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Pharmacokinetic Differences between Chlorofluorocarbon and Chlorofluorocarbon-free Metered Dose Inhalers of Beclomethasone Dipropionate in Adult Asthmatics

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Abstract

We have compared the serum pharmacokinetics of the metabolites of beclomethasone dipropionate after inhalation from chlorofluorocarbon (CFC) and hydrofluoroalkane HFA-134a (HFA) formulations in asthmatic patients.

Twenty-three patients completed this open-label, randomized, single-dose, three-period crossover study. Each patient received in separate periods 200 μg or 400 μg HFA–beclomethasone dipropionate, or 400 μg CFC–beclomethasone dipropionate. Venous blood samples were collected over 24 h for the determination of beclomethasone esters and beclomethasone in the serum.

Significant differences in pharmacokinetics following HFA– and CFC–beclomethasone dipropionate were observed. Following a 400 μg beclomethasone dipropionate dose, the HFA formulation gave mean maximum concentrations (C_{max}) and area under the curve (AUC) values of beclomethasone esters of 1153 pg mL^{-1} and 4328 pg h mL^{-1}, respectively, and beclomethasone C_{max} and AUC values of 69 pg mL^{-1} and 682 pg h mL^{-1}, respectively. These values were approximately 2–3-fold those seen with the CFC formulation (beclomethasone esters C_{max} and AUC of 380 pg mL^{-1} and 1764 pg h mL^{-1}, respectively; beclomethasone C_{max} and AUC of 41 pg mL^{-1} and 366 pg h mL^{-1}, respectively). Beclomethasone esters, the major component of beclomethasone dipropionate in the serum, peaked significantly earlier for the HFA formulation (0·8 h) than for the CFC formulation (2 h). Tests for dose proportionality of beclomethasone esters pharmacokinetics following HFA–beclomethasone dipropionate showed that the two hydrofluoroalkane strengths were proportional.

The more rapid and greater efficiency of systemic drug delivery of the HFA formulation compared with the CFC formulation can be explained if most of each inhalation from CFC–beclomethasone dipropionate is swallowed and absorbed orally, whereas most of each inhalation from HFA–beclomethasone dipropionate is absorbed through the lungs. There is a need for comprehensive dose–response efficacy trials, with the use of the steep portion of the dose–response relationship, to evaluate the significance of these pharmacokinetic differences.

Current chlorofluorocarbon (CFC) metered dose inhalers (MDIs) of beclomethasone dipropionate deliver drug particles of approximately 3·5 $\pm$ μ mass mean aerodynamic diameter (mmad). However, the reformulated MDI with the non ozone-depleting propellant hydrofluoroalkane HFA-134a delivers drug particles of about 1·1 $\pm$ μ mmad (Leach et al 1998). To determine the effect of the different particle size on the effectiveness of the two beclomethasone dipropionate MDIs, efficacy studies were conducted to compare the CFC formulation and the HFA formulation in asthmatic patients (Davies et al 1998). Pharmacokinetic comparisons were also conducted to provide a quicker and more sensitive systemic evaluation of the product differences than would pharmacological measures. The purpose of this study was to

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compare the serum pharmacokinetics of beclomethasone dipropionate-derived metabolites from CFC and HFA formulations in asthmatic patients. A limitation of the study design was that although pharmacokinetics could be related to the administered dose, pharmacokinetics could not be directly extrapolated to anti-asthmatic efficacy (Lawrence et al 1997). Thus, pharmacokinetic study results may have a limited clinical interpretation.

A preliminary report on some of the pharmacokinetic results of this study has been presented (Seale & Harrison 1998).

Materials and Methods

Inhalers

The HFA–beclomethasone dipropionate MDIs delivered 50 μg beclomethasone dipropionate ex-valve and were obtained from a production lot (3M Health Care Ltd, Loughborough, UK). The CFC–beclomethasone dipropionate MDIs delivered 50 μg beclomethasone dipropionate ex-valve and were obtained from a commercial source (Allen & Hanburys, NC). All inhalers were primed before use.

