CHARACTERIZATION OF CORTISOL CIRCADIAN RHYTHM AND LACK OF CORTISOL SUPPRESSION BY A NEW CORTICOSTEROID, CICLESONIDE

M. Pfister MD, S. Krishnaswami PhD, S. Rohatagi PhD MBA
Aventis Pharmaceuticals, Bridgewater, NJ 08807, US

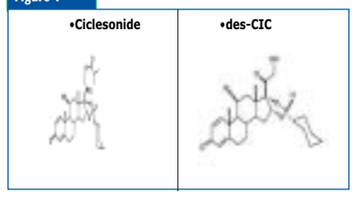
ABSTRACT

Ciclesonide (CIC) is a new inhaled glucocorticoid for the treatment of asthma that is converted into the active metabolite desisobutyryl-CIC (des-CIC) in the lungs. Study objectives were to characterize the circadian rhythm of endogenous cortisol release and to quantify the effect of systemic des-CIC concentrations on the endogenous cortisol release. Data from 12 Phase I and 3 Phase III studies in adults and 2 Phase III studies in pediatrics were pooled. A one-compartment model with first order absorption adequately described the des-CIC concentration–time profile. A simple one-compartment model with first order absorption, an endogenous "pre-dose" cortisol concentration at dose-interval and a lag-time based on a fixed, hypothetical cortisol dosing time of 10 PM could adequately characterize the circadian rhythm of endogenous cortisol release and was superior to other models such as the cosine model. The doses of CIC (up to 1280 μg) and the AUC were not significant covariates for cortisol concentrations suggesting negligible effects on endogenous cortisol concentrations. With an E_{max} model, an EC_{50} of des-CIC of 1.96 ng/mL was estimated. Less than 1% of all observed des-CIC concentrations are higher than the EC_{50}, indicating a negligible effect of des-CIC on cortisol concentrations.

BACKGROUND

- Ciclesonide (CIC), an inactive parent compound that is activated primarily in the lung to the active metabolite, C21-desisobutyryl-CIC (des-CIC) (Figure 1), is a novel inhaled corticosteroid that has low oral bioavailability, high systemic clearance, and high protein binding. CIC has been shown to be safe and effective for the treatment of mild, moderate, and severe asthma in clinical trials (Postma, 2001; Engelstatter, 2002).
- Ciclesonide has low local and systemic side effects, while maintaining high anti-asthmatic activity (Weinbrenner et al, 2002, LaForce AAAAI 2003, Bernstein AAAAI 2004).
- When inhaled corticosteroids are used, every attempt is made to localize activity within the lung and to minimize systemic absorption.
  - Suppression of endogenous cortisol production is a major systemic side-effect of inhaled corticosteroids (Moellman, 1995; Lipworth, 1998; Koopmans, 1992). Cortisol concentration measurements in urine and serum are suitable markers to quantify systemic corticosteroid activity.
  - However, precise quantification of cortisol suppression is complex due to marked circadian rhythm in cortisol release, with cortisol reaching a peak in the morning (6 to 10 am) and a trough at night (8 pm to 2 am) (Moellman, 1995; Lipworth, 1998; Koopmans, 1992).
  - Hence, to employ cortisol as a marker for systemic safety, there is a need for accurate characterization of endogenous cortisol concentrations in the presence or absence of treatment with corticosteroids.

Figure 1



- Several Phase I studies were conducted to characterize the pharmacokinetics (PK) of des-CIC in healthy subjects as well as in subjects with mild asthma and other conditions, and a pooled analysis of population PK in those studies was conducted previously (Rohatagi, 2003).
  - Body weight was the only significant covariate that influenced PK parameters in that study.
  - Since then, additional clinical studies have been completed using ciclesonide in a metered dose inhaler (MDI) to assess its safety and efficacy in the treatment of mild, moderate, and severe asthma.
  - Furthermore, PK and pharmacodynamic (PD) data from phase III studies in pediatric populations have become available.
  - Ciclesonide has only 1/100 the binding affinity for the glucocorticoid receptor compared to des-CIC (Rohatagi, 2003) and des-CIC is the major circulating metabolite of ciclesonide.

OBJECTIVES

- This analysis pooled PK/PD data for des-CIC from Phase I and III studies to
  - Describe circadian cortisol concentrations, and
  - To characterize the relationship between systemic exposure to des-CIC and endogenous cortisol release.

DATA AND METHODS

- Demographic and PK/PD data from 12 Phase I, 3 Phase III studies in adults and 2 Phase II studies in pediatrics (ex-actuator dose: 40-2880 μg) were pooled for analysis by NONMEM.

