Systemic Effect Comparisons of Six Inhaled Corticosteroid Preparations

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The goal of this study was to establish a reliable method to evaluate systemic bioavailability and to determine equisystemic effects (microgram dose producing equal systemic cortisol suppression) of inhaled corticosteroids (ICS). Steroid naive asthma subjects (n = 156) were enrolled at six centers. A 1-week doubling dose design was used for each of six ICS and matched placebos for a total of four doses. Systemic effect was evaluated by hourly plasma cortisol concentrations (8 P.M. to 8 A.M.), 12- and 24-hour urine cortisol concentrations, and a morning blood osteocalcin. The area under the concentration–time curve for hourly cortisol concentrations was the best outcome variable to assess systemic effect. For the six ICS and matching placebos (beclomethasone-chlorofluorocarbon [CFC], budesonide dry powder inhaler [DPI], fluticasone DPI, fluticasone-CFC metered dose inhaler [MDI], flunisolide-CFC, and triamcinolone-CFC), only the placebo group and fluticasone DPI did not demonstrate a significant dose–response effect. Thus microgram comparison of all ICS could only be performed at a 10% cortisol suppression: flunisolide-CFC – 936; triamcinolone-CFC – 787; beclomethasone-CFC – 548; fluticasone DPI – 445; budesonide DPI – 268; fluticasone-CFC MDI – 111. This study represents the first step in evaluation of ICS efficacy based on equisystemic (cortisol suppression) effects of a given ICS, rather than doses judged arbitrarily to be comparable on a microgram basis.

Keywords: inhaled corticosteroids; systemic effects; cortisol suppression

Inhaled corticosteroids (ICS) are being recommended for treatment of all stages of persistent asthma (1). The choice of an ICS is often based on convenience (e.g., number of micrograms per actuation, taste, patient preference) or cost factors. However, the potential for adverse systemic effects (2) is not commonly considered. Because of these effects, it is important to be able to compare the different available preparations and delivery systems with respect to both their systemic effects and their efficacy, to determine an optimal asthma treatment strategy. The goals of this Asthma Clinical Research Network (ACRN)-initiated trial in asthmatic subjects were to establish a method to evaluate systemic bioavailability and to establish doses with equivalent systemic bioavailable doses (equisystemic doses) for use in a future ACRN trial that would include respiratory efficacy outcomes, thus permitting a determination of efficacy, controlling for risk.

METHODS

Subjects

One hundred and fifty-six corticosteroid-naive patients with asthma were recruited at six ACRN centers and their consent to this Institutional Review Board approved study obtained. These patients were appropriately distributed by sex (58% male) and by ethnicity (31% ethnic minority) (Table 1).

Subject inclusion criteria were as follows: all subjects were postpubertal (3), with a 12% improvement in FEV_1 following a β-2 agonist or a provocative concentration of methacholine needed to produce a 20% fall in FEV_1 (PC_{20}) of 8 mg/ml or less, and an FEV_1 between 65 and 90% of predicted value.

Exclusion criteria included treatment with any oral or injectable corticosteroid within the year before enrollment. If such treatment was received for more than 2 weeks duration 1–2 years before enrollment, then a normal low dose (1.0 μg) Cortrosyn (adrenocorticotropic hormone) stimulation test was required (4–6). Patients who had used oral or nasally inhaled or cutaneously prescribed corticosteroids within 6 months of enrollment were excluded from participation. If such corticosteroids were used 6–12 months before enrollment, a normal adrenocorticotropic hormone stimulation test was needed. For nonprescription cutaneous corticosteroids, there was a 2-month exclusion period.

Additional exclusion criteria were: (*1*) use of medication known to significantly interact with corticosteroid metabolism within 6 weeks of enrollment; (*2*) presence of other lung disease; (*3*) other significant medical illnesses; (*4*) respiratory infection or asthma exacerbation within 6 weeks; (*5*) pregnancy; (*6*) the use of any hormonal birth control methods; (*7*) a daily schedule that included an altered day–night cycle; and (*8*) body mass index (BMI) greater than 35. Cigarettes in the year before study onset or tobacco use greater than 10 pack years were exclusionary.

