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Pharmacokinetics of a novel submicron budesonide dispersion for nebulized delivery in asthma

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ABSTRACT

The objective of this study was to evaluate the safety and pharmacokinetics of unit dose budesonide (UDB), an aqueous dispersion of submicron-sized budesonide particles, and a commercially available budesonide suspension formulation. This was a randomized, double-blind, active-controlled, 4-period, 4-way crossover trial in 16 healthy, adult volunteers. Subjects received UDB 0.24, 0.12, and 0.06 mg or commercial budesonide 0.25 mg via a jet nebulizer. T_{max} was significantly ($p < 0.05$) earlier for UDB 0.06, 0.12, and 0.24 mg (4.5 ± 3.3, 3.1 ± 1.5, 3.7 ± 1.5 min) vs. commercial budesonide (9.1 ± 7.1 min). C_{max} was significantly ($p < 0.05$) higher for UDB 0.24 mg vs. commercial budesonide 0.25 mg (434.5 ± 246.9 pg/mL vs. 303.5 ± 177.4 pg/mL) but not between UDB 0.12 mg (239.9 ± 140 pg/mL) and commercial budesonide 0.25 mg ($p = 0.448$). $AUC_{0-\infty}$ was marginally, but significantly lower for UDB 0.24 mg than commercial budesonide 0.25 mg. AUCs for UDB 0.12 mg were lower than commercial budesonide 0.25 mg. UDB 0.24 mg was absorbed more rapidly and achieved higher peak concentrations than commercial budesonide 0.25 mg, but had a lower $AUC_{0-\infty}$. UDB 0.12 mg also was absorbed more rapidly but had lower C_{max} and AUCs than commercial budesonide 0.25 mg.

1. Introduction

Inhaled corticosteroids (ICS) are recognized as standard therapy for pediatric and adult asthma (GINA, 2006; National Asthma Education and Prevention Program, 2007). A number of devices are available for administration of ICS, however, infants and young children often are unable to coordinate most inhaler devices (Dolovich et al., 2005; Giraud and Roche, 2002; Kofman et al., 2004; O'Connell, 2005). Consequently, a nebulizer may be recommended in the young asthmatic (Dolovich et al., 2005; Szefler and Eigen, 2002; Berger and Shapiro, 2004). Although nebulizers offer advantages over metered dose inhalers in infants and children, their use may be limited by the need for expensive equipment (e.g. air compressor) and a power supply, by lengthy administration times, by concentrating effects that result in the delivery of drug late in the nebulizer cycle, and by variable device performance (Rau, 2006).

One of the greatest challenges when administering ICS is delivering a sufficient concentration of drug to the lower respiratory tract in order to provide a therapeutic response (Giraud and Roche, 2002). Existing ICS formulations for nebulization are available only as suspensions and consist of insoluble drug particles with a mass median aerodynamic diameter in excess of 2 μm (Luangvala et al., 2008a,b; Kraft et al., 2004). These insoluble particles require carrier droplets of a larger diameter in order to leave the nebulizer and be carried into the lungs. The large particle size prevents them from being carried by a significant fraction of the aqueous droplets generated by conventional jet nebulizers that are of appropriate size for lung deposition (<5 μm) (Schüepp et al., 2005; Rubin, 2004). Smaller aqueous droplets are important as they are responsible for carrying drug to the smaller airways, especially those of young children. As a result, drug delivery is inefficient. In addition, a large fraction of the active drug that can be carried out of the nebulizer (in the larger droplets) will deposit either in the upper airway or oropharynx providing minimal, if any, therapeutic benefit (Schüepp et al., 2005). This can be further compromised if the child is uncooperative or fussy during treatment administration (Geller, 2005), when even less aerosolized drug is inhaled due to their lack of compliance, and compounded by lengthy administration time. Improving the mass of drug carried by small, respirable droplets delivered early in, or consistently throughout the nebulization cycle might improve drug deposition, and may lead to increased therapeutic benefit to young children.