Table 1. Demographic Characteristics

Covariate	Category	Distribution, N (%)*
Gender	Male	300 (47.2)
	Female	310 (48.8)
Population	Healthy	180 (28.3)
	Mild-Moderate Asthmatics	253 (39.8)
	Severe Asthmatics	105 (16.5)
Race	White	471 (74.2)
	Japanese	72 (11.3)
	Black	20 (3.1)
	Other	72 (11.3)
Age	Children (≤12 years)	53 (8.3)
	Adults (12 – 65 years)	536 (84.4)
	Elderly (≥65 years)	21 (3.3)

*Note: not all percentages add up to 100%, since not all data was available across the studies

DATA AND METHODS - ANALYTICAL METHODS

- Concentrations of ciclesonide and des-CIC were determined in serum samples using solid-phase extraction and reversed-phase HPLC with tandem mass spectrometric detection (LC/MS/MS) as described previously (Rohatagi JCP, 2003).
  - The lower limit of quantification (LLOQ) was 25 pg/mL for ciclesonide and 10-25 pg/mL for des-CIC. The upper calibration limit for both analytes was 2000 pg/mL.
- For Phase I studies, serum cortisol was measured using a commercially available fluorescence polarization immunoassay (TDxFlx, Abbott, Wiesbaden, Germany), with a LLOQ of 25 ng/mL. For Phase III studies, serum cortisol was measured using radioimmunoassay (LLOQ of 7.24 ng/mL).
- Data were analyzed using non-linear mixed-effects modeling with NONMEM software, version V level 1.1, NM-TRAN version III level 1.0, and PREDPP version IV level 1.0 on a Linux cluster system with Kernel version 2.4.18 based on SuSe Linux 8.0 and a g77 compiler. Graphical representations useful for model diagnoses were produced from NONMEM generated tables with S-Plus software, version 6.1 running under UNIX.
- A one compartment model was selected for the PK modeling and only weight and liver status were covariates of interest but not of clinical significance (data not shown).
- The principle of parsimony was applied to the model development.
- Diagnostic plots, point and interval estimates of parameters, and minimum value of the objective function were used to guide model building and assess goodness-of-fit.
- The selection of an appropriate pharmacostatistical model was based on:
  - A significant reduction in the objective function value based on the Likelihood Ratio Test or Akaike Information Criterion (AIC).
  - A decrease in standard error, inter-individual variance of the parameters, and residual error.
  - Diagnostic plots such as PRED versus DV, RES and WRES versus PRED, and IPRED versus DV, where DV stands for dependent variable i.e. the plasma/serum concentration (PK/PD), PRED (IPRED) denote NONMEM predictions using either population (individual) parameters and RES (WRES) denotes (weighted) residuals.

METHODS - CORTISOL BASELINE

- For PD analyses of diurnal cortisol levels, a one-compartment model with first-order elimination and first order input (constant rate of cortisol release) was fitted to plasma/serum cortisol concentrations.
- In addition, endogenous trough plasma/serum cortisol concentrations (C_{trough}) were estimated at each dose interval. Cortisol "dose" (total daily endogenous cortisol release) was arbitrarily set to 100 μg, with a hypothetical "dosing" time at 10 pm.
- Inclusion of a lag-time into the pharmacodynamic model allowed the estimation of administration time (i.e., onset of endogenous cortisol production).
- The inter-individual (IIV) was modeled as in equation 1, and inter-patient variability for all parameters was modeled the same way. Residual variability was modeled as additive and proportional.

METHODS - EFFECT OF EXOGENOUS CORTICOSTEROID-1

- Ciclesonide dose and des-CIC AUC were included as a covariate on cortisol clearance (CL) to assess the effect of ciclesonide on cortisol concentrations.
- The parameter-covariate relationship between ciclesonide dose and serum cortisol was modeled as follows:

$$\hat{TVCL}_X = \theta_1 + \theta_x Dose_X$$

$$CL_j = \hat{TVCL}_X \exp(\eta_{jCL})$$

- where $\hat{TVCL}_x$ is the population mean of CL, θ values are the parameters to be estimated, and the subscript X denotes a dose or a range of doses.

