Plasma concentrations of inhaled corticosteroids in relation to airflow obstruction in asthma

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Aims

To compare the pharmacokinetic profiles of beclometasone, budesonide, fluticasone and mometasone following inhalation in patients with asthma, and explore the relationship between lung function and plasma drug concentrations.

Methods

Thirty subjects with asthma and a forced expiratory volume in 1 s (FEV₁) ranging from 36 to 138% predicted, inhaled 800 µg beclometasone, budesonide and mometasone and 1000 µg fluticasone in random order. Plasma drug concentrations were measured over 8 h and the relationship between the area under the plasma concentration–time curve (AUC_{0–8}) and lung function was modelled using linear regression. Estimated AUC_{0–8} values at 50 and 100% predicted FEV₁ were compared for each drug.

Results

Pharmacokinetic profiles differed markedly between the drugs. Correlation coefficients for the relation between FEV₁% predicted and AUC_{0–8} values for beclometasone, budesonide, fluticasone and mometasone were 0.37 ($P = 0.05$), 0.33 ($P = 0.08$), 0.25 ($P = 0.2$) and 0.52 ($P = 0.004$), respectively, and estimated AUC_{0–8} values were 1.3 [95% confidence interval (CI) 1.0, 1.8], 1.3 (95% CI 1.0, 1.8), 1.4 (95% CI 0.9, 2.2) and 2.2 (95% CI 1.3, 3.5) times higher for the four drugs, respectively, at 100 compared with 50% predicted FEV₁.

Conclusion

The higher plasma concentrations of inhaled corticosteroids in patients with a higher FEV₁% predicted suggests that, for any given dose, these patients will be at greater risk of developing adverse systemic effects with long-term use.

Introduction

Although inhaled corticosteroids are used widely to treat asthma and chronic obstructive pulmonary disease (COPD), recent evidence suggests that they are responsible for adverse systemic effects [1]. Currently available drugs are absorbed into the systemic circulation, predominantly from the lung and more variably from the gastrointestinal tract [2]. The risk of adverse systemic effects from inhaled corticosteroids will depend on the

extent of systemic absorption and is likely to differ between agents due to their different physicochemical and pharmacokinetic properties. Recent studies have shown that absorption and systemic effects of fluticasone propionate are greater in healthy subjects than in patients with asthma or COPD who have marked airflow obstruction [3–6]. However, this is not the case for budesonide [4, 5]. A further study has shown that the extent of adrenal suppression following 500 µg flutica-

sone propionate was closely related to lung function, cortisol suppression being greater with increasing forced expiratory volume in 1 s (FEV₁) [7]. Whether the systemic absorption of other inhaled corticosteroids relates to lung function is unknown. To explore this, we compared plasma concentrations of beclometasone monopropionate, budesonide, fluticasone propionate and mometasone furoate following inhalation of a single dose in subjects with asthma who had a wide range of FEV₁ values. The study also provided comparative data on the pharmacokinetic profiles of the four inhaled corticosteroids in the same subjects for the first time.

Methods

Subjects

Thirty nonsmoking subjects with asthma aged between 18 and 70 years were recruited between October 2003 and February 2004 from our volunteer database. Subjects were selected to provide a range of FEV₁ values from 30% predicted [8] upwards. Only those with stable asthma defined as no change in asthma symptoms or treatment for at least 2 months were recruited. There were no restrictions based on treatment, but subjects were excluded if they had significant comorbidity, were taking any medication known to alter the metabolism of corticosteroids, were pregnant or lactating, or had a greater than 20 pack year smoking history. The study was approved by Nottingham Research Ethics Committee and written informed consent was obtained from all subjects.