Budesonide is the only ICS approved in the United States for delivery via a nebulizer in children with asthma under age 8 (Geller,

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2005). Results from clinical trials indicate that nebulized budesonide is effective for managing asthma in infants and children (Baker et al., 1999; Kemp et al., 1999; Shapiro et al., 1998), and it is widely accepted as a first-line therapy for treating infants and children with asthma (Berger and Shapiro, 2004; Banov, 2004; Berger, 2005). A recent survey found improved outcomes with nebulized budesonide vs. other asthma medications among children treated in the emergency department (McLaughlin et al., 2007) even with the potential drawbacks of conventional nebulization. Commercially available nebulized budesonide has some potential limitations. Administration of an effective dose may require up to 16 min, which has the potential to reduce compliance and thus effectiveness, especially for restless toddlers (Kraft et al., 2004). Commercial budesonide cannot be administered effectively using ultrasonic or next generation ("vibrating mesh") nebulizers, which are designed to have potentially faster drug administration times. As only a small percentage of drug is nebulized in the first few minutes of administration, much of the commercial budesonide dose is delivered later in the administration cycle (Luangvala et al., 2008a,b) and carried as large particles in large aerosol droplets (Bosco and Uster, 2007). Delivery of commercial budesonide in large droplets results in drug being deposited in the back of the mouth and throat, where it can lead to localized immune suppression and local side effects, such as oral yeast infections and dysphonia, and remains available for systemic absorption (and hence adverse effects) without providing therapeutic benefit.

A new submicron formulation of budesonide for nebulization (unit dose budesonide or UDB) is in clinical development, which may offer faster delivery of drug to the airways by increasing mass of drug aerosolized over the critical first few minutes of nebulization (Luangvala et al., 2008b; Bosco and Uster, 2007) as well as improved delivery efficiency and delivery consistency at a lower dose. The active ingredient is submicron budesonide in a sterile aqueous formulation containing surface modifiers in an isotonic buffer of sodium chloride, citric acid, sodium citrate, and disodium edentate dehydrate, at a pH of 4.0–5.0. The stability of the UDB formulation at 25 °C for up to 12 months has been confirmed.

UDB consists of a smaller, consistently reproducible budesonide particle less than 1 μm in diameter, which allows for more drug particles to be collected and transported into the lung by the small aerosol droplets generated by the nebulizer, especially in the initial minutes of nebulization (Luangvala et al., 2008b; Bosco and Uster, 2007).

The aerodynamic particle size distribution of two formulations of UDB (0.12 mg/2 mL and 0.24 mg/2 mL) was characterized using the Andersen Cascade Impactor (ACI) operated at room temperature at a flow rate of 28.3 LPM. Each formulation was tested using the Pari LC Plus jet nebulizer paired with the Pari ProNeb Ultra compressor. A 2 mL unit dose vial was loaded into the reservoir of the Pari LC Plus and connected to a mouthpiece adapter attached to a USP inlet on the ACI. Nebulizers were sampled into the impactor for 6 min. Three different nebulizer and compressor combinations were characterized with three replicates each ($n = 9$). After sampling was complete, the ACI was disassembled and the USP inlet and each individual stage were chemically assayed with an appropriate diluent to recover the impacted mass of budesonide. The fine particle fraction (FPF), defined as the total % of impacted particles that are less then 4.7 μm in diameter, was 63 ± 1% and 61 ± 1% for the 0.12 mg/2 mL and 0.24 mg/2 mL formulations, respectively. The deposition of budesonide in the USP inlet was <1% for both formulations, with the greatest mass of budesonide impacting on stages 3, 4 and 5 of the impactor, which represent effective cutoff diameters of 4.7, 3.3, and 2.1 μm, respectively (Fig. 1).

The objective of this study was to evaluate the pharmacokinetics and safety profile of unit dose budesonide (UDB), a proprietary formulation of submicron particle-sized budesonide dispersion, administered at three strengths via a jet nebulizer in healthy subjects, compared with a commercially available budesonide suspension formulation.

