Original articles

Exposure of infants to budesonide through breast milk of asthmatic mothers

Anette Fält, BSc,[a] Thomas Bengtsson, MSc,[a] Britt-Marie Kennedy, BSc,[b] Ann Gyllenberg, RN,[a] Bengt Lindberg, MD,[a,c] Lars Thorsson, PhD,[a] and Kerstin Stråndgarden, MSc[a] *Lund and Malmo, Sweden*

Background: Maintenance treatment with inhaled corticosteroids is often required for asthmatic nursing women. Data on the transfer of inhaled corticosteroids from plasma to breast milk and the subsequent exposure of the breast-feeding infant has been unavailable.

Objective: We sought to assess budesonide concentrations in milk and plasma of asthmatic nursing women receiving maintenance treatment with the Pulmicort Turbuhaler and estimate the exposure of their breast-fed infants.

Methods: Milk and plasma samples were collected up to 8 hours after dosing from 8 mothers receiving budesonide maintenance treatment (200 or 400 μg twice daily). Pharmacokinetic parameters were calculated from budesonide milk and plasma concentrations. Infant exposure was estimated based on average milk budesonide concentrations. A single blood sample was obtained from 5 infants close to expected infant maximum concentration.

Results: Budesonide concentrations in milk reflected those in maternal plasma, supporting passive diffusion of budesonide between plasma and milk, and was always lower than that in plasma. The mean milk/plasma ratio was 0.46. The estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma, assuming complete infant oral bioavailability. Budesonide concentrations in infant plasma samples were all less than the limit of quantification.

Conclusion: Maintenance treatment with inhaled budesonide (200 or 400 μg twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants.

Clinical implications: These data support continued use of inhaled budesonide during breast-feeding. (J Allergy Clin Immunol 2007;120:798-802.)

Key words: *Pulmicort, budesonide, asthma, breast milk*

Inhaled corticosteroids (ICSs) are first-line therapy for persistent asthma in adults and children. Pregnant and nursing women with chronic asthma often require continued treatment and need to feel safe to do this with ICS therapy.

Epidemiologic data with the ICS budesonide indicate no increased risk of congenital malformations[1] and normal pregnancy outcomes[2] when the drug is used during pregnancy. This is supported by recent pregnancy and congenital malformation data with inhaled budesonide from a large randomized controlled trial.[3] In addition, recent treatment guidelines recommend the use of budesonide during pregnancy[4] because it has become clear that the benefits outweigh any possible concerns.[5]

The passage of oral steroids into breast milk has been studied.[6-8] However, there is no information available on the passage of inhaled budesonide or other ICSs into breast milk, and this information is important both for clinicians devising treatment plans and for the confidence of mothers to continue their treatment during breast-feeding.

The aim of this study was to assess budesonide concentrations in breast milk and plasma of asthmatic women receiving maintenance treatment with budesonide (administered through the Pulmicort Turbuhaler, AstraZeneca, Södertälje, Sweden) and to estimate the systemic exposure of breast-fed infants. The study was generally conducted according to recommended study methodologies for assessment of drug transfer into breast milk, infant dose, and extent of infant exposure.[9]

METHODS

Patients and study design

This was an open-label, single-center study that included 8 asthmatic breast-feeding women and their infants. Eligible mothers had been receiving maintenance treatment with inhaled budesonide administered through the Pulmicort Turbuhaler (200 or 400 μg twice daily) for at least 3 months and were considered to be at steady state. Four mothers were included at each dose level. Mothers were excluded if they had any clinically relevant concomitant disease or were pregnant or if their infants had experienced a significant illness within the previous 2 weeks. Mothers were to abstain from intake of concomitant medication (prescribed and nonprescribed) and grapefruit juice 1 week before the study day.

From [a]Clinical Development and [b]Development DMPK and Bioanalysis, AstraZeneca R&D, Lund, and [c]the Department of Paediatrics, University Hospital Malmö.

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Reprint requests: Anette Fält, BSc, Clinical Development, AstraZeneca R&D, Lund S221 87, Sweden. E-mail: anette.falt@astrazeneca.com.