Protocol

Subjects were screened at an initial visit to measure FEV₁, assess their suitability for the study and for them to familiarize themselves with the placebo dry powder inhalers. Subjects taking fluticasone propionate, budesonide or mometasone furoate were changed to beclometasone dipropionate at least 4 days before the study. All subjects were then asked to omit the beclometasone dipropionate from the evening before the study to allow time for beclometasone monopropionate to be cleared from the plasma. Subjects attended the department in the morning of the study, a venous cannula was inserted and blood taken for baseline drug assay. After 10 min of rest, FEV₁, forced vital capacity (FVC) and peak expiratory flow (PEF) were measured on two occasions 5 min apart. Subjects then inhaled two doses from each of four inhalers in random order, according to a computer-generated code, with a mouth rinse after each drug. The drugs and total doses administered were beclometasone dipropionate 800 µg (Becodisks®; Allen & Hanburys, Uxbridge, UK), budesonide 800 µg (Turbohaler®; Astra-

Zeneca, Luton, UK), fluticasone propionate 1000 µg (Accuhaler®; GlaxoSmithKline, Middlesex, UK) and mometasone furoate 800 µg (Asmanex Twisthaler®; Schering-Plough, Kenilworth, NJ, USA). Ten-millilitre venous blood samples were transferred into sodium fluoride/EDTA tubes at 0, 5, 15, 30, 60 min and 2, 3, 4, 6 and 8 h after drug administration, centrifuged at 190 g for 10 min and the plasma was extracted and frozen at -70 °C.

The main study end-point was the relationship between the percent predicted FEV₁ and the area under the plasma concentration-time curve (AUC₀₋₈) for each drug. Power calculations based on a linear regression model showed that studying 30 patients would give 90% power to detect a correlation between FEV₁% predicted and AUC of ≥0.5.

Measurement of lung function

FEV₁ and FVC were measured with a dry bellows spirometer (Vitalograph, Buckingham, UK) as the higher of two successive readings within 100 ml. The same spirometer was used for all measurements and was calibrated weekly. PEF was measured with a mini-Wright flowmeter as the best of three readings.

Drug analyses

The plasma concentrations of budesonide, beclometasone monopropionate (the active metabolite of beclometasone dipropionate), fluticasone propionate and mometasone furoate were determined using validated high-performance liquid chromatography/tandem mass spectrometry methods with a Micromass Quattro LC-Z triple quadrupole mass spectrometer (Beverly, MA, USA) at the College of Pharmacy, Department of Pharmaceutics, University of Florida, USA [9-12]. The lower limits of detection for the assays were 15 pg ml⁻¹ for beclometasone monopropionate, fluticasone propionate and mometasone furoate and 50 pg ml⁻¹ for budesonide. The intra- and interbatch coefficients of variation for the assays were 3.8-12.4% and 11.6% for beclometasone monopropionate at a concentration of 0.5 ng ml⁻¹, 2.6-6.4% and 5.4% for budesonide at a concentration of 0.5 ng ml⁻¹, 8.3-15.6% and 13.7% for fluticasone propionate at a concentration of 0.1 ng ml⁻¹ and 2.6-10.9% and 6.4% for mometasone furoate at a concentration of 0.12 ng ml⁻¹.

Data analysis

Plasma concentrations of beclometasone monopropionate, budesonide, fluticasone propionate and mometasone furoate were plotted against time for each subject. Pharmacokinetic parameters [maximum

plasma concentration ($C_{\max}$), time to $C_{\max}$, AUC_{0-8} , mean residence time and terminal half-life] were calculated using WinNonlin® (Professional Version 3.1; Pharsight Corporation, Mountain View, CA, USA). Concentrations below the limit of quantification were reported as missing and extrapolated during noncompartmental analysis.

Plasma drug AUC_{0-8} values were log transformed to normality and then plotted against the mean of the two baseline FEV_1 measurements, $FEV_1\%$ predicted and FEV_1/FVC ratio, and against PEF and PEF% predicted [13]. The correlation coefficient (r) was calculated and trendlines fitted using linear regression. Partial correla-

tion coefficients were calculated for the relationship between lung function and AUC_{0-8} after controlling for two potential confounding factors, age and gender. To estimate the magnitude of the effect of lung function on AUC_{0-8} , the equation derived from the linear regression model was used to predict the ratio of AUC_{0-8} values at 100% and 50% predicted FEV_1 and PEF.