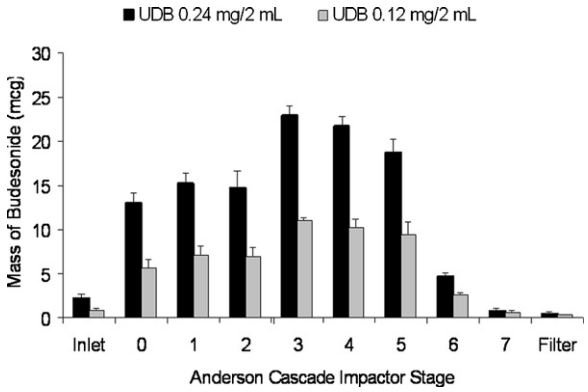

Fig. 1. Distribution of the impacted mass of budesonide reaching the ACI when sampling at 28.3 L/min.

2. Methods

This was a randomized, double-blind, active-controlled, 4-arm, 4-period single dose, crossover study of UDB and the commercially available budesonide inhalation suspension (Pulmicort Respules®, AstraZeneca, Wilmington, DE) approved for use in a jet nebulizer, conducted at Q-Pharm Pty Limited, Brisbane, Australia. The study protocol was reviewed and approved by an independent Institutional Review Board, and the study was conducted in accordance with the Declaration of Helsinki and guidance on Good Clinical Practice. All subjects provided written informed consent prior to participating in the study.

Subjects were healthy, non-smoking adult volunteers, of either gender, aged 18–50 years. Women were non-pregnant, non-lactating, and if of childbearing age, were using an approved form of contraception. Subjects also were required to demonstrate comfortable cooperation with nebulized saline administration, as evidenced by the absence of tingling around the mouth, pins and needles or tingling of the fingers, chest tightness or discomfort, dizziness or lightheadedness with use of the Pari LC Plus jet nebulizer operated with the Pari ProNeb Ultra compressor. Subjects were issued their own individual jet nebulizer that was cleaned and re-used for all four dose administrations.

Each subject was screened and then randomized within 2–14 days. Subjects who met the study criteria were randomized in blocks of 4 to receive one of four treatment sequences, which determined the order in which they received the four treatments (UDB 0.06, 0.12, and 0.24 mg or commercially available budesonide 0.25 mg per dose). A 2 mL dose of the study drug was administered via a Pari LC Plus jet nebulizer operated with the Pari ProNeb Ultra compressor. Following an overnight fast, single doses of the various budesonide suspensions were prepared by a trained pharmacist or technician without subject or clinical staff observation and administered double-blind therefore on each of the four occasions. Subjects were observed for a minimum of 8 h after each dosing. Each dose was separated by a washout period, such that subjects started to receive their next dose of study treatment within 72 h (±1 h) of starting to receive their previous dose. Subjects returned for a final termination visit 3–4 days after the last treatment administration was initiated. Each subject was in the study for a maximum of 27 days.

Table 1
Baseline clinical and demographic characteristics

Characteristic	$n = 16$
Male:female	8:8
Age (year)	
Mean ± standard deviation (S.D.)	23.3 ± 4.3
Median	22.5
Range	19–33
Weight (kg)	
Mean ± S.D.	72.9 ± 14.4
Median	72.2
Range	47.0–97.8
Height (cm)	
Mean ± S.D.	175.3–13.1
Median	176.5
Range	153–199
FEV_1 (L)	
Mean ± S.D.	4.19 ± 0.88
Median	4.30
Range	2.75–6.10
FEV_1 % predicted	
Mean ± S.D.	99.94 ± 10.79
Median	97.50
Range	82–127

Spirometry, pulse oximetry, and vital signs were obtained immediately before dose administration and at 5, 15, and 30 min and 1, 1.5, 2, 3, 4, 6, and 8 h post-dose. Blood samples were obtained prior to each dose for biochemical and hematological measurements. Time of dosing was initiated when the compressor was started and was terminated after 10 min. The time to first "sputter" was identified and recorded. Subjects were required to use the same compressor, nebulizer, and tubing for each dosing.

The occurrence of adverse events was collected from study entry until 2–6 days after study termination or upon study withdrawal. Adverse events were tabulated according to severity, seriousness, and relationship to study drug.