Study Medication

At the initiation of this study, five ICS compounds were available by prescription in the United States. Each of these five compounds (with one, fluticasone propionate [FP], evaluated both in its pressurized metered dose inhaler [MDI] and dry powder inhaler [DPI] formulations) and matched placebos were evaluated in the study; the doses studied are shown in Table 2. Doses were administered at 5–10 A.M. and 9–11 P.M. The more liberal morning time span is based on the fact that this interval has minimal effect on cortisol suppression (7). The DPI preparations, i.e., budesonide (BUD) and FP, were delivered via their own delivery device. A valved chamber device (OptiChamber; Respironics HealthScan, Cedar Grove, NJ) was used to administer chlorofluorocarbon (CFC) beclomethasone dipropionate (BDP), flunisolide (FLU)-CFC, and FP-CFC MDI; triamcinolone acetonide (TAA)-CFC MDI was administered with its built-in tube spacer. The placebo used was matched

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TABLE 1. SUBJECT CHARACTERISTICS

Number	M/F (%)	Minority (%)	Age (*Years, Mean ± SD*)	FEV_1 (*% Predicted, Mean ± SD*)	Body Mass Index (*Mean ± SD*)
156	90/66 (58/42)	48 (31)	30.1 ± 8.3	78.8 ± 6.9	25.5 ± 3.8

for each corresponding ICS. The dose ranges for each ICS were those predicted to produce cortisol suppression between 10 and 50% (8–15). The canister labeled dose ranges and emitted doses (ED; dose delivered to the patient) are described in Table 2.

Study Design

The proposed study used a progressively escalated dose–response (Figure 1). A 1-week single blind placebo run-in period evaluated drug adherence. Adherence was acceptable if at least 11 of 14 scheduled doses occurred with dose-time intervals verified by the Doser (number of actuations per day) and by the Airwatch System (time of administration, i.e., peak flow measurements performed at time of ICS dosing). This was considered to be a reasonable surrogate for ICS dosing time. For DPI, the number of doses remaining was determined.

The subjects were then randomized to one of the six corticosteroid and matched placebo groups. The subjects were given detailed training on proper technique for use of the particular ICS delivery system to which they were assigned. A scoring system was developed for the proper technique specific for each ICS preparation and two consecutive perfect technique scores were needed to continue in the protocol. Following randomization, the adherence criterion was continued or termination occurred.

At visits 3–7 (Figure 1), the subjects were admitted for overnight testing. Between 8 A.M. and 8 P.M., an out-of-laboratory 12-hour urine collection was performed. In-laboratory urine cortisol collection and hourly blood sampling for cortisol were conducted between 8 P.M. and 8 A.M. Medications were administered at 10 P.M. and lights turned off at 11 P.M; blood for osteocalcin concentration was obtained at 7 A.M.; spirometry was performed at 8 A.M. The two 12-hour urine collections were pooled for a separate 24-hour analysis. Cortisol concentrations were analyzed by high pressure liquid chromatography and osteocalcin concentrations by radioimmunoassay (16). The urinary cortisol concentrations were corrected for the corresponding creatinine concentration.

In Vitro Measurements

Labeled dose. The labeled dose was taken from the pharmaceutical company's label claim. For BUD, the 100 μg label claim is not available in the United States and was provided by AstraZeneca.

Emitted doses. The ED, in micrograms, was measured by collecting individual ICS doses into a unit dose collection tube (UDCT). Each ICS MDI with its paired OptiChamber was primed before use by discharging 12 doses (study protocol) from the MDI into the spacer at 30-second intervals. MDI used an airflow of 28.3 L/minute, actuated directly into the UDCT or into the OptiChamber, hermetically attached to the UDCT; DPI used an airflow of 60 L/minute. Between three and six individual MDI, with and without the OptiChamber, and DPI were sampled for a total of 30–60 dose measurements per drug.