METHODS - EFFECT OF EXOGENOUS CORTICOSTEROID-2

- The parameter-covariate relationships between the AUC of des-CIC and serum cortisol was modeled as follows:

$$\hat{TVCL} = \theta_1 + \theta_2 AUC_{des-CIC}$$

$$CL_j = \hat{TVCL} \bullet \exp(\eta_{jCL})$$

- where the covariate $AUC_{des-CIC}$ was centered around its mean value to allow the intercept (θ_1) to represent the CL estimate for mean covariate values.

METHODS - EFFECT OF EXOGENOUS CORTICOSTEROID-3

- Individual predicted (IPRED) des-CIC plasma/serum concentrations ($C_{des-CIC}$) obtained from the final PK model for des-CIC were used to describe the direct effect of des-CIC concentrations on plasma/serum cortisol concentrations using an E_{max} model:

$$C_{cort} = E_{max} \bullet \left(1 - \frac{C_{des-CIC}}{C_{des-CIC} + EC_{50}}\right) + C_{trough}$$

- where
  - C_{cort} is the endogenous cortisol concentration in serum or plasma, E_{max} is the maximum possible suppression of endogenous cortisol concentrations,
  - EC_{50} is the des-CIC concentration exhibiting 50% maximum suppression and
  - C_{trough} is the estimated endogenous cortisol trough concentration in serum or plasma.
- The analyses were performed using 100% for E_{max} (i.e., cortisol concentration equal to 0 ng/mL), and were repeated with an estimated E_{max}. Interindividual variability of E_{max} and EC_{50} were tested as well as additional and proportional residual intra-patient random error.

RESULTS

Figure 2. Panel A. Des-CIC area under the curve (AUC) versus dose box plot. Panel B. Cortisol area under the curve (AUC) versus dose box plot

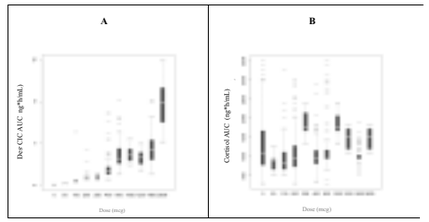


Figure 3. Panel A. Observed cortisol concentration versus time. Panel B. Cortisol concentration versus IPRED des-CIC concentrations.

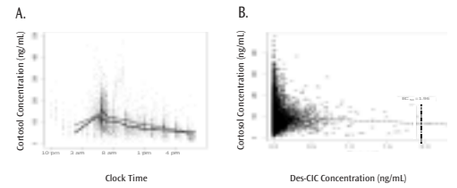
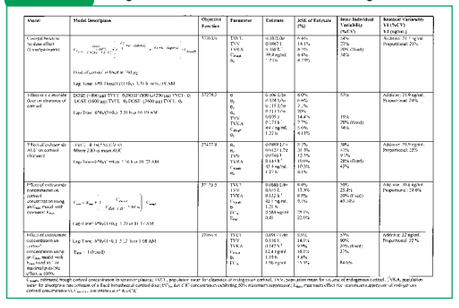


Table 2. Development of Pharmacodynamic Models For Endogenous Cortisol Release and Effect of Exogenous CIC



- A goal of this study was to develop a simple yet accurate mechanistic model to describe endogenous cortisol concentrations and to quantify effects of exogenous corticosteroids (such as ciclesonide) on endogenous cortisol release using various measures for the systemic corticosteroid (des-CIC) exposure.
- A simple one-compartment model with first-order absorption (i.e., rate constant of cortisol release to the system) and a lag time based on a fixed, hypothetical cortisol dosing time of 10 pm adequately characterized the circadian rhythm of endogenous cortisol release.
- The estimated half-life of cortisol (0.693 V/CL) was 0.56 h, which was in agreement with the half-life of 1.5 h reported previously (Derendorf, 1991; Rohatagi, 1996).
- This new model is simple.
- The cortisol release model is an existing model in NONMEM and other PK softwares providing more stability to data fitting.
- There are fewer parameters as compared to previous models, including the cosine model.
- Further work to evaluate the models is ongoing.
- Lack of a clear dose dependent effect on cortisol AUC and large inter-individual variability of cortisol AUC (55%), indicate these differences in AUC may not be real.
- Using individual predicted concentrations or AUC of des-CIC as PK measures, exogenous effects of ciclesonide on endogenous cortisol release were negligible.
- The estimated EC_{50} of des-CIC was 1.96 ng/mL, which is similar to the 90th percentile for maximum des-CIC concentration that was predicted after administration of the highest clinically relevant dose of 1600 μg (1280 μg ex-actuator).
- Less than 1% of all des-CIC concentrations were greater than 1.96 ng/mL, despite the use of ciclesonide doses up to 2880 μg (ex-actuator).
- Thus, less than 1% of all ciclesonide concentrations are higher than the EC_{50}. In addition, as only the unbound concentrations of des-CIC are pharmacologically relevant, the very low protein-unbound fraction of des-CIC (~1%) may further explain the lack of cortisol suppression associated with ciclesonide treatment
- Furthermore, additional analysis estimated the actual E_{max} value for ciclesonide to be 41%, where 100% refers to complete suppression of cortisol.
- This agreed with the estimated 49% decrease for the 2880 mg (ex-actuator) dose of ciclesonide in the covariate cortisol model, and suggests that even at the highest dose (more than double the highest therapeutic dose) of ciclesonide, complete suppression of cortisol concentrations is not expected.
- These findings are in agreement with data from several studies examining the effects of ciclesonide on cortisol concentrations (Weinbrenner, 2002; LaForce 2003).
- These studies showed no effect of ciclesonide on HPA-axis function.