2.1. Pharmacokinetic parameters

To compare systemic exposure to budesonide, venous blood samples were obtained pre-dose and at 2, 5, 15, and 30 min and 1, 2, and 8 h following dosing to determine peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area-under-the-concentration curve for 0–8 h (AUC_{0-8}), area-under-the-concentration curve for 0 to infinity ($AUC_{0-\infty}$), and half-life ($t_{1/2}$) for all subjects from each of the four treatments. Plasma budesonide concentrations were determined by a validated HPLC/MS-MS method with lower limit of assay quantitation validated at 10 pg/mL (personal communication).

2.2. Statistical analysis

A sample size of 16 was chosen to ensure that the upper 95% binomial confidence interval for the incidence rate of bronchospasm (defined as a 15% fall in FEV_1) would not exceed 0.2—if bronchospasm did not occur in any subject. This is based on the binomial confidence interval calculated for 0 occurrences out of 16 trials. The upper 95% confidence limits were 0.194 for Wilson's method or 0.206 for the exact method.

For the pharmacokinetic parameters using non-compartmental methods for C_{max}, T_{max}, AUC_{0-8}, $AUC_{0-\infty}$, and $t_{1/2}$, descriptive statistics were determined including arithmetic mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation (CV) and 90% confidence intervals (CI) for treatment group means. In addition, pharmacokinetic parameters were analyzed using a linear mixed model, including fixed effect terms for treatment group and period and random effect terms for subjects and residuals. Individual means for UDB and commercial budesonide were compared using Dunnett's procedure. Least square means were computed for each treatment. Analysis of variance (ANOVA) was performed on untransformed and on log-transformed C_{max}, T_{max}, AUC_{0-8}, and $AUC_{0-\infty}$. The ANOVA model included terms for period, treatment, sequence, and subject nested by sequence. For log-transformed analysis, adjusted means for each treatment group were calculated for C_{max}, T_{max}, AUC_{0-8}, and $AUC_{0-\infty}$ and were transformed back to an arithmetic scale. For log-transformed data, a 90% CI was calculated for the ratio of any two means. For untransformed data, any two treatments were compared for the 90% CI for the difference between means. For FEV_1, untransformed values were more normally distributed than log-transformed values. Therefore, statistical analysis was based on untransformed data and 90% CI for differences between FEV_1 treatment means were calculated. Dose proportionality for UDB was determined by linear regression on AUC and C_{max} vs. dose, by fitting a power model to AUC and C_{max} vs. dose, and by performing ANOVA on dose-adjusted AUC and C_{max} with dose as the main effect.

3. Results

Sixteen subjects were enrolled in the study and completed all four study periods. These 16 subjects comprised the Intent-to-Treat Population for each of the four doses of budesonide and were included in the safety analysis. One subject did not receive a complete dose of drug on one occasion due to nebulizer malfunction and was excluded from pharmacokinetic analyses for that dose (0.06 mg UDB). Baseline demographic and clinical characteristics were typical for a population of healthy volunteers (Table 1). Body mass index for the 16 subjects ranged from 18.1 to 27.6 kg/m^2.

3.1. Safety and tolerability

No clinically significant changes in laboratory values were detected except for low but fluctuating hemoglobin and red blood cell count in three female subjects that was deemed clinically significant but unrelated to the study drug. No differences were observed between treatment groups for laboratory values or vital signs.

Table 2
Mean time to sputter by treatment group (all 2.0 mL volumes)

	Commercial budesonide 0.25 mg ($n = 16$)	Unit dose budesonide 0.06 mg ($n = 15$)[a]	Unit dose budesonide 0.12 mg ($n = 16$)	Unit dose budesonide 0.24 mg ($n = 16$)
Mean (min:s)	3:52	2:56	3:05	3:35
S.D. (min:s)	0:53	0:42	0:30	1:01
Minimum (min:s)	2:41	1:50	2:00	1:00
Maximum (min:s)	6:11	3:54	4:07	5:40

[a] One subject did not receive the dose of UDB 0.06 mg due to equipment failure.