ICS assay was performed using standard procedures and UV spectrophotometry (Varian spectrophotometer, Model 50; Cary Probe, Victoria, Australia) at the wavelength specific to each drug. All measurements were performed under ambient conditions.

Particle size distribution. Particle size distribution was measured using an 8-stage nonviable Anderson cascade impactor operated at 28.3 L/minute for the MDI and MDI plus OptiChamber or tube spacer and with a United States Pharmacopea stainless steel inlet stage to the impactor. The DPI were sized with the Anderson cascade impactor operated at 60 L/minute and using a twin impinger glass bulb inlet. The fine particle fraction (FPF), i.e., percentage of particles below 4.7 μm, was determined from the cumulative mass distribution plot. Total drug weight sampled was at least 500 μg. The stage plates of the impactor were washed with methanol, and the amount of drug was determined by spectrophotometry. The fine particle dose (FPD = ED × FPF) was calculated.

STATISTICAL DESIGN AND METHODS

The major objective of this randomized trial was to investigate dose–response relationships for six ICS–inhaler combinations. Although inclusion of a placebo group was not necessary for this objective, the placebo group was necessary to maintain double-blinding within the trial. In order not to compromise resources for this trial, however, it was decided to minimize the number of subjects in the placebo group (n = 2 for each ICS–inhaler combination for a total n = 12).

Randomization of eligible subjects to active and placebo ICS–inhaler combinations was stratified according to clinical center and sex. Randomization was performed electronically, wherein the clinical center staff member entered the appropriate data for an eligible subject into the ACRN network server and was relayed the appropriate drug packet number to use for that subject. Only a few staff members at the data coordinating center were aware of the actual identity of placebo and active drug packets.

The target sample size of 24 subjects for each of the six ICS–inhaler combinations (target total n = 144 for active ICS) was based on data from a pilot study with 32 subjects randomized to three ICS–inhaler combinations. The statistical criterion was that the target sample size for each ICS–inhaler combination would provide adequate precision for estimating the CS_{30}, the dose that yields 30% suppression, based on its 95% confidence interval.

Plasma cortisol area under the curve (AUC) was calculated from the trapezoidal rule over the 12-hour period of the hourly blood draws. The actual time points of plasma sampling, rather than the nominal hourly

TABLE 2. WEEKLY DOSE INCREMENTS OF INHALED CORTICOSTEROIDS

ICS	BDP-CFC MDI				BUD DPI				FLU-CFC MDI			
Dosing week	1	2	3	4	1	2	3	4	1	2	3	4
Labeled dose*	168	336	672	1,344	200	400	800	1,600	500	1,000	2,000	4,000
Emitted dose*†	52	103	206	413	123	245	490	981	158	315	630	1,261
ICS	**FP DPI**				**FP-CFC MDI**				**TAA-CFC MDI**			
Dosing week	1	2	3	4	1	2	3	4	1	2	3	4
Labeled dose†	100	200	400	800	88	176	352	704	800	1,600	3,200	6,400
Emitted dose*†	99	198	395	790	54	108	216	432	314	627	1,254	2,507

Definition of abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide; CFC = chlorofluorocarbon; DPI = dry powder inhaler; FLU = flunisolide; FP = fluticasone propionate; ICS = inhaled corticosteroid; MDI = metered dose inhaler; TAA = triamcinolone acetonide.

* Microgram doses delivered at one-half total dose twice daily.

† Emitted dose for BDP-CFC, FLU-CFC, and FP-CFC. MDI was from exit port of the OptiChamber; for BUD-DPI and FP-DPI ex-DPI mouthpiece; and for TAA-CFC from its integral tube spacer. Dose is rounded to nearest whole number of micrograms.

