

Repeated-Dose Pharmacokinetics of Inhaled Ciclesonide (CIC-HFA) in Japanese Children with Bronchial Asthma: A Phase I Study

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ABSTRACT

Background: Ciclesonide (CIC) is a highly safe, inhaled corticosteroid (ICS) that is converted into a pharmacologically active metabolite (des-isobutyryl-ciclesonide); this metabolite, in turn, exerts a local anti-inflammatory effect on lung tissue. The present study was undertaken to analyze the pharmacokinetics of des-isobutyryl-ciclesonide in the serum of Japanese children with bronchial asthma treated by repeated doses of CIC and to compare the data thus obtained with those obtained for Caucasian children with bronchial asthma.

Methods: Eight Japanese children with bronchial asthma were treated for 7 days with CIC-hydrofluoroalkane (CIC-HFA) 200 µg/day administered by a metered-dose inhaler. The study was designed to assess the pharmacokinetics after 7-day repeated administration by which the steady state can be achieved, based on the results of an earlier study involving healthy Japanese adult males who received 7-day repeated administration of CIC-HFA. Blood was sampled at multiple time points on Day 7 of treatment for measurement of the serum des-isobutyryl-ciclesonide level.

Results: The pharmacokinetic parameters (AUC from time zero to last observed concentration [AUC_t], AUC over the dosage interval τ at steady state [AUC_{ss}], maximum concentration [C_{max}], and terminal elimination half-life [T_{1/2}]) and the temporal changes in the serum levels of des-isobutyryl-ciclesonide after repeated administration of CIC-HFA (200 µg/day) in Japanese children with bronchial asthma differed only slightly from those in Caucasian children with bronchial asthma. No serious adverse events were noted during the study period. Additionally, no abnormalities were detected in the serum cortisol level, other laboratory parameters, or vital signs.

Conclusions: Our results suggest that there is little difference in the pharmacokinetics of des-isobutyryl-ciclesonide up on repeated administration of CIC-HFA between Japanese and Caucasian children with bronchial asthma. And our study suggests that CIC-HFA (200 µg/day, once daily) can be administered safely for 7 days, without raising any safety concerns.

KEY WORDS

bronchial asthma, ciclesonide, inhaled corticosteroid, pharmacokinetics, safety evaluation

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Conflict of interest: KS and HY are employed by Teijin Pharma. The rest of the authors have no conflict of interest.

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Received 18 October 2011. Accepted for publication 31 May 2012.

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INTRODUCTION

Ciclesonide (CIC) has a unique mechanism of action that combines proven efficacy with good tolerability. It is a prodrug that is converted into an active metabolite (des-isobutryl-ciclesonide) in lung tissue by esterase-induced hydrolysis.^{1,2} The active metabolite des-isobutryl-ciclesonide has about 100 times greater affinity for the glucocorticoid receptor than CIC, which has almost no affinity for this receptor; the affinity of the former is comparable to that of other ICSs such as fluticasone and budesonide.¹⁻³ CIC and des-isobutryl-ciclesonide are highly soluble in lipids.² Furthermore, des-isobutryl-ciclesonide is retained for long period in the lung because it undergoes reversible fatty acid conjugation in lung cells.^{4,5} As a result, des-isobutryl-ciclesonide exerts a local, long-lasting, anti-inflammatory effect on the lung tissue, thereby enabling control of asthma by once-daily administration.

CIC is expected to be less likely to induce systemic adverse reactions. Its properties include low bioavailability up on oral administration (1%),⁶ a high protein-binding rate in the plasma (99%),⁷ and rapid degeneration and inactivation in the liver.⁸ Furthermore, since it is administered using a pressurized, metered-dose inhaler (pMDI), with HFA-134a (a substitute freon) as a propellant, the percentage of the drug reaching the lung is high (52%).⁹ The drug remains only for a short period in the oral cavity and pharynx,⁹ and therefore, CIC is activated only to a small extent in the oral cavity.^{10,11} Hence, it is believed that this drug is less likely to induce local adverse reactions such as oral candidiasis^{12,13} and hoarseness,^{13,14} which are commonly observed in the case of conventional ICSs.