Results

All 30 subjects (mean age 57 years, 16 men) successfully completed the study. Baseline characteristics of the subjects are shown in Table 1. FEV_1 prior to drug inhalation ranged from 36% to 138% predicted.

Table 1

Baseline characteristics

Subject	Gender	Age, years	BMI	$FEV_{1,}$ l	$FEV_{1,}$ % pred.	FVC, l	$FEV_{1,}/FVC$	PEF, l min ⁻¹	PEF, % pred.	Smoking history, pack-years	Usual inhaled corticosteroid
1	M	70	22.6	1.3	48	3.6	0.35	270	50	0	Beclometasone dipropionate
2	M	52	29.7	3.1	90	4.3	0.71	480	79	0	Nil
3	M	61	24.9	1.3	36	3.9	0.32	245	42	0	Beclometasone dipropionate
4	F	61	30.0	2.3	98	2.9	0.79	425	97	10	Beclometasone dipropionate
5	F	53	23.0	2.1	86	2.8	0.74	360	79	0	Beclometasone dipropionate
6	M	49	33.4	2.7	78	4.2	0.65	460	75	5	Fluticasone propionate
7	M	48	28.7	2.2	66	3.7	0.59	360	59	1	Fluticasone propionate
8	M	61	32.2	3.3	106	4	0.82	555	96	20	Beclometasone dipropionate
9	F	45	36.6	2.7	100	3.1	0.88	425	90	10	Beclometasone dipropionate
10	M	61	24.6	2.5	82	3.2	0.78	450	78	0	Nil
11	M	55	24.2	1.4	42	3	0.47	350	58	0	Beclometasone dipropionate
12	M	46	26.8	3.2	74	4.3	0.74	530	82	0	Budesonide
13	F	56	22.2	3.5	138	4.1	0.86	460	101	0	Beclometasone dipropionate
14	F	68	26.1	1.2	62	1.9	0.63	255	62	0	Beclometasone dipropionate
15	F	44	27.1	3.2	113	4.3	0.74	455	95	0	Beclometasone dipropionate
16	F	61	29.6	1.8	72	2.15	0.81	310	70	10	Beclometasone dipropionate
17	F	62	26.7	2.2	96	3	0.72	465	107	0	Beclometasone dipropionate
18	M	50	25.9	2.6	75	4.2	0.63	430	70	0	Nil
19	F	35	23.3	2.4	93	3.3	0.73	460	97	0	Budesonide
20	M	67	29.0	1.9	65	3.1	0.61	390	71	10	Fluticasone propionate
21	F	58	29.2	0.9	47	2	0.44	195	45	0	Nil
22	M	60	30.1	1.7	53	3.2	0.53	235	40	0	Nil
23	M	41	23.5	2.3	57	3.8	0.59	455	71	0	Budesonide
24	F	58	33.6	2.1	87	2.6	0.78	370	83	15	Beclometasone dipropionate
25	F	66	37.0	1.5	77	2.3	0.66	300	72	0	Beclometasone dipropionate
26	M	51	27.8	1.7	46	3.2	0.54	415	67	0	Nil
27	M	63	29.2	1.3	43	2.8	0.46	275	48	0	Beclometasone dipropionate
28	F	63	30.2	2.5	99	3.2	0.8	485	110	20	Budesonide
29	F	66	28.7	0.8	44	1.5	0.55	180	43	0	Budesonide
30	M	68	34.1	1	40	2.6	0.36	220	41	0	Budesonide
Mean		57	28.3	2.1	74	3.2	0.6	376	73	3.4	
(SD)		(9)	(4.0)	(0.8)	(25)	(0.8)	(0.2)	(104)	(21)	(6.2)	

BMI, Body mass index; $FEV_{1,}$ forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

Figure 1

Mean (SE) plasma concentration–time curves for beclometasone monopropionate (BMP), budesonide (BUD), fluticasone propionate (FP) and mometasone furoate (MF) following inhalation. (Note that ordinates have different scales.)

