



1-1-2004

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Recommended Citation

Kraft, Walter; Steiger, Barry; Beussink, Don; Quiring, John N.; Fitzgerald, Nancy; Greenberg, Howard E.; and Waldman, Scott A., "The pharmacokinetics of nebulized nanocrystal budesonide suspension in healthy volunteers." (2004). *Department of Medicine Faculty Papers*. Paper 197. <https://jdc.jefferson.edu/medfp/197>

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The Pharmacokinetics of Nebulized Nanocrystal Budesonide Suspension in Healthy
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This study was supported by Sheffield Pharmaceuticals, Rochester, NY

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Abstract

Nanocrystal budesonide (nanobudesonide) is a suspension for nebulization in patients with steroid-responsive pulmonary disease such as asthma. The pharmacokinetics and safety of the product were compared to those of Pulmicort[®] Respules[™]. Sixteen healthy volunteers were administered nanobudesonide 0.5 and 1.0 mg, Pulmicort[®] Respules[™] 0.5 mg and placebo in a four-way, randomized crossover design. All nebulized formulations were well-tolerated, with no evidence of bronchospasm. Nebulization times were significantly shorter for nanobudesonide compared to Pulmicort[®] Respules[™]. Because of a low oral bioavailability, plasma concentration of budesonide is a good marker of lung-delivered dose. The pharmacokinetics of nanobudesonide 0.5 and 1.0 mg were approximately dose proportional with respect to C_{max} , $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Nanobudesonide 0.5 mg and Pulmicort[®] Respules[™] 0.5 mg exhibited similar AUC's, suggesting a similar extent of pulmonary absorption. A higher C_{max} was noted with nanobudesonide 0.5 mg and the T_{max} was significantly different, suggesting a more rapid rate of drug delivery of nanobudesonide 0.5 than Pulmicort[®] Respules[™]. In conclusion, nebulized nanobudesonide 0.5 mg was safe in healthy volunteers, with a similar extent of absorption as Pulmicort Respules.

Inhaled anti-inflammatory corticosteroid therapy is an important component of the treatment regimen for chronic asthma. Practice guidelines recommend their use as first-line therapy for all cases of asthma, except mild intermittent asthma^{1,2}. The use of inhaled steroids early in the course of the disease is associated with improved outcomes compared to treatment with beta 2 adrenergic agonists.³ Indeed, the early use of inhaled corticosteroids may alter the natural history of the disease⁴, and possibly reduce the irreversible airway obstruction associated with chronic inflammation of the lungs⁵.

Budesonide is a potent anti-inflammatory corticosteroid with low oral bioavailability. It forms reversible intracellular fatty acid esters in airway and lung tissue, which may prolong lung retention.⁶ Budesonide is available as a dry powder inhaler (DPI) and as Pulmicort[®] Respules[™] (AstraZeneca, Wilmington, DE), a suspension for inhalation with a jet-air table-top nebulizer. Pulmicort[®] Respules[™] is the only corticosteroid suspension for inhalation available in the United States. The DPI form of inhalation therapy is often limited by difficulty with coordination of inspiration, especially in pediatric patients. In addition, the DPI's require adequate inspiratory flow for drug delivery. For these reasons, budesonide delivered by a table-top nebulizer has found increasing use as the best alternative for delivery of corticosteroids to the lungs in children.

Nanobudesonide is a new formulation of budesonide that has been developed for use in a table-top nebulizer. Suspended drug particles (the disperse phase) are in the 75-300 nanometer range in this formulation. This compares to particle size of ~4,400 nanometer for Pulmicort[®] Respules[™].⁷ The small crystal size of budesonide in the nanocrystal formulation gives the suspension solution-like characteristics, which may shorten delivery time and improve intrapulmonary distribution compared to the existing preparation. In this

study, the safety, delivery, and pharmacokinetics of nebulized nanobudesonide were compared to Pulmicort[®] Respules[™].

METHODS

Subjects

Sixteen healthy volunteers (13 males and 3 females) with a mean age of 32.5 (range 25-40), mean height of 171.0 ± 8.4 cm, and mean weight 76.8 ± 14.5 kg participated in this study. The study was approved by the Institutional Review Board of Thomas Jefferson University in Philadelphia, PA. All subjects gave written informed consent to participate prior to undergoing any study procedures. No study subject used a topical or systemic corticosteroid, or ingested a cytochrome P4503A inhibitor within 4 weeks of study initiation. Subjects with a history of bronchospasm or a screening FEV1/FVC of <80% of predicted were excluded from participation.