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Abbreviations used
AUC: Area under the curve
C_{av}: Average steady-state concentration
C_{max}: Maximum concentration
ICS: Inhaled corticosteroid
LC-APCI-MS/MS: Liquid chromatography and atmospheric pressure chemical ionization tandem mass spectrometry
LOQ: Limit of quantification

Ethics

The study was performed in accordance with the ethical principles of the Declaration of Helsinki and was consistent with good clinical practice. The study was approved by the Regional Ethics Committee in Uppsala (Sweden), and written informed consent was obtained before any study procedure.

Study procedures

Eligible women were asked to record the times of budesonide inhalation in a diary over the 2 days preceding the study day and to ensure steady-state status and were instructed to take their last dose 12 hours before the scheduled dosing on the study day. Mothers arrived at the clinic in the morning and inhaled a single dose of budesonide, 200 or 400 μg, through the Turbuhaler according to their normal maintenance regimen. The first breast-feeding was to be given 20 minutes to 1 hour after the budesonide inhalation. The time of drug inhalation and breast-feeding were recorded.

Blood and breast milk collections

Venous blood samples (5 mL, heparinized) were collected from an intravenous cannula before dosing and 10, 20, and 40 minutes and 1, 2, 3, 4, 6, and 8 hours after dosing. Blood samples were collected before breast milk sampling, except for the predose sample. Plasma samples were frozen before analysis of budesonide. Breast milk was collected before dosing and at 20 minutes and 1, 3, 6, and 8 hours after dosing. The breast was cleaned before each collection, and all milk was collected from one breast by using an electric pump (maximum sampling time, 20 minutes). Well-mixed aliquots of 15 mL were frozen before analysis. Mothers were allowed to nurse their infants on the breast not used for breast milk collection at any time during the study period.

A single venous blood sample (2 mL, heparinized) was collected from 5 infants. Samples were to be collected close to expected infant maximum concentration (C_{max}; ie, preferably at 1–1.5 hours after the first breast-feed after inhalation). These time points were based on the assumptions that budesonide equilibrates rapidly between plasma and breast milk and time to maximal concentration (t_{max}) after oral administration of budesonide occurs at approximately the same time in infants as in adults.

Plasma and breast milk analyses

The plasma samples were analyzed by using the liquid chromatography and atmospheric pressure chemical ionization tandem mass spectrometry (LC-APCI-MS/MS) method with a $^2H_8$-labeled analogue as the internal standard to determine the concentration of budesonide at TNO Nutrition and Food Research, Zeist, The Netherlands.[10]

The method is based on automated solid-phase extraction, followed by LC-APCI-MS/MS. The calibration range was from 0.0100 to 10.0 nmol/L by using a sample volume of 1.00 mL, with an accuracy ranging from 96% to 100% and precision ranging from 13% to 2.4%.

The method was also validated for smaller plasma volumes, 0.250 and 0.500 mL, with calibration ranges of 0.0200 to 20.0 nmol/L (accuracy of 106% to 97% and precision of 4.1% to 3.6%) and 0.0400 to 40.0 nmol/L (accuracy of 105% to 92% and precision of 9.71% to 3.1%).[11]

The breast milk samples were analyzed by using a LC-APCI-MS/MS method with a $^2H_8$-labeled analogue as the internal standard to determine the concentration of budesonide at Development DMPK and Bioanalysis, AstraZeneca R&D, Lund, Sweden. Milk samples were precipitated with acetonitrile and thereafter subjected to solid-phase extraction on disposable C_{18} columns, followed by LC-APCI-MS/MS. The method was calibrated over the concentration range of 0.0500 to 6.08 nmol/L, with a lower limit of quantification (LOQ) of 0.0500 nmol/L. The mean accuracy values from the quality control samples at 0.150, 3.00, and 5.00 were 109%, 106%, and 104%, respectively, and the corresponding precision values were 1.4%, 4.0%, and 3.0%, respectively (data on file).

TABLE I. Baseline demographics of mothers and infants

	Budesonide, 200 μg twice daily (n = 4)	Budesonide, 400 μg twice daily (n = 4)
Mothers		
Age* (y)	29 (26–32)	32 (30–34)
Weight* (kg)	64 (50–74)	64 (56–77)
BMI* (kg/m^2)	24 (19–29)	25 (21–30)
Time since diagnosis† (y)	11	18
Infants		
Age* (mo)	5 (4–6)	3.3 (2–4)
Sex (male/female)	2/2	2/2
Weight* (kg)	7.6 (5.7–9.4)	5.9 (4.4–6.7)

BMI, Body mass index.
*Mean (range).
†Median.