Study population

Twenty-seven patients with stable mild asthma, between the ages of 18 and 50 years, were enrolled and received medication in period 1. Both sexes were allowed in the study. Female subjects had to be at least two years postmenopausal, surgically sterile, or if of childbearing potential be using a barrier method or intrauterine device for birth control. All patients had a pre-study forced expiratory volume in 1 s $\geq$ 70% of predicted normal, were within 20% of ideal body weight, demonstrated proper use of a placebo MDI and were otherwise healthy as judged by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory tests. All patients were non-smokers; of the patients who had smoked in the past, all had abstained from smoking for at least one year. Patients were excluded if they had received any new or non-asthma related prescription drug within four weeks, or any intramuscular steroid, steroid-containing contraceptive, or more than one dose of an oral steroid within three months of recruitment. Inhaled β-agonist use was not allowed within 4 h of each study period. All patients gave written informed consent. An independent medical ethics review committee approved the protocol.

Study design

This study was an open-label, randomized, single-dose, three-period crossover. Each patient received in separate periods 200 μg or 400 μg HFA–beclomethasone dipropionate, or 400 μg CFC–beclomethasone dipropionate as multiple inhalations from the appropriate inhaler. The patient self-administered all inhalations while under the supervision of a study coordinator. Inhalations began at the same time of day ($\pm$ 15 min) in each period. Patients were instructed in proper inhalation technique using a 10-s breath hold and took each inhalation 30 s apart. Time zero for each dose was defined as the time when the inhaler was first actuated. Safety was monitored throughout the study.

Beclomethasone. Beclomethasone was separated from the serum by a liquid-liquid extraction procedure. Serum samples were extracted with ethyl ether, and the ether phase was evaporated under nitrogen and reconstituted in mobile phase. A sample was injected into a liquid chromatograph equipped with a triple quadruple mass spectrometer, operated under negative ion chemical ionization with the use of argon. This method had a calibration range of 10–300 pg mL^{-1} in 1 mL serum. The intra- and interday coefficients of variation were less than 10% at the limit of quantitation of the assay. Further details of this method have been published elsewhere (Harrison et al 1997).

Beclomethasone esters. Beclomethasone dipropionate and metabolites were separated from the serum by the liquid–liquid extraction procedure described above for beclomethasone. The sample extracts were then hydrolysed to convert any beclomethasone dipropionate and beclomethasone monopropionate esters (17-BMP and 21-BMP) to beclomethasone, which is referred to as total-beclomethasone. The total-beclomethasone was then assayed as indicated above for beclomethasone. The linear range of this method was 36–709 pg mL^{-1} in 1 mL serum to allow for the higher beclomethasone concentrations in the hydrolysed samples. The intra- and interday coefficients of variation were less than 10% at the limit of quantitation of the assay. The serum concentration of beclomethasone esters was calculated by subtracting beclomethasone from the total beclomethasone.

Results

Study population

Twenty-three patients with mild asthma (17 males and 6 females) between 21 and 49 years of age (mean 30·6 years) completed the study. Four additional patients withdrew from the study for reasons unrelated to the drug treatments. No clinically meaningful abnormalities were found in vital signs, physical examinations or clinical laboratory tests at the end of the study.

Most adverse events were attributed to the primary disease. Only two adverse events were coded as possibly related to study treatments. One patient reported a mild cough within 15 min of receiving the 400-μg HFA formulation and one patient reported moderate chest tightness within 15 min of receiving the 400-μg CFC formulation.

Pharmacokinetics of beclomethasone esters

Examination of the serum levels for the first 2 h following CFC- or HFA–beclomethasone dipropionate clearly showed a marked difference between these two products in the appearance of beclomethasone esters (Figure 1). Similar serum levels of beclomethasone esters were seen at 2 h and thereafter for the 400-μg CFC formulation and the 200-μg HFA formulation. Consistent with these observations, the 400 μg HFA–beclomethasone dipropionate produced higher serum levels at all sampling times than did the 400 μg CFC-beclomethasone dipropionate formulation (Figure 1).

Intersubject variability in the pharmacokinetic parameters appeared to be higher for the CFC than for the HFA formulation. Coefficients of variation for beclomethasone esters C_{max} and AUC ranged from 26 to 34% for HFA–beclomethasone dipropionate, and the C_{max} and AUC for CFC–beclomethasone dipropionate were 43% and 50%, respectively (Table 1). Significant differences in the pharmacokinetics of the HFA and the CFC formulations were observed (Table 3); the two products were not pharmacokinetically equivalent for C_{max}, AUC or T_{max}.