Study Design

This was a randomized, double-blind, four-arm, single-dose cross-over study that compared the pharmacokinetics and safety of nanobudesonide and Pulmicort[®] Respules[™]. The four study arms were (1) placebo, (2) 0.5 mg of Pulmicort^R Respules[™], (3) 0.5 mg of nanobudesonide and (4) 1.0 mg of nanobudesonide. Healthy volunteers were admitted to the Clinical Pharmacology Research Unit of Thomas Jefferson Hospital the day before each treatment. Following an overnight fast, they received one of the four randomized treatments. The study protocol specified that each subject was to receive treatments not less than 5 or more than 10 days apart.

Spirometry, oximetry, clinical laboratory tests, ECG and vital signs were performed at baseline and at specified intervals. The spirometer was calibrated on a daily basis. Adverse events were monitored throughout the study. Twenty-four hours after each treatment, subjects were reevaluated and discharged from the unit.

Test Drugs and Administration

Nanobudesonide and placebo were manufactured by Automated Liquid Packaging, (Woodstock, IL) using plastic blow/fill/seal ampules. Packaging and labeling were performed by PCI Services - Clinical Services (Philadelphia, PA). The nanobudesonide placebo consisted of the same ingredients as nanobudesonide without the budesonide. Pulmicort® Respules™ were purchased from a commercial source. Nebulizers were filled by an unblinded investigational pharmacist. The fill volume for all treatments was 4.0 ml. For the 0.5 mg nanobudesonide treatment arm, 2.0 ml of placebo was added to 2.0 ml of active drug.

All treatments were administered by nebulization with a Pari LC Jet nebulizer and a Pari LC Ultra compressor (PARI Respiratory Equipment, Inc., Monterey, CA). A new nebulizer was used for each treatment and each subject had all four treatments administered with the same compressor. Compressors were checked with a calibration nebulizer each day of use. Research personnel reviewed the inhalation procedure with each subject prior to each treatment using a training nebulizer. Subjects were in a sitting position and trained to inhale slowly and steadily through a mouthpiece with a target respiratory rate of 14 to 20 breaths per minute. Nose clips were utilized to avoid inspiration/expiration through the nose. Nebulization was continued until one minute after sputtering was heard. The duration of nebulization and the residual volumes were measured.

Pharmacokinetics

Blood was drawn for budesonide levels pre-dose, at 5, 10, 15, 20, 25, 30, 40, and 60 min, and 2, 3, 4, 6, 8, and 24 h post-dose. Time zero was the beginning of nebulization. Samples were collected in tubes containing sodium heparin, immediately placed on ice, spun at 2200 g for 10 min.

Analysis of plasma samples was performed by Analytical BioChemistry Laboratories (Columbia, MO) utilizing a validated HPLC-MS/MS method. Using nominal standard concentrations of 60.1 pg/mL and 802 pg/mL, precision for this assay was 12.9% and 4.7% CV respectively, while accuracy was -8.6 to -2.8% RE of nominal standard concentrations. Plasma was assayed for budesonide in 1.0 ml aliquots. Samples were extracted on a 96-well C-18 SPE plates on a Tomtec Quadra 96® model 320. Desonide (11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione) 30-1,000 pg/ml was used as an internal standard. During validation, the correlation coefficient (r) was ≥ 0.9976 .

Statistical Analyses

Statistical analyses were performed using SAS® Version 6.12 (SAS Institute, Cary, NC). Safety variables of FEV1, adverse events and vital signs were analyzed with an analysis of covariance at each time point. Clinical laboratory measurements and oximetry were evaluated in each subject. The pharmacokinetic analyses were performed with SAS using the sorting procedure, PROC GLM, PROC MEANS and G-PLOT. The slope of the terminal phase was used to estimate $AUC_{(0-\text{inf})}$. Analysis of variance (ANOVA) was performed on untransformed and log transformed AUC and C_{max} parameters. The model included subject, period, and treatment. For the log transformed analysis adjusted means

and confidence intervals were calculated for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, T_{max} and C_{max} and back-transformed to the arithmetic scale. For untransformed data, treatments were compared for the 95% confidence intervals for the difference between means. For transformed data, a 95% confidence interval was calculated for the ratio of two means. Subjects were evaluated on an intent-to-treat basis, and those receiving at least one dose of the trial medication were included in analyses.