Table 3
Incidence of adverse events by treatment group

Event	Prior to therapy ($n = 16$)	Commercial budesonide 0.25 mg ($n = 16$)	Unit dose budesonide		
			0.06 mg ($n = 16$)	0.12 mg ($n = 16$)	0.24 mg ($n = 16$)
Any event	2	4	4	3	3
Abdominal pain	1	0	0	0	0
Anemia	0	0	0	2	1
Dysmenorrhea	0	2	0	0	0
Epistaxis	0	0	0	0	1
Eye irritation	0	1	0	0	0
Headache	0	0	1	0	0
Infections	0	1	2	0	0
Throat pain	1	0	1	0	0
Thrombophlebitis	0	0	0	1	1

Table 4
Percent predicted FEV_1 before and after treatments

Variable	Commercial budesonide 0.25 mg ($n = 16$)	Unit dose budesonide		
		0.06 mg ($n = 16$)	0.12 mg ($n = 16$)	0.24 mg ($n = 16$)
Pre-dose	96.81	97.19	97.13	97.13
Change from pre-dose to				
15 min	0.56	0.81	1.06	0.44
30 min	1.50	1.13	1.75	1.56
2 h	0.94	0.94	1.69	2.25
8 h	0.25	0.63	1.06	−0.06
Maximum increase	2.88	2.63	3.38	3.06
Maximum decrease	−0.88	−0.88	−0.50	−1.25

Pairwise comparisons were made for each time point using Dunnett's test between change from baseline with UDB (at each dose) and commercial budesonide 0.25 mg. No significant differences were detected with p values ranging from 0.5 to 1.

Mean time to sputter (Table 2) in this population of healthy adult volunteers, showed a relationship between dose and administration time with all doses of UDB being faster than the commercial preparation, at the same 2.0 mL volume. All adverse events experienced in this study were classified as mild, and none were classified as related to the study drug (Table 3). No serious adverse events were reported. There were no significant between-treatment differences in the incidence of adverse events.

A 15% decline in FEV_1 is generally considered to be clinically significant. No change in FEV_1 from baseline of this degree was seen with any treatment in this study (Table 4). The maximum decline in FEV_1 shown by any subject was 8.5%, and the maximum increase was 14.8%. There was no significant difference between treatments in terms of FEV_1, % predicted FEV_1, or the observed changes in either parameter.

3.2. Pharmacokinetic results

Descriptive summary of the pharmacokinetic parameters showed a dose-proportional increase in C_{max} and AUC with UDB dose (Table 5). Mean values of AUC_{0-8}, and half-life were similar for commercial budesonide 0.25 mg and UDB 0.24 mg, however, C_{max}, $AUC_{0-\infty}$, and T_{max} were significantly ($p < 0.05$) different at 434.5 pg/mL, 25,290 pg min/mL ($\log_e = 9.97$) and 3.7 min with

Table 5
Pharmacokinetic parameters for each treatment

	C_{max} (pg/mL)	T_{max} (min)	AUC_{0-8} (pg min/mL)	$AUC_{0-\infty}$ (pg min/mL)	Half-life (min)
Commercial budesonide 0.25 mg					
N	16	16	16	16	16
Mean	303.5	9.1	29,040	31,480	145.4
S.D.	177.4	7.1	9,316	10,690	40.8
CV%	58.5	78.6	32.1	33.9	28.1
Unit dose budesonide 0.06 mg					
N	15	15	15	12	12
Mean	106.2	4.5	3,978	4,391	73.0
S.D.	63.5	3.3	1,974	1,423	33.4
CV%	59.8	73.2	49.6	32.4	45.8
Unit dose budesonide 0.12 mg					
N	16	16	16	13	13
Mean	239.9	3.1	8,626	7,842	78.4
S.D.	140.1	1.5	4,184	3,647	27.1
CV%	58.4	48.0	48.5	46.5	34.6
Unit dose budesonide 0.24 mg					
N	16	16	16	14	14
Mean	434.5	3.7	22,130	25,290	140.0
S.D.	246.9	1.5	9,675	11,750	54.2
CV%	56.8	39.3	43.7	46.5	38.7

