achieved instantaneously. ANOVA analysis indicated dose-dependent statistical differences in AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. Furthermore, dose-adjusted estimates for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ parameters as analyzed by TOST showed a lack of equivalence. This suggests a lack of dose linearity. The main PK parameters for the solution-based product were compared with literature data of the aqueous solution-based product.

The average pharmacokinetic concentration-time profiles of the solution-based product were fitted to a one-compartment body model with first-order absorption (for fits, see Figure 1). In addition, literature data for the aqueous suspension-based formulation (110 µg, 220 µg, 440 µg; for PK fit, see Figure 1) were used to predict the equivalent concentration-time profile for a single dose (see Materials and Methods section). These fits were used to predict the potential cortisol suppression of both TAA formulations using the PK/PD model described in the Materials and Methods section. Figure 2 compares the resulting 24-hour cortisol plasma levels after active treatment with baseline levels (no treatment) for day 1 (100 µg: A1, 200 µg: A2, 400 µg: A3) and day 7 (shown for the 200 µg dose in Figure 2B) for the solution-based product. Simulations were also performed to convert previously published pharmacokinetic profiles for equivalent doses of aqueous suspension-based TAA into corresponding cortisol suppression data (shown for the 220 µg dose in Figure 2C). These simulations were performed only for single-dose administrations, as the available PK data were too limited to predict the multiple dosing situation. For the highest doses of both preparations, the resulting cortisol suppression estimates were less than 20% and between 10% and 13% for the clinically recommended doses of 200 and 220 µg TAA after administration of the solution and suspension-based formulations, respectively. Post hoc analysis of these data, assuming an interindividual variability of 25%, suggested that dif-

Table I Mean Pharmacokinetic Parameters (n = 28) after Single Once-Daily Dosing of 100, 200, and 400 µg of Triamcinolone Acetonide Given as Tri-Nasal® on Days 1 and 7

	Day 1			Day 7		
Parameter	**100 µg**	**200 µg**	**400 µg**[a]	**100 µg**	**200 µg**	**400 µg**
C_{max} (ng/ml)	0.52 (0.34)	0.77 (0.42)	1.27 (0.85)	0.57 (0.31)	0.80 (0.37)	1.26 (0.67)
t_{max} (h)	0.41 (0.30)	0.48 (0.62)	0.40 (0.28)	0.38 (0.24)	0.39 (0.24)	0.42 (0.29)
$AUC_{0\text{-}t}$ (ng•h/ml)	1.20 (1.16)	1.86 (1.18)	3.35 (2.18)	1.29 (0.89)	2.08 (1.15)	3.56 (2.16)
$AUC_{0\text{-}\infty}$ (ng•h/ml)	1.54 (1.30)	2.25 (1.29)	3.83 (2.27)	1.68 (0.95)	2.58 (1.26)	4.09 (2.21)
MRT (h)	3.2 (1.6)	3.9 (4.4)	3.5 (1.1)	4.5 (3.9)	3.8 (1.1)	3.6 (0.9)
k_{term} (h^{-1})	0.40 (0.15)	0.42 (0.18)	0.33 (0.10)	0.37 (0.12)	0.31 (0.12)	0.32 (0.11)

Values are given as mean (± *SD*).
a. n = 26.

ferences between placebo and active treatment were not statistically significant for any of the dosing regimens tested. No statistical differences were predicted between the two formulations.

DISCUSSION

Potential systemic side effects of topical glucocorticoid therapy include growth retardation in children, reduc-

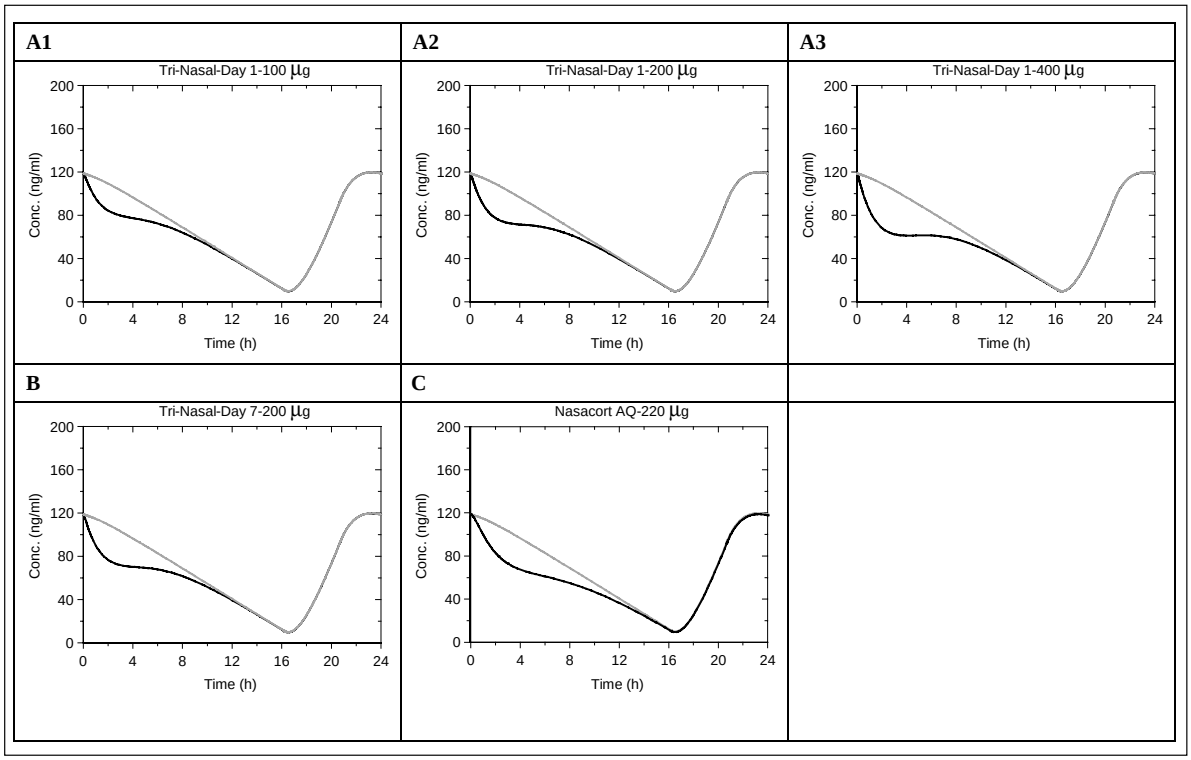

Figure 2. Predicted hydrocortisone serum levels after nasal administration of triamcinolone acetonide (TAA) (solid lines): results are shown for the administration of a single dose of 100 µg (A1), 200 µg (A2), and 400 µg Tri-Nasal® on day 1 (A3), 400 µg Tri-Nasal® on day 7 (B), and after administration of a single dose of 440 µg TAA after administration of Nasacort® AQ (C). TAA plasma concentrations in Figure 1 were used to predict the change of cortisol plasma levels from baseline (---). Simulations were performed with the PK/PD model described in the Materials and Methods section and previously described pharmacodynamic parameters for cortisol suppression of TAA.[7]

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