RESULTS

Demographics

Sixteen subjects were enrolled and all completed the study. One subject exceeded the maximum ten day window permitted between treatment arm 3 and 4 by four days. This protocol variance did not jeopardize study integrity and this subject was included in the analysis.

Pharmacokinetics

This study compared the pharmacokinetics of Pulmicort[®] and nanobudesonide delivered by inhalation (Table 1). Because of the rapid absorption and the limited number of time points during the first 10 min after the initiation of inhalation, T_{max} values obtained are considered estimates. Nevertheless, pairwise comparisons between Pulmicort[®] Respules[™] and nanobudesonide 0.5 mg revealed significant T_{max} ($p=0.001$) differences between treatments. Indeed, maximum concentrations were achieved sooner in the nanobudesonide 0.5 mg treatment compared to Pulmicort[®]. In addition, pairwise comparisons of the log transformed data revealed that the C_{max} for nanobudesonide 0.5 mg was significantly ($p<0.001$) higher than for a comparable dose of Pulmicort[®] Respules[™]. The extent of

absorption of Pulmicort® Respules™ 0.5 mg and nanobudesonide 0.5 mg, estimated by $AUC_{(0-t)}$ and $AUC_{(0-inf)}$, was comparable, though formal bioequivalence testing was not performed. The pharmacokinetics of nanobudesonide 0.5 mg and 1.0 mg were approximately dose proportional with respect to C_{max} , $AUC_{(0-t)}$, and $AUC_{(0-inf)}$.

Nebulization Times and Residual Volumes

Nebulization was continued until 1 min after sputtering, which was not detected in one subject receiving Pulmicort® Respules™ and one receiving 0.5 mg of nanobudesonide (Table 2). The nebulization times for these subjects were 15 and 16 min, respectively. Nebulization times ranged from 4.0 to 16.0 min across all treatments and mean nebulization times were 8.7 min for Pulmicort® Respules™, 7.1 min for nanobudesonide 0.5 mg, and 7.0 min for nanobudesonide 1.0 mg. The mean nebulization time for the subjects receiving Pulmicort® Respules™ was significantly longer compared to that of the nanobudesonide 0.5 mg group ($p=0.027$) and the nanobudesonide 1.0 mg group ($p=0.029$). There were 5, 3 and 2 subjects with nebulization times greater than 10 min in the Pulmicort® Respules™, nanobudesonide 0.5mg and nanobudesonide 1.0 mg groups, respectively.

Seven subjects had residual volumes greater than 1.0 ml; 4 in the Pulmicort® Respules™ group, 2 in the nanobudesonide 0.5 mg group, 1 in the nanobudesonide 1.0 mg group, and one in the placebo group. There was no clear relationship between higher residual volumes and longer nebulization times. Three subjects had residual volumes greater than 1.0 ml in more than one crossover treatment period.

Safety

There were no significant adverse effects associated with the administration of the test drugs. Four subjects reported a total of 8 adverse events after dosing with placebo. Two subjects reported a total of 4 adverse events (nausea, dizziness, paresthesia, and rhinitis) after dosing with Pulmicort® Respules™. One adverse event was reported with each of the nanobudesonide groups. These included rhinitis (nanobudesonide 0.5 mg) and edema at a venipuncture site (nanobudesonide 1.0 mg). All adverse effects were classified as mild. There was no evidence of bronchospasm in any of the treatment arms. For FEV₁, the overall treatment effect was not significant at any evaluation ($p \geq 0.111$). In addition, there were no clinically significant abnormalities in measured vital signs, pulse oximetry, electrocardiograms, or clinical laboratory tests.

DISCUSSION

Inhaled steroids are the preferred anti-inflammatory therapy in the treatment of asthma. Budesonide delivered by nebulization is effective in controlling pediatric asthma, as measured using multiple clinical endpoints.^{8,9,10,11} The efficacy of inhaled budesonide is predominantly mediated by local action, with systemic absorption contributing little, if anything, to the control of inflammation in the lungs.¹² Budesonide has an excellent safety profile in children. Pediatric patients administered chronic inhaled steroids grow to a normal adult height.¹³ However, safety concerns of a transient, decreased growth velocity in children¹⁴ have resulted in under-utilization of inhaled corticosteroids in this age group.¹⁵ The goal of the new nanocrystal formulation budesonide is to maximize efficiency of pulmonary delivery of drug, which may serve to obviate some of these safety concerns.