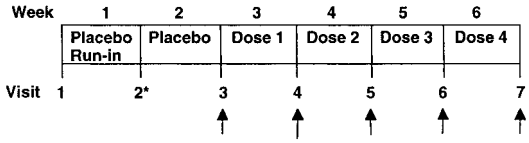

Figure 1. This figure demonstrates the study design. The placebo run-in tested for regimen adherence. The placebo week was postrandomization and used placebo inhalers matched to the subject's randomized treatment. For each ICS, there was a doubling dose design with each dose administered for 1 week (for exact doses *see* Table 2). *Arrows* represent the overnight study time points.

time points, were used for the calculation and standardized to a 12-hour period. Urinary cortisol measurements were corrected for urinary creatinine by division. Kendall correlations were calculated to investigate associations, and the concordance correlation coefficient (17) was used to assess the agreement between plasma cortisol AUC calculated from measurements taken every hour and measurements taken every 2 hours.

A repeated measurements linear model (18) was fit to the natural logarithm of each plasma and urine response variable. Linear models for the log-transformed data provided better fits than linear models for the untransformed data. Descriptive statistics for tables and figures were expressed in terms of geometric means (and coefficients of variation) of the percentages of baseline values. The linear models for the plasma and urinary response variables contained treatment group effects for the intercept, the slope based on dosage (0, 1, 2, 4, 8), sex (−1 for male, +1 for female), and BMI. Subgroup analyses were performed for plasma cortisol AUC in terms of males versus females and whites versus nonwhites. Analogously, a repeated measurements linear model (18) was fit to the spirometry response variables (untransformed), which accounted for sex and BMI. However, instead of an intercept–slope model of dose for the spirometry variables, mean effects were modeled for each dosage. All of the repeated measurements analyses assumed unstructured variance matrices for the set of measurements from each treatment group, and Satterthwaite's correction (18, 19) was applied to adjust the degrees of freedom for the resultant t statistics. Restricted maximum likelihood estimation from PROC MIXED of SAS Version 8.1 (19) was used for all repeated measurements analyses.

The dose that yields $100\gamma\%$ suppression ($0 < \gamma < 1$) with respect to plasma cortisol AUC was defined from the linear model of the log-transformed response as $CS_{100}\gamma = -\log(1 - \gamma)/\text{slope}$. CS_{10}, CS_{20}, CS_{30}, CS_{40}, and CS_{50} were estimated for each treatment arm, except in cases where extrapolation beyond the fitted model was required. The variance for the estimated $CS_{100}\gamma$ was calculated via the delta method (20), so that an approximate 95% confidence interval for $CS_{100}\gamma$ is based on t critical values. The relative potency of any two ICS–inhaler combinations was determined as the ratio of their $CS_{100}\gamma$ estimates, which reduces to the ratio of their slope estimates. This approach to estimating relative potency is analogous to, but statistically more rigorous than, Finney's method (21).

RESULTS

Subjects

The ICS and placebo groups were comparable at baseline with respect to sex, ethnicity, age, BMI, morning or evening peak expiratory flow rate, daily symptom scores, daily number of β-2 agonist actuations, FEV_1, or percentage change in FEV_1 following β-2 agonist reversibility testing (data not shown). Eleven of the 156 randomized subjects (7.1%) were terminated from the study due to nonadherence to the ICS regimen. These subjects were distributed across the groups, specifically three BDP-CFC, two BUD DPI, two FLU-CFC, one FP DPI, one FP-CFC MDI, and two TAA-CFC.

ICS Canister Labeled Dose, ED, FPD

To evaluate and compare an effect of an ICS, it is important to know the dose delivered to the subject. Table 2 demonstrates for each study week the difference between the labeled dose for each ICS and the ED, i.e., the dose delivered to the subject's mouth. For BDP-CFC, FLU-CFC, and FP-CFC MDI, the ED was from the OptiChamber port, for BUD-DPI and FP DPI the ED was ex-mouthpiece, and for TAA-CFC MDI the ED was from the tube spacer. There was marked variability between ICS for the ED, similar to that for the label dose claim.