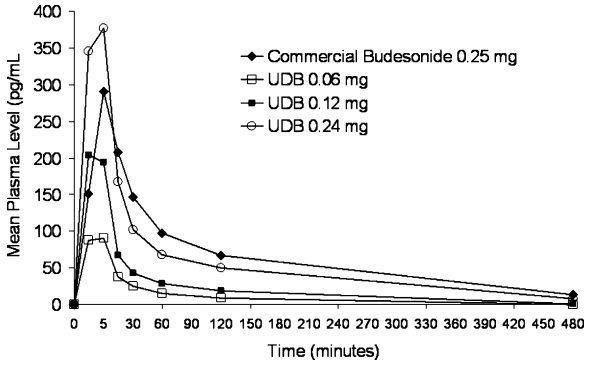

Fig. 2. Mean plasma concentrations of budesonide over time with each treatment.

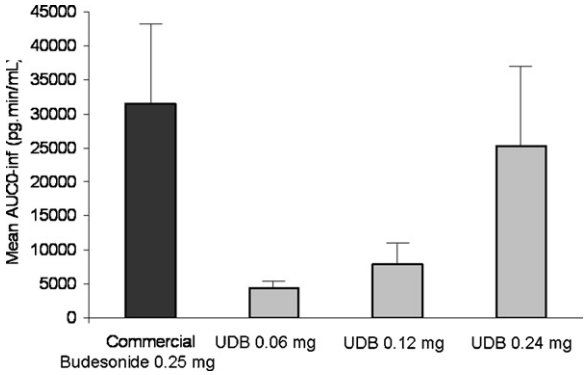

Fig. 3. Mean (standard deviation) $AUC_{0-\infty}$ for each treatment.

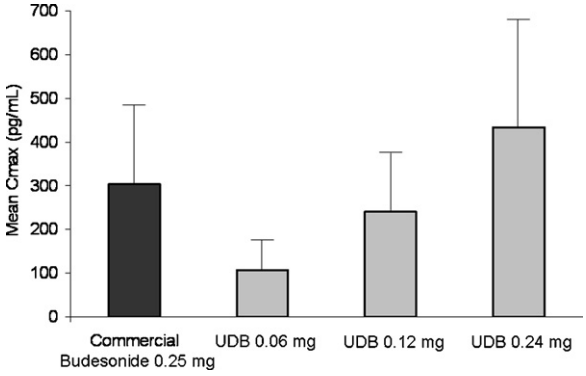

Fig. 4. Mean (standard deviation) C_{max} for each treatment.

UDB 0.24 mg and 303.5 pg/mL, 31,480 pg min/mL ($\log_e = 10.28$) and 9.1 min with commercial budesonide. Fig. 2 illustrates the mean plasma concentrations of budesonide for commercial budesonide 0.25 mg, UDB 0.06 mg, UDB 0.12 mg, and UDB 0.24 mg vs. sampling time.

Comparison of differences between treatment means for pharmacokinetic parameters was accomplished with ANOVA (Table 6). As expected, C_{max}, AUC_{0-8}, and $AUC_{0-\infty}$ for UDB showed significant ($p < 0.05$) increases with increasing dose. The value for $AUC_{0-\infty}$ was significantly ($p < 0.05$) lower for UDB doses, even for UDB 0.24 mg, compared to commercial budesonide 0.25 mg with UDB values being 13.9%, 24.9%, and 80.3% of the commercial product. AUC_{0-8} values were 13.7%, 29.7%, and 76.2% respectively for UDB 0.06, 0.12, and 0.24 mg of the commercial budesonide 0.25 mg dose (Fig. 3), although the result for UDB 0.24 mg was not statistically different from commercial budesonide, due to higher variance than was seen with the $AUC_{0-\infty}$ result. In contrast, C_{max} was significantly ($p = 0.04$) higher for UDB 0.24 mg than for commercial budesonide 0.25 mg, but no significant difference ($p = 0.448$) was observed for C_{max} between UDB 0.12 mg and commercial budesonide 0.25 mg (Fig. 4). These differences in C_{max} are consistent with the significantly ($p < 0.05$) faster T_{max} observed with UDB doses compared with commercial budesonide. This significant difference in C_{max} and T_{max} for UBD vs. commercial budesonide at a similar dose clearly suggests that the novel submicron particle formulation of UDB allows for budesonide to be absorbed more rapidly than the existing marketed formulation of commercial budesonide.