CONCLUSIONS

- This novel but simple method using a one-compartment model, a hypothetical cortisol dose, cortisol time of dose and a lag-time could describe complex circadian endogenous cortisol concentrations.
- The effects of des-CIC exposure on endogenous cortisol concentrations were negligible over the dose range tested.

REFERENCES

- Bernstein JA; Noonan MJ; Rim C; Fish J; Kundu S; Williams J; Banerji DD; Hamedani P. Ciclesonide has minimal oropharyngeal side effects in the treatment of patients with moderate-to-severe asthma. J Allergy Clin Immunol 2004 Feb; 113(2 Suppl): S113, Abs: 349.
- Chapman KR, D'Urzo AD, Oedekoven C, Steinijans VW, Wurst W. Effects of ciclesonide versus placebo on lung function after 12 weeks of treatment in patients with asthma. Am J Resp Crit Care Med. 2002;165: A767.
- Derendorf H. Pharmacokinetic and pharmacodynamic properties of inhaled corticosteroids in relation to efficacy and safety. Respir Med. 1997;91 Suppl A:22-8.
- Engelstatter R, Langdon C, Bethke T, Rathgeb, Steinijans VW, Wurst W. Efficacy of ciclesonide after twelve-week treatment of bronchial asthma. Am J Respir Crit Care Med. 2002;165(8):A766.
- Koopmans RP, Braat MC, Oosterhuis B, van Boxtel CJ. Time-dependent effects of dexamethasone administration on the suppression of plasma hydrocortisone, assessed with a pharmacokinetic model. J Pharmacol Exp Ther. 1992;262 (2):503-508.
- LaForce CF; Baker JW; Amin D; Rohatagi S; Mendes P; Williams J; Kundu S; Banerji D. Ciclesonide, a novel inhaled steroid, has no effect on hypothalamic-pituitary-adrenal (HPA)-axis function in mild-to-moderate asthmatics. J Allergy Clin Immunol 2003 Feb; 111(2): S218, Abs: 596.
- Lipworth BJ, Wilson B. Dose response to inhaled corticosteroids. Semin Respir Crit Care Med 1998;19:625–46.
- Moellman, H et al. Pharmacokinetic-pharmacodynamic correlations of corticosteroids. In Handbook of pharmacokinetic/pharmacodynamic correlation. H. Derendorf, G. Hochhaus, eds. CRC Press. Handbooks in pharmacology and toxicology Vol:19 Boca Raton,1995.
- Nave R, Zech K. Bethke TD. Oropharyngeal deposition of inhaled ciclesonide and budesonide in healthy subjects. *J Allergy Clin Immunol*. 2003;111(part 2):A606.
- Postma DS, Sevette C, Martinat Y, Schlosser N, Aumann J, Kafe H. Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. Eur Respir J. 2001;17(6):1083–8.
- Rohatagi S, Arya V, Zech K, Nave R, Hochhaus G, Jensen BK, et al. Population pharmacokinetics and pharmacodynamics of ciclesonide. J Clin Pharmacol. 2003;43(4):365-78.
- Rohatagi S, Derendorf H, Zech K, Nave R, Banerji D. PK/PD of inhaled cortidosteroids: the risk/benefit of inhaled ciclesonide. J Allergy Clin Immunol. 2003;111(part 2):A598.
- Weinbrenner A, Huneke D, Zschiesche M, Engel G, Timmer W, Steinijans VW, et al. Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide. J Clin Endocrinol Metab. 2002;87(5):2160-3.

Funded by Aventis Pharmaceuticals and ALTANA Pharma