METHODS

SUBJECTS

Eight Japanese children (age: 5-15 y; 6 boys and 2 girls) with bronchial asthma (mild and moderate persistent types) were enrolled in this open study. The phase I clinical study in Japanese children was conducted based on an overseas clinical study in children.¹⁵ The study protocol was approved by the Institutional Review Board of Gifu University Hospital and was in accordance with the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice (GCP). Written informed consent was obtained from each patient and his/her parents before the start of the study.

TREATMENT AND BLOOD SAMPLING

Each patient inhaled 2 puffs of CIC-HFA 100 µg/day (80 µg/day ex actuator) once daily in the morning (200 µg/day), no spacer used, every morning, for 7 days, no mouth rinsing. It has been shown that when CIC-HFA was repeatedly administrated to healthy

Table 1 High-performance liquid chromatography conditions (Gradient table) for the determination of Ciclesonide (CIC) and des-isobutryl-ciclesonide

Time (min)	Mobile Phase A (ratio %volume)	Mobile Phase B (ratio %volume)
0.00	40	60
3.00	5	95
6.00	5	95
6.01	40	60
7.00	40	60

Mobile Phase A: 10 mM acetic acid in water/acetone 80/20 (v/v).

Mobile Phase B: 10 mM acetic acid in ethanol/acetone 80/20 (v/v).

Flow rate: 1 mL/min.

Japanese adult males for 7 days, the steady state was achieved after at least 4-day repeated administration.¹⁶ Based on the above result, the study was designed to assess the pharmacokinetics in Japanese children after 7-day repeated administration. On the screening test day and before the investigational drug administration on the last day of treatment (day 7), each patient practiced inhalation technique using CIC-HFA (placebo) with the maximum of 3 puffs. Blood samples (2.0 mL each time) for analysis of pharmacokinetic parameters were obtained immediately before and 0.5, 1, 1.5, 3, 6, 9, 12, and 24 h after the dose was administered on Day 7 (dosing at the clinical site). Each blood sample was immediately cooled and centrifuged at a low temperature, and the serum (1.0 mL) was isolated and stored frozen until it was used for analysis.

SERUM DRUG-LEVEL MEASUREMENT

For the measurement of serum CIC and des-isobutryl-ciclesonide levels, the serum was mixed with internal standards, i.e., deuterium-labeled CIC (d11-CIC) and d11-des-isobutryl-ciclesonide (deuterium-labeled des-isobutryl-ciclesonide). Then, liquid-liquid extraction was carried out using isopropyl ether. The pretreated sample was subjected to LC-MS/MS for the measurement of the serum drug levels. Calibration ranges are both 10-2000 pg/mL.

High-performance liquid chromatography (HPLC) was performed at a flow rate (1 mL/min) by using the analytical column Luna (Phenomenex®) C18(2) (5 µm, 100 Å, 50 mm × 4.6 mm). Chromatographic conditions are shown in Table 1. Detection was done in the negative-ion mode with selected-reaction monitoring by atmospheric pressure photoionization, by using API 5000 (MDS Sciex, Concord, Canada).

SAFETY EVALUATION METHOD

Safety was evaluated by analyzing the number and severity of adverse events (abnormalities in vital signs, results of hematological tests, values of biochemical parameters, data of urinalysis, changes in subjective

Table 2 Summary of the results of validation studies on the measurement method

Item	Summarized results	
	Ciclesonide (CIC)	des-isobutyryl-ciclesonide
Substance	Serum (0.3 mL)	
Matrix	Serum (0.3 mL)	
Lower limit of quantification	10 pg/mL	10 pg/mL
Range of measurement	10-2000 pg/mL	10-2000 pg/mL
Intra-day reproducibility	Accuracy: -9.0% to -1.8% (relative deviation) Precision: $\leq 5.7\%$ (cv)	Accuracy: -7.0% to 0.3% (relative deviation) Precision: $\leq 7.9\%$ (cv)
Inter-day reproducibility	Accuracy: -7.4% to -1.2% (relative deviation) Precision: $\leq 4.6\%$ (coefficient of variation)	Accuracy: -8.4% to -3.2% (relative deviation) Precision: $\leq 7.2\%$ (coefficient of variation)
Yield	70.0% to 75.6%	64.5% to 69.3%
Dilution reproducibility (1 : 10 dilution with pooled serum)	Accuracy: -2.8% (relative deviation) Precision: 3.6% (coefficient of variation)	Accuracy: -4.4% (relative deviation) Precision: 1.1% (coefficient of variation)
Dilution reproducibility (1 : 100 dilution with pooled serum)	Accuracy: -8.3% (relative deviation) Precision: 3.4% (coefficient of variation)	Accuracy: -5.3% (relative deviation) Precision: 5.2% (coefficient of variation)
Specificity/Matrix effect	No interfering peak was noted in the vicinity of the retention time on the chromatogram for the test substance and its deuterium-labeled form (interval standard). The data after addition to individual serum samples revealed no difference in the matrix effect between Japanese and Western (Caucasian) individuals of both sexes (3 each of Japanese and Caucasian male and female subjects).	