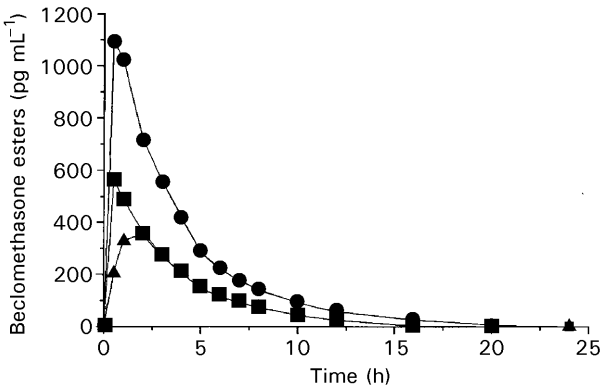

Figure 1. Mean serum concentrations of beclomethasone esters following 200 μg HFA–beclomethasone dipropionate (■), 400 μg HFA–beclomethasone dipropionate (●), and 400 μg CFC–beclomethasone dipropionate (▲).

Tests for dose proportionality of the beclomethasone esters pharmacokinetics following 200 and 400 μg HFA–beclomethasone dipropionate showed that the two strengths were proportional and there was no statistical difference in T_{max} (Table 3).

Pharmacokinetics of beclomethasone

Levels of beclomethasone were less than one tenth those of beclomethasone esters and appeared later in the serum than the esters (Figure 2). The intersubject coefficients of variation for beclomethasone C_{max} and AUC ranged from 26 to 39% for the HFA formulation, and were 36% and 56% for CFC–beclomethasone dipropionate C_{max} and AUC, respectively (Table 2). The same trends in the pharmacokinetic results observed for this metabolite were observed for beclomethasone esters, although paired differences between treatments did not always reach statistical significance for beclomethasone (Table 3). The elimination half-life of beclomethasone was calculated for the three treatments. Mean values ($\pm$ s.d.) of $7{\cdot}1 \pm 1{\cdot}4$, $6{\cdot}5 \pm 1{\cdot}2$, and $6{\cdot}3 \pm 1{\cdot}3$ h were calculated following the 200 μg HFA–beclomethasone dipropionate, 400 μg HFA–beclomethasone dipropionate, and 400 μg CFC–beclomethasone dipropionate treatments, respectively.

The mean percentages ($\pm$ s.d.) of beclomethasone in the hydrolysed samples following inhalation of 200 μg HFA–beclomethasone dipropionate, 400 μg HFA–beclomethasone dipropionate, and 400 μg CFC–beclomethasone dipropionate were $12{\cdot}9 \pm 2{\cdot}7$, $13{\cdot}8 \pm 2{\cdot}1$, and $17{\cdot}0 \pm 3{\cdot}5$%, respectively. These percentages of beclomethasone in the hydrolysed samples from the HFA formulations were significantly different from that of the CFC formulation. For example, the 90% confidence interval of the ratio of 200 μg HFA–beclomethasone dipropionate to 400 μg CFC–beclomethasone dipropionate was 0·70–0·83.

Discussion

A sensitive bioanalytical method to detect low levels of beclomethasone in human serum was developed, which allowed the study of beclo-

Table 1. Pharmacokinetic results for beclomethasone esters.