4. Discussion

The results from this study found no evidence of any difference between the commercially available budesonide 0.25 mg and UDB 0.06, 0.12 and 0.24 mg as determined by the incidence of adverse

Table 6
Mean, standard error (S.E.) and *p*-values for differences between UDB and commercial budesonide for pharmacokinetic parameters

Variable	Treatment	Mean	S.E.	Adjusted *p*-value
Half-life (min)	Commercial budesonide 0.25 mg	145.4	9.1	–
	UDB 0.06 mg	68.7	11.4	<0.001
	UDB 0.12 mg	77.3	11.0	<0.001
	UDB 0.24 mg	138.1	10.5	0.903
T_{max} (min)	Commercial budesonide 0.25 mg	9.1	0.9	–
	UDB 0.06 mg	3.9	1.1	0.001
	UDB 0.12 mg	3.7	1.0	0.001
	UDB 0.24 mg	3.5	1.0	<0.001
$\log_e AUC_{0-8}$	Commercial budesonide 0.25 mg	10.22	0.16	–
	UDB 0.06 mg	8.16	0.17	<0.001
	UDB 0.12 mg	9.04	0.17	<0.001
	UDB 0.24 mg	9.96	0.17	0.201
$\log_e AUC_{0-\infty}$	Commercial budesonide 0.25 mg	10.28	0.13	–
	UDB 0.06 mg	8.26	0.14	<0.001
	UDB 0.12 mg	8.91	0.13	<0.001
	UDB 0.24 mg	9.97	0.13	0.009
$\log_e C_{max}$	Commercial budesonide 0.25 mg	5.54	0.17	–
	UDB 0.06 mg	4.49	0.19	<0.001
	UDB 0.12 mg	5.34	0.18	0.448
	UDB 0.24 mg	5.96	0.18	0.040

events, abnormal laboratory values, vital signs, ECG, pulse oximetry or spirometry (FEV_1) measurements.

The three doses of UDB demonstrated consistent dose-proportionality for the measured pharmacokinetic parameters. The pharmacokinetics results indicate that UDB is absorbed more rapidly than commercial budesonide as demonstrated by the significantly greater C_{max} for UDB 0.24 mg vs. commercial budesonide 0.25 mg and supported by the significantly faster T_{max} for all three doses of UDB vs. commercial budesonide. However AUC with UDB did not exceed the systemic exposure seen with commercial budesonide even at similar dose (0.24 mg vs. commercial 0.25 mg dose), indeed the $AUC_{0-\infty}$ with UDB 0.24 mg was marginally, but statistically significantly, lower than commercial budesonide 0.25 mg ($p = 0.009$). The lack of a significant difference in C_{max} between UDB 0.12 mg and commercial budesonide 0.25 mg supports the view that UDB is more rapidly absorbed.

The small size of UDB particles resulted in approximately twice as much UDB being nebulized in the first 2 min when compared to commercial budesonide (Bosco et al., 2006), which may be especially helpful in uncooperative toddlers. The low label dose of UDB has the potential to treat asthma effectively at approximately half of the lowest dose of commercial budesonide, with lower C_{max} and AUC. UDB is efficiently delivered to the surface of the lung, reducing the amount of drug deposited in the back of the mouth and throat, which may result in reduced oral thrush (which was not reported by any subject in this repeat single dose study) and less systemic cortisol suppression.

In conclusion, the results of this study show that UDB is safe and well tolerated in healthy, adult volunteers. Improvements in relative delivery time of the same dose volume were noted in inverse proportion to label strength. Clinical trials are ongoing with UDB in asthmatic children to confirm its efficacy and safety.

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References

Baker, J.W., Mellon, M., Wald, J., Welch, M., Cruz-Rivera, M., Walton-Bowen, K., 1999. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. Pediatrics 103, 414–421.