Pharmacokinetic calculations

Pharmacokinetic parameters (area under the curve [AUC], C_{max}, t_{max}, and terminal half-life) for budesonide were calculated from plasma and breast milk concentrations by using standard noncompartmental methods. The AUC was calculated over a dosing interval of 12 hours by using the trapezoidal method and assuming monoexponential decay from the last observation above the LOQ. The average steady-state concentration (C_{av}) was calculated as AUC/12 hours. The milk/plasma ratio was calculated as AUC milk/AUC plasma.

The infant dose (in micrograms per kilogram per day) was calculated as the product of C_{av} in milk and the daily average milk intake (150 mL/kg/d).[12] The maternal dose was calculated as $F_{Pulmicort\ Turbuhaler} \times Daily\ dose/Maternal\ weight$ to reflect the amount of budesonide reaching the systemic circulation. $F_{Pulmicort\ Turbuhaler}$ equals 39% based on results from a previous study.[13] The relative infant dose (as a percentage) was calculated as infant dose/maternal dose.

Average infant plasma concentration ($C_{av\ infant}$) was estimated from infant oral bioavailability (set to 100% as the worst-case scenario), infant dose, and infant clearance (estimated as 29.5 mL/min/kg based on results from a study performed in children 3-6 years of age[14]) as follows: $Infant\ oral\ bioavailability \times Infant\ dose/Infant\ clearance$.

Pharmacokinetic parameters for the lactating women were compared with those for a reference group of 37 nonlactating women using 200 μg once daily or 400 μg twice daily budesonide. Women

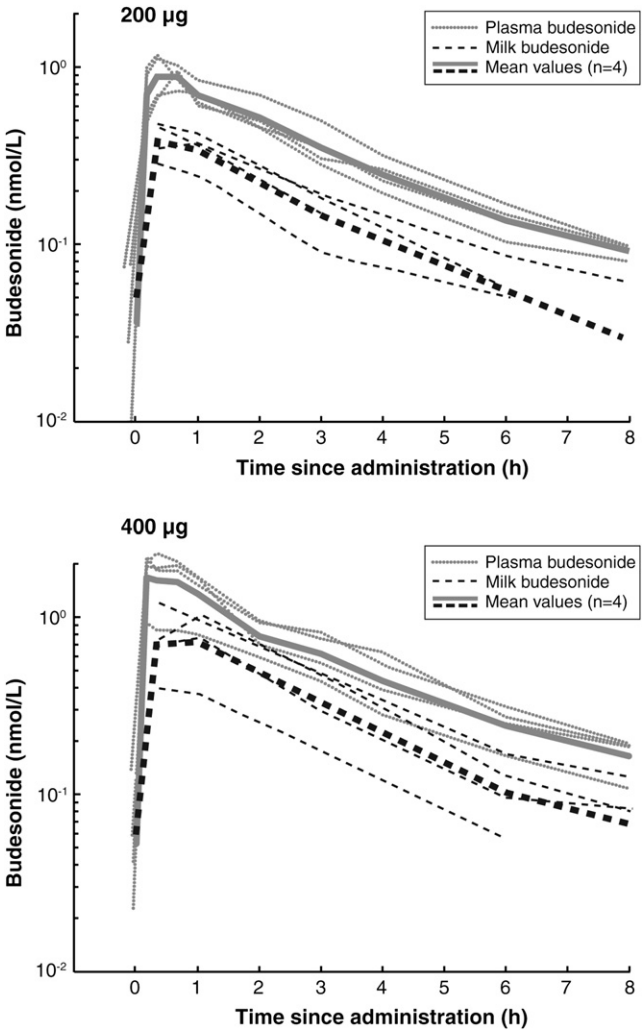

FIG 1. Budesonide plasma and breast milk concentrations at steady state after maintenance treatment with 200 μg (n = 4) and 400 μg (n = 4) twice daily administered through the Pulmicort Turbuhaler.

selected for inclusion in the reference groups were aged between 18 and 45 years and participated in two 3-month efficacy studies, with pharmacokinetic measurements at steady state.

RESULTS

Eight women, 4 at each dose level, aged 26 to 34 years and their infants aged 2 to 6 months were included in the study. Demographic features for the women and their infants in each dose group are summarized in Table I.