Patient no.	200 μg HFA–beclomethasone dipropionate			400 μg HFA–beclomethasone dipropionate			400 μg CFC–beclomethasone dipropionate		
	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	T_{max} (h)	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	T_{max} (h)	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	T_{max} (h)
1	673	2235	0·5	1284	4063	1	452	1404	1
2	520	2157	0·5	1330	3734	1	253	1094	2
3	617	2719	2	828	3542	0·5	374	2117	2
4	419	2083	0·5	571	2962	1	230	801	1
5	715	2600	0·5	1643	6416	0·5	896	4602	2
6	384	1792	0·5	1220	4839	0·5	330	1837	1
7	764	2501	0·5	1624	4962	0·5	284	1423	0·5
8	642	3057	1	1625	6899	0·5	523	2829	2
9	581	2013	0·5	1418	5513	0·5	605	2667	2
10	1104	3030	0·5	1648	6005	0·5	467	2013	2
11	345	1487	0·5	631	2768	1	116	559	2
12	467	1577	0·5	1030	3728	0·5	288	1133	1
13	743	2224	0·5	1736	5366	0·5	503	2413	2
15	264	890	0·5	613	2860	0·5	262	1202	2
16	358	1516	1	788	3207	0·5	314	1301	2
17	434	1898	0·5	1004	3639	0·5	382	2411	2
18	400	1576	0·5	660	3569	1	463	1739	1
19	805	2900	0·5	1050	4886	1	345	1850	2
20	684	1815	0·5	1614	4114	0·5	428	1418	1
21	697	2102	0·5	1100	4517	3	248	1129	2
22	702	2095	0·5	1241	4363	0·5	479	2242	1
23	438	1629	0·5	981	3732	0·5	157	779	2
24	409	1570	0·5	878	3873	1	343	1606	1
Mean	572	2064	0·6	1153	4328	0·8	380	1764	2
s.d.	196	551	0·3	379	1129	0·5	165	874	0·5
CV%	34	27	55	33	26	71	43	50	34

Table 2. Pharmacokinetic results for beclomethasone.

Patient no.	200 μg HFA–beclomethasone dipropionate			400 μg HFA–beclomethasone dipropionate			400 μg CFC–beclomethasone dipropionate		
	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	T_{max} (h)	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	T_{max} (h)	C_{max} (pg mL^{-1})	AUC (pg h mL^{-1})	T_{max} (h)
1	27	227	2	80	594	2	41	280	2
2	34	174	3	77	600	2	20	111	3
3	31	284	5	47	588	5	46	431	3
4	31	329	4	53	516	3	17	92	3
5	35	384	3	68	895	5	75	931	7
6	37	396	4	98	888	3	41	338	4
7	34	293	3	52	594	5	33	272	3
8	49	593	5	85	1185	5	63	792	2
9	30	251	3	103	884	2	56	470	4
10	48	454	2	90	952	4	58	479	4
11	22	197	2	40	418	3	16	75	4
12	32	262	5	72	666	4	36	296	3
13	43	309	2	76	712	2	46	420	5
15	15	111	5	47	520	5	36	256	2
16	29	230	2	52	510	2	28	224	4
17	31	282	4	52	565	2	54	551	4
18	28	237	6	70	817	4	49	449	4
19	54	561	3	72	879	4	48	482	4
20	38	269	2	107	583	1	36	267	2
21	31	338	2	51	543	4	40	270	3
22	56	405	4	90	698	3	49	449	2
23	26	180	3	43	361	3	25	187	5
24	30	250	3	62	725	3	29	296	4
Mean	34	305	3	69	682	3	41	366	4
s.d.	10	118	1·2	20	196	1·2	15	205	1·2
CV%	29	39	37	29	26	37	36	56	34

Table 3. Results of statistical analyses.

	Comparison (A vs B)		
	400 μg HFA–beclomethasone dipropionate[b] vs 400 μg CFC–beclomethasone dipropionate	200 μg HFA–beclomethasone dipropionate vs 400 μg CFC–beclomethasone dipropionate	400 μg HFA–beclomethasone dipropionate[b] vs 200 μg HFA–beclomethasone dipropionate
Beclomethasone esters			
C_{max}			
Geometric means[a] ratio (A/B)	1·57	1·56	1·01
90% CI for ratio[c]	1·39 to 1·77	1·38 to 1·76	0·89 to 1·14
P[d]	0·998	0·998	0·003
AUC			
Geometric means[a] ratio (A/B)	1·33	1·25	1·06
90% CI for ratio[c]	1·18 to 1·49	1·11 to 1·41	0·94 to 1·19
P[d]	0·80	0·51	0·010
T_{max}			
Geometric means[a] difference (A−B)	−0·83	−0·99	0·15
P[e]	< 0·001	< 0·001	0·26
Beclomethasone			
C_{max}			
Geometric means[a] ratio (A/B)	0·87	0·86	1·01
90% CI for ratio[c]	0·79 to 0·97	0·78 to 0·96	0·91 to 1·13
P[d]	0·084	0·12	< 0·001
AUC			
Geometric means[a] ratio (A/B)	1·06	0·91	1·16
90% CI for ratio[c]	0·92 to 1·23	0·79 to 1·05	1·01 to 1·34
P[d]	0·031	0·069	0·20
T_{max}			
Geometric means[a] difference (A−B)	−0·3	−0·2	−0·1
P[e]	0·35	0·53	0·76