symptoms and objective findings, and underwent specified test), causal relationship of adverse events to CIC-HFA, and the nature of the adverse events.

COMPARISON BETWEEN CAUCASIAN CHILDREN WITH BRONCHIAL ASTHMA AND THEIR JAPANESE COUNTERPARTS

The data on the serum drug levels in Japanese children with bronchial asthma were compared with those obtained in a pharmacokinetic study on CIC-HFA in Caucasian children with bronchial asthma.^{15,16}

RESULTS

VALIDATION OF THE MEASUREMENT METHOD

We assessed the validity of the measurement method developed by us for the simultaneous quantification of serum CIC and des-isobutyryl-ciclesonide. The results are shown in Table 2. The lower limit of quantification for a 0.3 mL serum sample was 10 pg/mL, which suggests that this method can be used to evaluate the time course of changes in the serum drug level in children.

PHARMACOKINETICS OF CIC-HFA IN JAPANESE CHILDREN WITH BRONCHIAL ASTHMA

Figure 1 shows the time course of changes in the serum des-isobutyryl-ciclesonide level of each Japanese

child with bronchial asthma, as observed on Day 7 of treatment. Table 3 shows the values of the pharmacokinetic parameters for des-isobutyryl-ciclesonide, calculated by non-compartment analysis (WinNonlin® version 5.2.1 Pharsight) of the data on the time course of changes in the serum drug level.

In all subjects, the pretreatment des-isobutyryl-ciclesonide level was less than the lower limit of quantification (10 pg/mL). The serum des-isobutyryl-ciclesonide level reached a peak (45.6-365.3 pg/mL) 0.5-1 h after the dose was administered. The level then decreased over time, to lesser than the lower limit of quantification (10 pg/mL) at 24 h after the 7th dose.

Means (SD) of AUC_t, AUC_{ss}, and C_{max} were 601.14 ± 391.32 pg · h/mL, 669.70 ± 409.31 pg · h/mL and 167.80 ± 105.20 pg/mL, respectively. T_{1/2} was 3.24 ± 1.47 h.

ADVERSE EVENTS

Two of the 8 children with bronchial asthma enrolled in this domestic phase I study developed adverse events (moderate abdominal pain and moderate wheezing in one patient each; 2 events in total). Both these events responded to treatment. No serious adverse event was noted. There were no abnormal changes in the serum cortisol level, no clinically significant reduction in the serum cortisol level, and no