Although the OptiChamber greatly influenced the ED, we found that the FPD (i.e., the dose delivered to the lungs) for a given ICS (BDP-CFC, FLU-CFC, and FP-CFC MDI) was essentially the same with or without the OptiChamber (Table 3).

AUC for Nocturnal Cortisol Plasma Concentrations

Figures 2A and 2B demonstrate the primary outcome variable (the AUC for hourly nocturnal cortisol plasma concentrations) for the six ICS preparations and combined matched placebos. With the exception of placebo and FP DPI, each preparation had a significant dose–response. Except for FP DPI, each ICS reached approximately the predicted prestudy suppression.

The estimated cortisol suppressive doses of each ICS can be seen in Table 4. The amount of ICS to produce cortisol suppression changes when comparing the labeled dose with the ED to the FPD. Also, the rank order of the different ICS producing the various degrees of cortisol suppression changes from the labeled dose to the ED to the FPD. Table 5 demonstrates this changing relationship of the ICS preparations between labeled dose, ED, and FPD. FLU-CFC, needing the greatest labeled microgram strength to produce a cortisol suppressive dose of 10%, is assigned the arbitrary numeric order of 1 with progressive ordering of the different ICS and the 95% confidence intervals (Table 5). Keeping this arbitrary labeled dose value of 1 for FLU-CFC, the ED ratios fall below 1 for FP DPI and TAA-CFC MDI. The ratio similarly narrows for BUD DPI and FP-CFC MDI.

The accuracy of the outcomes from this model-based analysis are dependent on obtaining significant slopes for the dose–response curves. However, this was not the case for all the drugs tested, specifically the FP DPI dose–response curve, which exhibited a slope close to zero. As a result, the dose estimates of relative potency for FP DPI given in Table 5 are not statistically reliable, as reflected by the extremely wide confidence intervals.

Although plasma cortisol concentrations measured every 2 hours were not a primary outcome, this evaluation was compared with the hourly analysis. The concordance correlation was $r = 0.96$ (95% confidence interval 0.96, 0.98), indicating excellent agreement.

Osteocalcin

The morning blood osteocalcin concentration was quite variable within a given ICS. Figure 3 demonstrates the dose–response aspects of the studied ICS and placebo. Four of the six ICS preparations had an appreciable dose–response. These were BUD DPI, FP-CFC MDI, FLU-CFC, and TAA-CFC. However, the coefficients of variation were great ($> 60\%$).

Urinary Cortisol

BUD DPI demonstrated a significant dose–response for the 12-hour daytime, 12-hour nighttime, and 24-hour urine collections. FP-DPI had a significant dose–response for the 12-hour daytime and 24-hour measurements and FP-CFC MDI for the 12-hour nighttime collection. None of the other ICS demonstrated a significant urinary cortisol dose–response (Table 6). This measurement, whether for the 12-hour collections or for the 24-hour collections, had very large coefficients of variation for all ICS.

TABLE 3. INHALED CORTICOSTEROIDS AND AMOUNT DELIVERED PER ACTUATION

ICS	BDP-CFC MDI	BUD-DPI	FLU-CFC MDI	FP-DPI	FP-CFC MDI	TAA-CFC MDI
Labeled dose	84	100	250	50	44	200
Emitted dose*						
MDI	72.7 ± 5.1	61.3 ± 2.5	219.2 ± 13.6	49.4 ± 2.8	47.4 ± 4.7	78.4 ± 8.8
+OptiChamber	25.8 ± 7.7	—	78.8 ± 10.3	—	27.0 ± 5.6	—
Fine particle dose†						
MDI	11.7 ± 2.8	31.6 ± 6.5	64.1 ± 8.7	5.4 ± 0.7	20.3 ± 2.0	25.7 ± 4.12
+OptiChamber	14.9 ± 4.2	—	61.3 ± 9.1	—	23.0 ± 4.8	—

For definitions of abbreviations, *see* Table 2.
* Micrograms (mean ± standard deviation) that are emitted ex-device for the DPI, or from the OptiChamber or tube spacer for the MDI.
† Micrograms (mean ± standard deviation) that are theoretically delivered to the lung from the inhaler device and with the OptiChamber or tube spacer (TAA).