Table 2

Geometric mean (95% CI) pharmacokinetic parameters for beclometasone monopropionate (BMP), budesonide (BUD), fluticasone propionate (FP) and mometasone furoate (MF)

	BMP	BUD	FP	MF
T_{max} (h)	2.51 (1.91, 3.31)	0.13 (0.10, 0.16)	0.90 (0.68, 1.20)	0.92 (0.60, 1.40)
MRT (h)	9.07 (7.14, 11.52)	3.47 (3.21, 3.76)	8.46 (6.70, 10.68)	6.61 (5.69, 7.70)
$T_{1/2}$ (h)	5.34 (4.10, 6.95)	2.63 (2.46, 2.82)	5.68 (4.46, 7.23)	4.46 (3.65, 5.45)
C_{max} (ng ml ⁻¹)	0.33 (0.28, 0.39)	1.46 (1.18, 1.79)	0.09 (0.07, 0.10)	0.07 (0.05, 0.09)
AUC_{0-8} (ng ml ⁻¹ h ⁻¹)	1.72 (1.46, 2.03)	3.28 (2.82, 3.81)	0.38 (0.30, 0.47)	0.32 (0.24, 0.43)

T_{max} Time of maximum plasma concentration; MRT, mean residence time; $T_{1/2}$, terminal half-life; C_{max} maximum plasma concentration; AUC_{0-8} area under the plasma concentration–time curve.

Four subjects had detectable plasma concentrations of one inhaled corticosteroid in their baseline sample. In two subjects this was beclometasone monopropionate (1152 pg ml⁻¹ and 46 pg ml⁻¹), in one, who normally took budesonide, this drug was detected (215 pg ml⁻¹) and in one who usually took beclometasone dipropionate, fluticasone propionate was detected (19 pg ml⁻¹). These data were excluded from the analysis.

All four inhaled corticosteroids were present at detectable plasma concentrations following inhalation

in all subjects and plasma concentrations were above the lower limit of quantification in the majority of samples (99%, 97%, 95% and 93% for budesonide, beclometasone monopropionate, fluticasone propionate and mometasone furoate, respectively).

The shape of the mean plasma drug concentration–time curves and the pharmacokinetic parameters varied considerably between drugs, as shown in Figure 1 and Table 2. Data from two subjects (involving beclometasone dipropionate and mometasone furoate) were

Figure 2

Relationship between forced expiratory volume in 1 s (FEV_1) % predicted and the area under the plasma concentration–time curve (AUC_{0-8}) for beclometasone monopropionate (BMP), budesonide (BUD), fluticasone propionate (FP) and mometasone furoate (MF) following inhalation. (Note that ordinates have different scales)

unsuitable for pharmacokinetic modelling and were excluded from the analysis.

Peak plasma concentrations following inhalation occurred within 10 min for budesonide and after 0.9, 0.9 and 2.5 h for fluticasone propionate, mometasone furoate and beclometasone monopropionate, respectively. Mean residence times showed a similarly wide variation from 3.5 h with budesonide to 9.1 h with beclometasone monopropionate. The terminal half-life ranged from 2.6 h for budesonide to 5.7 h for fluticasone propionate. The magnitude of the peak plasma concentration also differed markedly between drugs, being highest for budesonide at 1.5 ng ml^{-1} , and 21, 16 and four times lower for mometasone furoate, fluticasone propionate and beclometasone monopropionate, respectively. AUC_{0-8} values ranged from $3.28 \text{ ng ml}^{-1} \text{ h}^{-1}$ for budesonide to $0.32 \text{ ng ml}^{-1} \text{ h}^{-1}$ for mometasone furoate (Table 2).

AUC_{0-8} values tended to be higher in patients with a higher FEV_1 % predicted, for all four drugs (Figure 2).