Budesonide in plasma and breast milk

Individual and mean plasma and breast milk concentration curves are shown in Fig 1. Budesonide could be quantified in all plasma samples, except for 1 predose sample. Postdose budesonide concentrations in milk could be followed for 8 hours in 4 patients, for 6 hours in 3 patients, and for 3 hours in 1 patient. Budesonide could only be quantified in 1 predose milk sample. Table II summarizes AUC, C_{av}, C_{max}, t_{max}, and terminal half-life values for plasma and breast milk and milk/plasma AUC ratio for the 200- and 400-μg twice daily groups, respectively. The pharmacokinetic parameters AUC and C_{max} seemed to be dose proportional. There was a linear relationship between budesonide concentrations in plasma and breast milk, with the concentration of budesonide in breast milk always being less than the corresponding plasma concentration in all patients and at all time points for both dose levels (Fig 2). The mean milk/plasma AUC ratio was 0.43 and 0.50 for the dose levels of 200 and 400 μg twice daily, respectively.

Pharmacokinetics in lactating mothers

The pharmacokinetics of budesonide in plasma in breast-feeding women were similar to the pharmacokinetics in a reference group of nonlactating women. Although higher variability was noted in the reference group, only minor differences in pharmacokinetic profiles were found. Dose-adjusted systemic exposure was 6.0×10^{-3} h/L for lactating mothers and 5.4×10^{-3} h/L for nonlactating mothers.

TABLE II. Pharmacokinetic parameters based on plasma and breast milk budesonide levels

Variable	Budesonide, 200 μg twice daily (n = 4)	Budesonide, 400 μg twice daily (n = 4)
Plasma		
AUC (nmol*h/L)*	2.95 (15%)	5.24 (32%)
C_{av} (nmol/L)*	0.246 (15%)	0.437 (32%)
C_{max} (nmol/L)*	0.977 (21%)	1.713 (44%)
t_{max} (min)†	30 (12)	20 (14)
$t_{1/2}$ (h)*	2.64 (15%)	2.90 (19%)
Breast milk		
AUC (nmol*h/L)*	1.26 (25%)	2.63 (51%)
C_{av} (nmol/L)*	0.105 (25%)	0.219 (51%)
C_{max} (nmol/L)*	0.390 (24%)	0.778 (52%)
t_{max} (min)†	32 (20)	43 (23)
$t_{1/2}$ (h)*	2.06 (28%)	2.04 (11%)
Breast milk and plasma		
Milk/plasma AUC ratio*	0.428 (25%)	0.502 (19%)

$t_{1/2}$, Terminal half-life.
*Geometric mean (coefficient of variation).
†Arithmetic mean (SD).

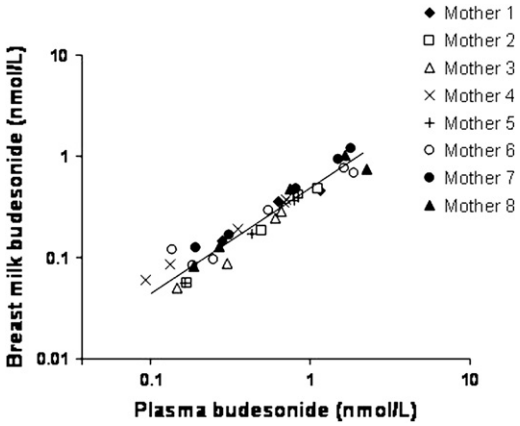

FIG 2. Relationship between budesonide concentrations in plasma and breast milk. Estimated slope 1.02 (95% CI, 0.91-1.13).

Infant exposure to budesonide

The infant dose was estimated to be 0.0068 and 0.0142 μg/kg/day after the maternal 200- and 400-μg doses, respectively (Table III). This corresponds to a daily infant dose of 0.3% of the daily maternal dose for both dose levels. Assuming complete oral bioavailability, the estimated average infant plasma concentrations were 0.37 and 0.77 pmol/L after the 200- and 400-μg doses, respectively; that is, the average infant plasma concentration was about 1/600th of the average maternal plasma concentration.

Plasma concentrations of budesonide were determined in 5 infants. Actual mean sampling time for infant blood samples was 1.5 hours (range, 0.7–2.0 hours) after the first breast-feeding after drug administration and 2.3 hours (range, 2.1–2.6 hours) after drug inhalation. All sample concentrations of budesonide were less than the LOQ limit (0.02–0.04 nmol/L).