Morning FEV_1

Although this was not an efficacy study, the morning laboratory FEV_1 was measured at all overnight visits. For each ICS, there was a between 5 and 15% improvement (*see* online data supplement) in overall response. At Week 4 the improvement for FP-CFC MDI and that for FP-DPI were similar.

DISCUSSION

The ACRN set out to develop a workable method to determine whether the available ICS differ in terms of systemic bioavailability on an equivalent microgram basis as measured by effect on cortisol suppression. An additional goal was to establish equivalent systemic bioavailable doses, so as to use this information in future ACRN trials of the efficacy of ICS preparations. To this end, we found that the most reliable method of evaluation (i.e., gave the smallest variability within a given dosage, yet demonstrated different mean values across doses) was the 12-hour AUC for the hourly overnight plasma cortisol measurements from 8 P.M. to 8 A.M. Although this method involves an in-laboratory overnight visit, by far it gave the most accurate assessment of ICS effect on cortisol function compared with either a 12-hour (8 A.M. to 8 P.M.) "at home" urinary cortisol collection or a 12-hour (8 P.M. to 8 A.M.) in-laboratory urinary cortisol collection. Even combining the two 12-hour time intervals, the variability was so great as to make urinary cortisol assays uninterpretable. It should be noted that other investigators have shown that the 24-hour urine cortisol collection (22) and the overnight collection (23) were sensitive measures of cortisol suppression. Wilson and Lipworth felt the overnight urinary cortisol collection gave the best signal to noise ratio in comparing two ICS (23).

Although hourly cortisol measurements best met our criteria for reliability, every 2 hours measurements were also accurate. The concordance correlation between hourly and every 2 hours measurements was very strong ($r = 0.96$ [95% confidence interval 0.96, 0.98]). Blood sampling every 2 hours allows for less potential sleep interruption and decreases cost for future studies.

Although 7 A.M. blood osteocalcin values showed significant dose–responses for four of the six ICS preparations, the coefficients of variation were large and the results in the placebo group were variable over the time points. However, similarities between the osteocalcin and plasma cortisol suppression are evident. Similar differences are found between FP DPI and FP-CFC MDI for osteocalcin and cortisol. TAA-CFC and FP-CFC MDI also demonstrated the same trends in osteocalcin and cortisol suppression. Other indications of systemic effect such as glaucoma, cataracts, osteoporosis, growth, and skin thinning were not evaluated, as they require both a long duration of study and varying age groups. Thus, although our findings do document systemic effect, caution needs to be taken in generalizing these findings to other organ systems or age groups.

To determine the dose–response of cortisol suppression from ICS, our study used a dose–response design in which the dose of the ICS was progressively escalated. Although we