[a]Geometric means adjusted for the effect of period. [b]C_{max} and AUC values in the 400 μg HFA–beclomethasone dipropionate divided by two before analysis. [c]Equivalence interval defined as 0·80 to 1·25. [d]Maximum P-value from two one-sided tests; $P \leq 0{\cdot}05$ for C_{max} and AUC comparisons indicates treatments met definition of equivalence. [e]P-value of pairwise comparison; $P \leq 0{\cdot}05$ for T_{max} comparisons indicates treatments were significantly different.

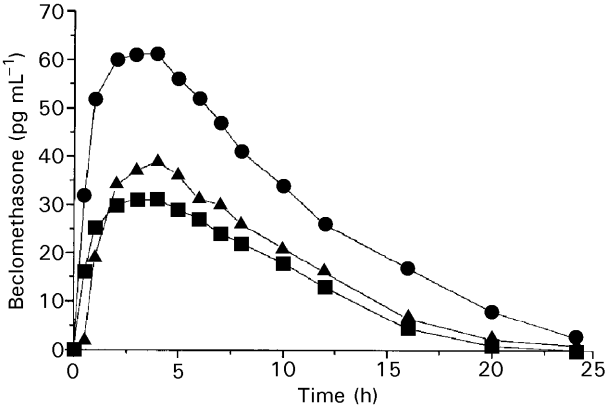

Figure 2. Mean serum concentrations of beclomethasone following 200 μg HFA–beclomethasone dipropionate (■), 400 μg HFA–beclomethasone dipropionate (●), and 400 μg CFC–beclomethasone dipropionate (▲).

methasone pharmacokinetics from beclomethasone dipropionate MDIs in two previous studies (Harrison et al 1997; Soria et al 1998). A unique feature of this study was the modification of the assay to allow for the measurement of the total amount of beclomethasone in a hydrolysed sample. With this approach, it was learnt that beclomethasone is only a small component of the material in the serum as compared with beclomethasone esters. Preliminary characterization of the material in the beclomethasone esters fraction (with assays still under development) revealed no detectable 21-BMP, and, with the sampling times chosen in this study, only minimal amounts of beclomethasone dipropionate within the first 2 h. Over 90% of the material in the beclomethasone esters fraction was 17-BMP.

The smaller particle size distribution of the HFA–beclomethasone dipropionate MDI resulted in a more rapid and greater efficiency of systemic drug delivery than did the larger particle size distribution of the CFC formulation. The extent of appearance of beclomethasone esters in the serum, as measured by AUC, was approximately 2·5-times greater following HFA–beclomethasone dipropionate than following CFC–beclomethasone dipropionate. This lower extent of absorption of the CFC formulation can be explained if most of each inhalation from CFC–beclomethasone dipropionate is swallowed and absorbed orally, whereas most of each inhalation from HFA–beclomethasone dipropionate is absorbed through the lungs.

Support for this explanation comes from in-vitro studies that show that the respirable mass of HFA–beclomethasone dipropionate was approximately twice that of CFC–beclomethasone dipropionate and from human deposition studies that show a much higher deposition in the lungs with HFA–beclomethasone dipropionate (Leach et al 1998). Pharmacokinetic support for this explanation comes from the observation that orally absorbed beclomethasone dipropionate has been shown to be absorbed slower and to require 2·5-times more drug to give the same beclomethasone serum levels and AUC as inhaled HFA–beclomethasone dipropionate because of poor oral bioavailability (Soria et al 1998).

The percent of beclomethasone in the hydrolysed fractions was found to be significantly higher following CFC–beclomethasone dipropionate compared with HFA–beclomethasone dipropionate. Assuming that most of the drug from CFC–beclomethasone dipropionate enters the body through the oral route, this observation may imply a preferential production of beclomethasone by the oral route, possibly as a first-pass effect.

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