Banov, C.H., 2004. The role of budesonide in adults and children with mild-to-moderate persistent asthma. J. Asthma 41, 5–17.

Berger, W.E., Shapiro, G.G., 2004. The use of inhaled corticosteroids for persistent asthma in infants and young children. Ann. Allergy Asthma Immunol. 92, 387–399.

Berger, W.E., 2005. Budesonide inhalation suspension for the treatment of asthma in infants and children. Drugs 65, 1973–1989.

Bosco, A.P., Armer, T.A., Uster, P.S., 2006. A submicron suspension of budesonide improves the mass of ICS delivered during early nebulization. Eur. Respir. J. 28, 712s.

Bosco, A.P., Uster, P.S., 2007. A novel submicron suspension formulation of nebulized budesonide significantly improves the fine particle dose and ultra-fine particle dose. J. Aerosol Med. 20, 171.

Dolovich, M.B., Ahrens, R.C., Hess, D.R., Anderson, P., Dhand, R., Rau, J.L., Smaldone, G.C., Guyatt, G., 2005. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 127, 335–371.

Geller, D.E., 2005. Comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler. Respir. Care 50, 1313–1321.

Giraud, V., Roche, N., 2002. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. Eur. Respir. J. 19, 246–251.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2006. Available from: http://www.ginasthma.org.

Kemp, J.P., Skoner, D.P., Szefler, S.J., Walton-Bowen, K., Cruz-Rivera, M., Smith, J.A., 1999. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. Ann. Allergy Asthma Immunol. 83, 231–239.

Kofman, C., Berlinski, A., Zaragoza, S., 2004. Aerosol therapy for pediatric outpatients. RT: The Journal for Respiratory Care Practitioners. Available from http://www.rtmagazine. com/issues/articles/2004-03_05.asp (last accessed April 18, 2007).

Kraft, W.K., Steiger, B., Beussink, D., Quiring, J.N., Fitzgerald, N., Greenberg, H.E., Waldman, S.A., 2004. The pharmacokinetics of nebulized nanocrystal budesonide suspension in healthy volunteers. J. Clin. Pharmacol. 44, 67–72.

Luangvala, M.M., Castillo, M.C., Bosco, A.P., 2008a. A novel submicron formulation of nebulized budesonide generates a significantly greater fine particle mass compared to a conventional budesonide suspension using an electronic micropump nebulizer. Am. J. Respir. Crit. Care Med. 177, A611.

Luangvala, M.M., Castillo, M.C., Bosco, A.P., 2008b. A novel submicron formulation of nebulized budesonide significantly improves delivery during the critical first minutes of nebulization using an electronic micropump nebulizer. Am. J. Respir. Crit. Care Med. 177, A610.

McLaughlin, T., Leibman, M., Patel, P., Camargo, C.A., 2007. Risk of recurrent emergency department visits or hospitalizations in children with asthma receiving nebulized budesonide inhalation suspension compared with other asthma medications. Curr. Med. Res. Opin. 23, 1319–1328.

National Asthma Education and Prevention Program, 2007. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J. Allergy Clin. Immunol. 120, S94–S138.

O'Connell, E.J., 2005. Optimizing inhaled corticosteroid therapy in children with chronic asthma. Pediatr. Pulmonol. 39, 74–83.

Rau, J.L., 2006. Practical problems with aerosol therapy in COPD. Respir. Care 51, 158–172.

Rubin, B.K., 2004. What does it mean when a patient says, "my asthma medication is not working?". Chest 126, 972–981.

Schüepp, K.G., Jauernig, J., Janssens, H.M., Tiddens, H.A., Straub, D.A., Stangl, R., Keller, M., Wildhaber, J.H., 2005. In vitro determination of the optimal particle size for nebulized aerosol delivery to infants. J. Aerosol Med. 18, 225–235.

Shapiro, G., Mendelson, L., Kraemer, M.J., Cruz-Rivera, M., Walton-Bowen, K., Smith, J.A., 1998. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. J. Allergy Clin. Immunol. 102, 789–796.

Szefler, S.J., Eigen, H., 2002. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. J. Allergy Clin. Immunol. 109, 730–742.