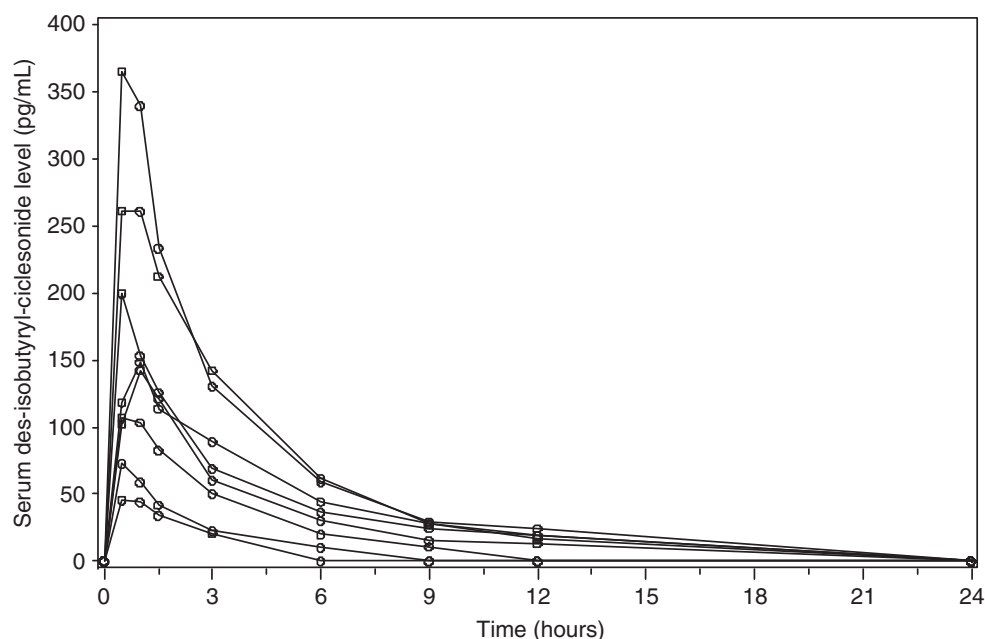


Fig. 1 Time course of serum des-isobutyryl-ciclesonide level in Japanese patients ($N = 8$) with bronchial asthma following repeated doses of CIC-HFA (200 $\mu\text{g/day}$).

Table 3 Pharmacokinetic parameters of Japanese children with bronchial asthma treated with inhaled CIC-HFA (200 $\mu\text{g/day}$)

Subject	Sex	Age	Body weight (kg)	AUC _t (pg·h/mL)	AUC _{ss} (pg·h/mL)	C _{max} (pg/mL)	T _{max} (h)	T _{1/2} (h)
1	M	7	28.3	172.3	204.6	72.8	0.5	2.2
2	M	8	29.6	1178.8	1264.1	365.3	0.5	2.8
3	M	13	36.4	1080.5	1150.2	261.4	0.5	2.8
4	F	13	58.0	670.9	799.3	199.6	0.5	6.4
5	M	15	43.4	695.2	784.4	148.3	1.0	4.3
6	F	11	45.8	379.8	417.8	106.8	0.5	2.5
7	M	11	45.8	538.4	589.4	142.6	1.0	3.1
8	M	5	21.0	93.3	147.8	45.6	0.5	1.8
Mean		10.4	38.5	601.14	669.70	167.80		3.24
SD		3.4	12.0	391.32	409.31	105.20		1.47
Geometric mean				458.49	535.75	139.44		3.01

AUC, area under concentration-time curve; C_{max}, maximum concentration; T_{max}, time reach to C_{max}; T_{1/2}, apparent elimination half-life; SD, standard deviation.

abnormal changes in any other laboratory test results or vital signs.

COMPARISON OF CIC-HFA PHARMACOKINETIC PARAMETERS IN JAPANESE AND CAUCASIAN CHILDREN WITH BRONCHIAL ASTHMA

Figure 2 shows the time course of serum des-isobutyryl-ciclesonide levels in Japanese and Caucasian children with bronchial asthma treated with CIC-HFA (200 $\mu\text{g/day}$) for 7 days. Table 4 shows the pharmacokinetic parameters of des-isobutyryl-ciclesonide, the ratio of the value of each pharmacokinetic

parameter in Japanese children to the corresponding value obtained for Caucasian children (geometric average), and the 90% confidence interval.

In terms of the time course of changes in the serum des-isobutyryl-ciclesonide level, there was no marked difference between the 2 races, with the median time to reach the C_{max} (T_{max}) being 0.5 h for each race.

The ratios for each of the 4 pharmacokinetic parameters—AUC_t, AUC_{ss}, C_{max}, and T_{1/2}—expressed as a geometric average (90% confidence interval), were 1.28 (0.76-2.14), 1.22 (0.81-1.83), 1.14 (0.77-