TABLE III. Estimated infant dose and infant average plasma concentration and measured infant plasma concentration for the 2 doses

	Budesonide, 200 μg twice daily	Budesonide, 400 μg twice daily
Estimated parameters*	n = 4	n = 4
Maternal dose (μg/kg/d)	2.46 (18%)	4.91(14%)
Infant dose (μg/kg/d)	0.0068 (25%)	0.0142 (51%)
Relative infant dose (%)	0.28 (31%)	0.29 (56%)
C_{av} infant (pmol/L)	0.371 (25%)	0.773 (51%)
C_{av} infant/C_{av} mother (%)	0.151 (25%)	0.177 (19%)
Measured parameter		
Infant budesonide concentration	<LOQ (n = 2)	<LOQ (n = 3)

*Geometric mean (coefficient of variation).

Information on serious adverse events and discontinuations caused by adverse events were collected, and none were reported during the study.

DISCUSSION

In this study maintenance treatment with inhaled budesonide (200 or 400 μg twice daily) in asthmatic women resulted in negligible systemic exposure to budesonide in breast-fed infants. The estimated daily infant dose of budesonide based on the average breast milk concentration was approximately 0.3% of the daily maternal dose for both 200 and 400 μg twice daily. Estimates were conservative in that complete infant oral bioavailability (100%) of budesonide was assumed, despite oral availability in adults being estimated at 10%. Furthermore, the daily maternal dose was corrected for lung bioavailability (39%) of budesonide administered through the Pulmicort Turbuhaler to reflect the amount of budesonide reaching the systemic circulation of the mothers. The absence of detectable budesonide concentrations in any of the infants' single blood samples support that negligible amounts of budesonide are transferred to infants through breast milk. The times of blood sampling were scheduled around the times of expected infant C_{max}. As a result of practical issues, the time intervals between drug inhalation, breast-feeding, and blood sampling varied slightly but were close to the intended time intervals. The actual time intervals were 0.5 to 1.5 hours between drug inhalation and first breast-feeding (target, 0.3–1 hour) and 0.7 to 2.0 hours between first breast-feeding after drug inhalation and infant blood sampling (target, 1–1.5 hours). The results from this study indicated an equilibrium between plasma and breast milk budesonide concentrations, supporting passive diffusion of budesonide as the source of drug transfer into breast milk. Budesonide concentrations were always less in milk than in plasma (milk/plasma AUC ratio, 0.46). Women included in the study were assumed to be at steady state

because they were required to have received maintenance treatment with the Pulmicort Turbuhaler for at least 3 months before sample collection. There was no supervision of dosing on the days before the study day, only recording of the time of budesonide inhalation in diaries.

In the present study women were using 200 or 400 μg twice daily, dose levels considered to be representative of the majority of nursing mothers with asthma because these women tend to lower their doses during pregnancy and lactation. The pharmacokinetic profile of budesonide in breast milk followed that observed in plasma and displayed approximate dose proportionality between the 200- and 400-μg twice daily levels. Plasma budesonide has shown dose proportionality across the dose range of 400 to 1600 μg twice daily in patients with asthma.[15] Comparing the pharmacokinetic profile of budesonide in lactating women with that in nonlactating women revealed no obvious differences. Given that the transfer of budesonide from maternal plasma to breast milk occurs through passive diffusion and depends on plasma concentration, these data are likely to apply to other inhaled/intranasal formulations containing budesonide and for which similar exposure is expected.

This study is the first to measure breast milk concentrations of a corticosteroid after inhalation. Studies have examined excretion of prednisolone in human breast milk after repeated oral administration of 10 to 80 mg/d and found that the estimated average amount a suckling infant would ingest was 1.9% of the weight-adjusted maternal daily dose.[16] The exposure to the infant in the present study with inhaled budesonide, 200 to 400 μg twice daily, was 0.3% of the maternal dose. Thus the relative dose to the infant is slightly smaller for inhaled budesonide than for oral prednisolone, which is reassuring because inhaled budesonide in the doses administered to the mothers in this study is considered to have less systemic effects than a standard dose of prednisolone 10 mg/d.

In conclusion, maintenance asthma therapy with inhaled budesonide (200 or 400 μg twice daily administered through the Pulmicort Turbuhaler) in asthmatic women results in negligible systemic exposure to budesonide in breast-fed infants, supporting continued maintenance treatment during breast-feeding.

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