The correlation coefficients for the relationship between FEV_1 % predicted and AUC_{0-8} for beclometasone monopropionate, budesonide, fluticasone propionate and mometasone furoate were 0.37 ($P = 0.05$), 0.33 ($P = 0.08$), 0.25 ($P = 0.20$) and 0.52 ($P = 0.004$), respectively. The same pattern was seen for the relationship between PEF % predicted and AUC_{0-8} with r -values for beclometasone monopropionate, budesonide, fluticasone propionate and mometasone furoate being 0.40 ($P = 0.03$), 0.32 ($P = 0.09$), 0.22 ($P = 0.25$) and 0.55 ($P = 0.002$), respectively. The correlation between other measures of lung function (absolute FEV_1 , PEF and FEV_1/FVC ratio) and AUC_{0-8} was similar but generally weaker than that between FEV_1 and PEF % predicted and AUC_{0-8} . Both age and gender caused a $\geq 10\%$ change in the correlation coefficients. The correlation between FEV_1 % predicted and AUC_{0-8} was stronger after adjusting for age, but weaker after adjusting for gender (Table 3).

Estimated AUC_{0-8} values were higher at 100% compared with 50% predicted FEV_1 , for all four drugs, the ratios for beclometasone monopropionate, budesonide, fluticasone propionate and mometasone furoate being 1.3 [95% confidence interval (CI) 1.0, 1.8], 1.3 (95% CI

1.0, 1.8), 1.4 (95% CI 0.9, 2.2) and 2.2 (95% CI 1.3, 3.5), respectively. The same pattern was seen with PEF% predicted (Table 4).

Discussion

This is the first study to compare the pharmacokinetic profiles of a range of inhaled corticosteroids following inhalation in the same patients and to explore the extent to which the systemic absorption of beclometasone monopropionate, budesonide, fluticasone propionate and mometasone furoate relates to lung function.

The pharmacokinetic profiles of fluticasone propionate and mometasone furoate were broadly similar but differed markedly from beclometasone monopropionate and budesonide. The latter drug, the most water-soluble of the four, had the shortest mean residence time, time to peak plasma concentration (T_{max}) and terminal half-life. Beclometasone monopropionate had the longest pulmonary residence time and T_{max} . Beclometasone monopropionate, fluticasone propionate and mometasone furoate had long half-lives compared with budesonide.

The pharmacokinetic parameters for budesonide are in keeping with previous data [3, 4, 6, 14, 15]. Rapid absorption is a function of its lower lipophilicity and greater solubility in bronchial fluid [16], whereas its short terminal half-life will reflect a lower volume of distribution, since high clearance is a feature of all inhaled corticosteroids [2]. Budesonide had a much higher peak plasma concentration than the other three drugs, an effect attributed to high pulmonary deposition

Table 3

Partial correlation coefficients (r) for the relationship between forced expiratory volume in 1 s (FEV_1) % predicted and $\log_{10}$ area under the plasma concentration–time curve (AUC_{0-8}) before and after adjusting for age and gender

	r	P -value
Beclometasone monopropionate		
Unadjusted	0.37	0.05
Age	0.48	0.01
Gender	0.29	0.14
Budesonide		
Unadjusted	0.33	0.08
Age	0.36	0.06
Gender	0.26	0.19
Fluticasone propionate		
Unadjusted	0.25	0.20
Age	0.38	0.05
Gender	0.07	0.73
Mometasone furoate		
Unadjusted	0.52	0.004
Age	0.56	0.002
Gender	0.41	0.03

Table 4

The estimated regression coefficient for the slope (95% CI) of the linear regression on $\log_{10}$ AUC and the estimated ratio (95% CI) of AUC at 100% vs. 50% predicted FEV_1

	Regression coefficient (95% CI)	Ratio of AUC_{0-8} at 100% vs. 50% predicted (95% CI)
<i>Beclometasone monopropionate</i>		
FEV_1 per % predicted	0.002 (0, 0.005)	1.3 (1.0, 1.8)
PEF per % predicted	0.003 (0, 0.006)	1.4 (1.0, 2.0)
<i>Budesonide</i>		
FEV_1 per % predicted	0.002 (0, 0.005)	1.3 (1.0, 1.8)
PEF per % predicted	0.003 (0, 0.006)	1.4 (1.0, 2.0)
<i>Fluticasone propionate</i>		
FEV_1 per % predicted	0.003 (– 0.001, 0.007)	1.4 (0.9, 2.2)
PEF per % predicted	0.003 (– 0.002, 0.008)	1.4 (0.8, 2.5)
<i>Mometasone furoate</i>		
FEV_1 per % predicted	0.007 (0.002, 0.011)	2.2 (1.3, 3.5)
PEF per % predicted	0.009 (0.004, 0.014)	2.8 (1.6, 5.0)