The delivery of budesonide by nebulization is a complex process that is affected by the characteristics of the nebulizer and compressor, droplet size, properties of the formulation,

breathing pattern of the patient, and respiratory tree anatomy. A small component of the orally deposited drug may be absorbed through the buccal mucosa. This was minimized in the present study by the use of a mouthwash after nebulization. There is little or no metabolism of budesonide in the lung.¹⁶ There is extensive hepatic first-pass metabolism of swallowed budesonide, with an oral bioavailability of ~11%.¹⁷ Pharmacokinetic evaluation of drug absorption from the lungs, therefore, provides an accurate and reproducible method for comparing the dose delivered to the lung by different inhaler systems or different formulations from the same inhaler system.^{18,19} A Medline search for published reports of the pharmacokinetics of budesonide suspension delivered by a table-top nebulizer yielded a single report from a study in 10 children.²⁰ However, neither the budesonide particle size in the suspension nor the manufacturer of the suspension is specified in this European study. Data on file with AstraZeneca reports that in children with asthma, the Pari LC Jet Plus nebulizer with the Pari Master compressor delivered approximately 25% of labeled budesonide to the patient.²¹ This delivered dose was comparable to that in healthy adults.

In this study of healthy volunteers, the 0.5 mg nanobudesonide and the 0.5 mg Pulmicort[®] Respules[™] formulations produce a comparable budesonide AUC in plasma, indicating a similar extent of absorption. Because the oral bioavailability of budesonide is relatively low, it is likely that this observation reflects comparable pulmonary deposition for each formulation. The nanobudesonide formulation exhibited approximate linear pharmacokinetics between the 0.5 and 1.0 mg formulations. The nebulization times of nanobudesonide 0.5 and 1.0 mg nanobudesonide were significantly shorter than those

observed with Pulmicort[®] Respules[™]. There were no significant adverse effects associated with the delivery of the nanobudesonide formulation.

The comparable AUC, higher C_{max} and lower T_{max} of 0.5 mg nanobudesonide compared to 0.5 mg Pulmicort[®] Respules[™] suggests more rapid drug delivery, or more rapid absorption. If these differences are due to more rapid absorption, two mechanisms are possible. Nanobudesonide could have more rapid dissolution of the in the airways, or a more distal delivery of drug may facilitate rapid absorption. However, the PK data presented do not allow discrimination between these possibilities. Drug distribution studies will be required to determine the degree and kinetics of pulmonary deposition. While some observations suggest that improved antiinflammatory drug distribution to small airways might result in increased clinical efficacy,²² there is no clinical proof that this is the case.²³ Finally, results reported here in healthy adults should be extrapolated to other populations with caution. Budesonide clearance²⁰ and lung deposition^{19,24} differ in pediatric and adult populations. Additionally, drug delivery to the lungs will differ in asthmatic and healthy lungs.²⁵ The subjects in this study were not balanced with regard to gender and no subgroup analysis was performed owing to the small number (3) of females participating. However, no gender differences are present in the pharmacokinetic parameters of Pulmicort[®] Respules[™].²¹ The potential for differential regional lung delivery of inhaled nanobudesonide based upon gender is unknown.²⁶

In conclusion, nanobudesonide exhibited pharmacokinetics that were dose-proportional, and nanobudesonide 0.5 mg yielded budesonide absorption that was comparable to Pulmicort[®] Respules[™]. The higher C_{max} and lower T_{max} of 0.5 mg nanobudesonide suggests a more rapid rate of either drug delivery or absorption compared to Pulmicort[®]

Respules™. In addition, nanobudesonide administration demonstrated a safety profile that was comparable to Pulmicort® Respules™. The significantly shorter nebulization time with nanobudesonide compared to Pulmicort® Respules™ should be advantageous with respect to patient compliance.