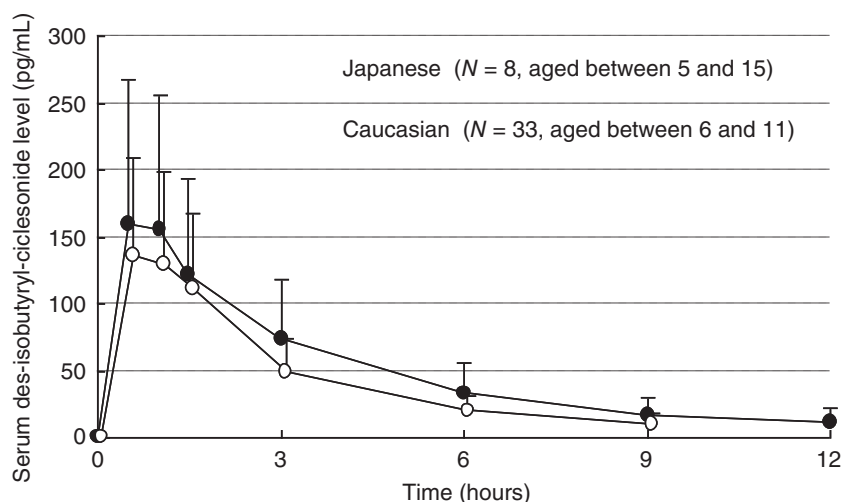


Fig. 2 Time course of serum des-isobutyryl-ciclesonide level in Japanese children (●) and Caucasian children (○) following repeated CIC-HFA administration (200 µg/day). Each point indicates the mean (SD) for Japanese children with bronchial asthma ($N = 8$) and Caucasian children with bronchial asthma ($n = 33$).

Table 4 Comparison of pharmacokinetic parameters for serum des-isobutyryl-ciclesonide after repeated CIC-HFA administration (200 µg/day) between Japanese and Caucasian children with bronchial asthma

Population	AUC _t (pg·h/mL)	AUC _{ss} (pg·h/mL)	C _{max} (pg/mL)	T _{max} (h)	T _{1/2} (h)
Japanese	601.1 ± 391.3 (458.5) [†]	669.7 ± 409.3 (535.7) [†]	167.8 ± 105.2 (139.4) [†]	0.5 (0.5-1.0)	3.2 ± 1.5 (3.0) [†]
Caucasian	442.5 ± 245.2 (359.1) [†]	504.6 ± 245.6 (440.1) [†]	141.0 ± 73.6 (122.0) [†]	0.5 (0.5-1.5)	3.0 ± 1.2 (2.8) [†]
Japanese/Caucasian ratio	1.28 [†]	1.22 [†]	1.14 [†]	-	1.09 [†]
90% confidence interval	0.76-2.14	0.81-1.83	0.77-1.69	-	0.82-1.44

AUC_t, area under concentration-time curve; C_{max}, maximum concentration observed; T_{max}, time reach to C_{max}; T_{1/2}, apparent elimination half-life.

[†] Geometric mean.

1.69), and 1.09 (0.82-1.44), respectively. All confidence intervals contained the value 1, suggesting that there was no marked difference in any pharmacokinetic parameter between the 2 races.

DISCUSSION

The phase I study conducted on Caucasian asthmatic children administered CIC-HFA (200 µg/day, once daily) for 7 days revealed that the drug could be safely administered and that it was tolerated well.^{15,16}

Because serum CIC and des-isobutyryl-ciclesonide levels are low and because adequate care is to be taken when obtaining blood samples from pediatric patients, we developed a highly sensitive, analytical method based on liquid chromatography/tandem mass spectrometry (LC-MS/MS) and confirmed the

validity of this method before using it in this study. Thus, using this LC-MS/MS method, we measured the serum drug levels in Japanese children with bronchial asthma and compared the data obtained for relevant pharmacokinetic parameters with those recorded for Caucasian children with bronchial asthma. There were no differences in background factors (age, height, weight and BMI) between Caucasian and Japanese children. As for the C_{max} and AUC_{ss} in all children including Caucasian children, the relation between age and exposure showed no clear trend within the range of variability. Our results showed that there is little difference in the pharmacokinetics of des-isobutyryl-ciclesonide up on repeated administration of CIC-HFA between Japanese and Caucasian children with bronchial asthma.

Similarly, the domestic phase I study involving healthy adult men who were administered single and repeated doses of the CIC-HFA, the drug did not give rise to any safety problems when administered at dose levels of up to 1600 µg.^{16,17}

Our study also did not show any safety problems, suggesting that CIC-HFA (200 µg/day, once daily) can be administered safely for 7 days, without raising any safety concerns.

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