AUC_{0-8} , area under the plasma concentration–time curve; FEV_1 , forced expiratory volume in 1 s; PEF, peak expiratory flow.

by the Turbohaler® [17], together with its more rapid absorption and lower volume of distribution compared with the other drugs.

Mean residence time and $T_{\max}$ for beclometasone monopropionate were long, reflecting its greater lipophilicity and greater oral bioavailability (up to 41% compared with 11% for budesonide and <1% for fluticasone propionate and mometasone furoate [2, 18–21]). Our values for mean residence time and terminal half-life for beclometasone monopropionate were greater than those reported in studies using metered dose inhalers [18, 21, 22], perhaps due to differences in particle characteristics and deposition pattern with dry powder inhalers. The lower peak plasma concentration of beclometasone monopropionate compared with budesonide is in keeping with its slower absorption and greater volume of distribution.

Fluticasone propionate and mometasone furoate had fairly similar absorption profiles. The long terminal half-life of fluticasone propionate may be due to its large volume of distribution or ‘flip-flop pharmacokinetics’, because of its slow release from the lungs. Both drugs had particularly low peak plasma concentrations, even though fluticasone propionate was given at a slightly higher dose than the other three inhaled corticosteroids. Slow absorption from the lungs, increased mucociliary clearance and high volumes of distribution are likely to explain these findings. Our pharmacokinetic data for fluticasone propionate are similar to those reported previously [3, 4, 6, 14, 15], whereas the only published data on mometasone furoate were obtained using a relatively insensitive assay and therefore are not comparable [23].

The AUC_{0-8} values tended to be higher in patients with better lung function for all four drugs. The findings suggest that the systemic absorption of beclometasone, budesonide, fluticasone propionate and mometasone furoate is 1.3, 1.3, 1.4 and 2.2 times higher at 100% predicted FEV_1 compared with 50% predicted FEV_1 . The effect was greatest for mometasone furoate, although the study was not powered to compare the magnitude of effect between drugs.

The inhaled corticosteroids were administered using powder inhalers, and decreased inspiratory flow in subjects with greater airflow obstruction may have caused less drug to be delivered to the airways and more central deposition. Drug in the larger airways would then be more likely to be removed by mucociliary clearance, particularly for those that dissolve slowly in airway lining fluid, such as mometasone furoate and fluticasone propionate, compared with drugs with high water solubility, such as budesonide [16].

The stronger relationship between lung function and AUC_{0-8} values after adjusting for age but weaker after adjusting for gender, indicates that factors other than lung function affect the systemic absorption of inhaled corticosteroids. Such a confounding factor will decrease the strength of any relationship between lung function and plasma AUC values in cross-sectional studies. This conclusion is supported by our parallel study, in which we compared plasma concentrations of budesonide and fluticasone propionate following inhalation with and without prior methacholine-induced bronchoconstriction (mean fall in FEV_1 of 33%). Mean AUC values were decreased for both drugs after lowering FEV_1 within subjects, but not when we compared differences in the effect of FEV_1 on AUC between subjects.

In conclusion, our study has shown marked differences in the pharmacokinetic profiles between beclometasone monopropionate, budesonide, fluticasone propionate and mometasone furoate following inhalation of single doses. The systemic absorption of all four inhaled corticosteroids appears to be greater in patients with a higher $FEV_1\%$ predicted, although other factors, including age and gender, affect this relationship. Our findings reinforce the importance of reviewing the need for higher doses of an inhaled corticosteroid, particularly in patients with relatively normal lung function, and in patients whose lung function improves with treatment.

Competing interests

The division of respiratory medicine has previously received financial support for clinical research from AstraZeneca and GlaxoSmithKline.

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