Table 1**Pharmacokinetics of Pulmicort and Nanobudesonide**

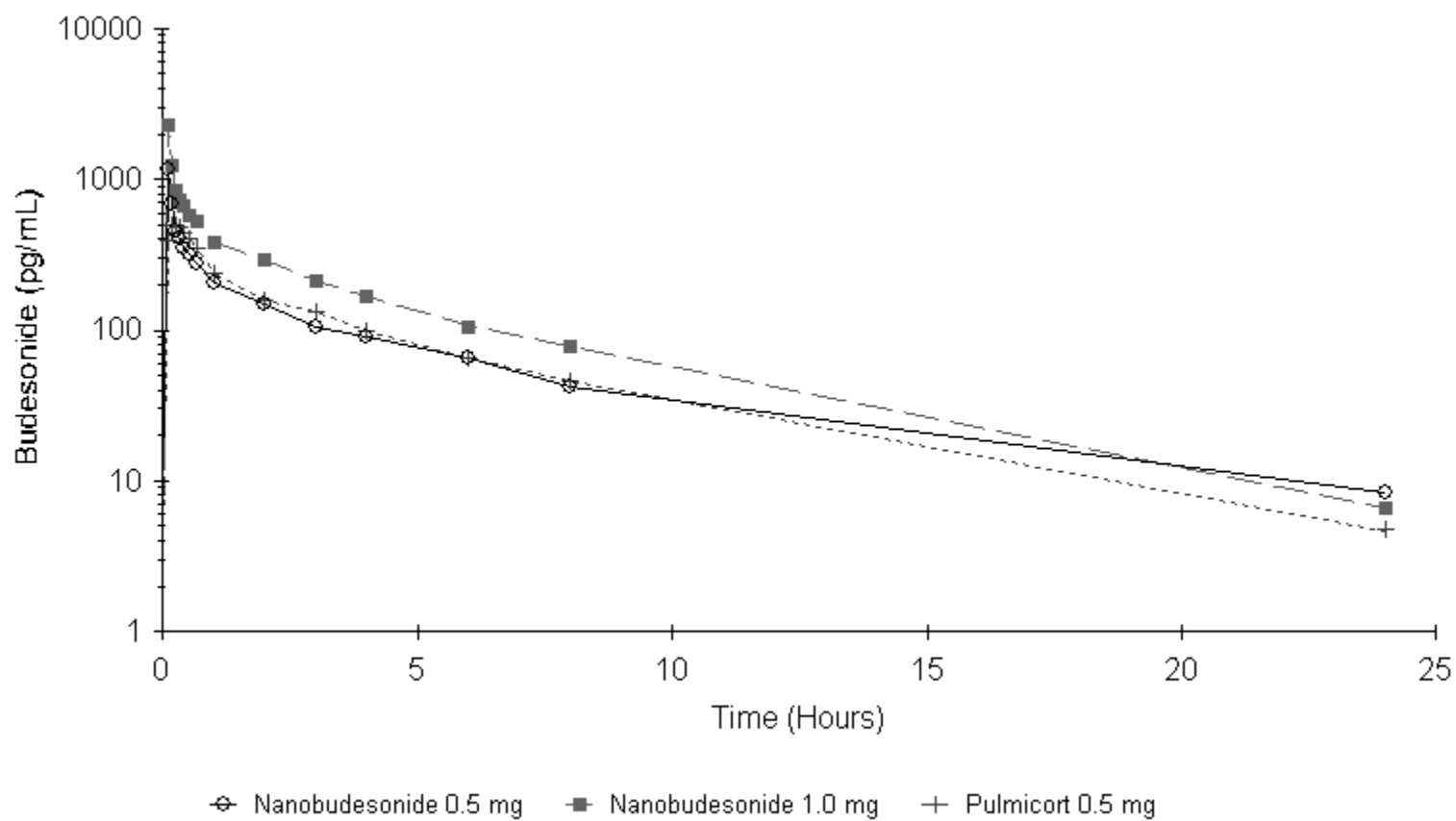
	Pulmicort (0.5 mg)	Nanobudesonide (0.5 mg)	Nanobudesonide (1.0 mg)
PK Parameter	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Tmax (min)	14.4 (11.4 – 18.0)	8.4 (5.4- 10.8)	11.4 (6.0- 16.2)
Cmax (pg/mL)	662 (416- 908)	1212 (751- 1674)	2484 (1236- 3733)
AUC(0-t) (pg·hr/mL)	1518 (1071- 1966)	1472 (1171- 1773)	2725 (1981- 3469)
AUC(0-inf) (pg·hr/mL)	1631 (1125- 2137)	1658 (1284- 2031)	2893 (2118- 3668)
T1/2 (hr)	5.42	6.62	5.46

Table 2

Mean Pulmicort and Nanobudesonide Nebulization Times

	Duration (min)	SD	Range
Placebo	6.56	1.75	5-10
Pulmicort® Respules™ (0.5 mg)	8.70	3.38	5-16
Nanobudesonide (0.5 mg)	7.06	3.11	5-16
Nanobudesonide (1.0 mg)	6.95	2.48	4-13

Figure. Time course of mean budesonide concentrations in plasma following oral administration of nanocrystal budesonide 0.5 mg (circles), nanocrystal budesonide 1.0 mg (squares), and Pulmicort® Respules™ 0.5 mg (+).



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