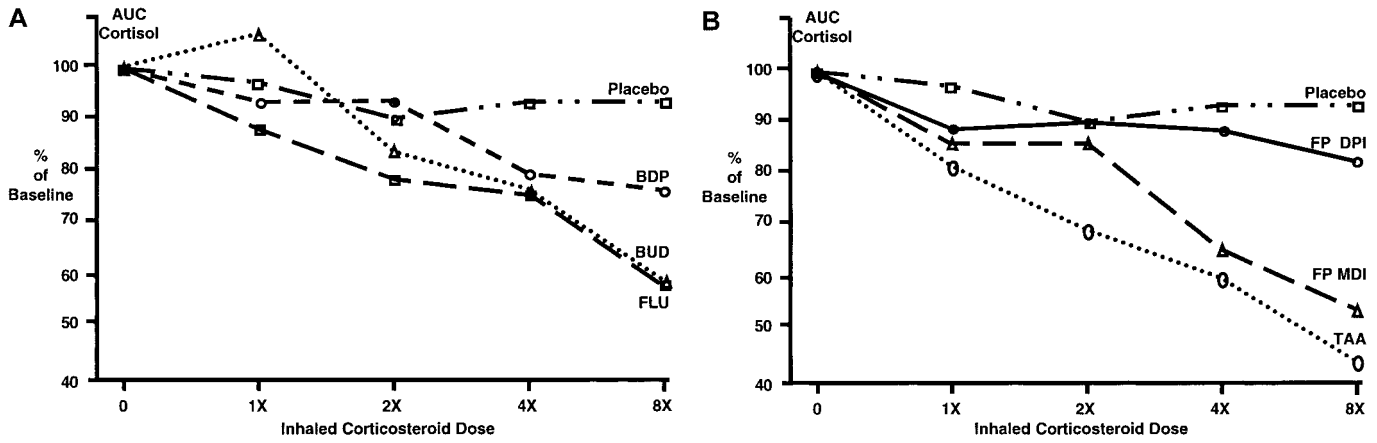

Figure 2. Dose–response to (*A*) placebo, beclomethasone-CFC (BDP), budesonide-DPI (BUD), and flunisolide-CFC (FLU), and dose–response to (*B*) placebo, FP, DPI, FP-CFC MDI, and TAA-CFC. The vertical axis is the percent of baseline for the area under the curve for hourly plasma cortisol concentrations (8 P.M.–8 A.M.). The *horizontal axis* represents the ICS or placebo dose: 0 = baseline; 1× = first dose (*see* Table 2 for both labeled dose and ED) with successive doubling doses represented by 2×, 4×, and 8×. There was a statistically significant dose–response for all three ICS but not for placebo.

TABLE 4. ESTIMATED CORTISOL SUPPRESSIVE DOSES

	CS_{10}*	CS_{20}*	CS_{30}*	CS_{40}*	CS_{50}*
Labeled dose					
FLU-CFC	936[†]	1981	3167		
	(484, 1387)[‡]	(1025, 2938)	(1639, 4695)		
TAA-CFC	787	1667	2664	3816	5178
	(627, 947)	(1329, 2005)	(2124, 3204)	(3042, 4589)	(4128, 6227)
BDP-CFC	548	1161			
	(230, 866)	(487, 1835)			
FP-DPI	445				
	(0, 918)				
BUD-DPI	268	567	907	1298	
	(153, 383)	(323, 811)	(517, 1297)	(740, 1857)	
FP-CFC	111	234	375	537	
MDI	(67, 154)	(142, 327)	(227, 522)	(326, 748)	
Emitted dose					
FLU-CFC	295	625	998		
	(153, 437)	(323, 926)	(516, 1480)		
TAA-CFC	309	653	1044	1496	2030
	(246, 371)	(521, 786)	(833, 1256)	(1192, 1799)	(1618, 2441)
BDP-CFC	168	356			
	(71, 266)	(149, 564)			
FP-DPI	440				
	(0, 907)				
BUD-DPI	164	348	556	796	
	(94, 235)	(198, 497)	(317, 795)	(453, 1138)	
FP-CFC	68	144	230	329	
MDI	(41, 95)	(87, 201)	(139, 321)	(200, 459)	
Fine particle dose					
FLU-CFC	229	486	777		
	(119, 340)	(251, 720)	(402, 1151)		
TAA-CFC	101	214	342	490	665
	(81, 122)	(171, 258)	(273, 412)	(391, 590)	(530, 800)
BDP-CFC	97	206			
	(41, 154)	(86, 325)			
FP-DPI	48				
	(0, 99)				
BUD-DPI	85	179	287	410	
	(48, 121)	(102, 256)	(163, 410)	(163, 410)	
FP-MDI	58	123	196	281	
	(35, 81)	(74, 171)	(119, 273)	(170, 391)	

Definition of abbreviations: AUC = area under the curve; BDP = beclomethasone dipropionate; BUD = budesonide; CFC = chlorofluorocarbon; CS = cortisol suppression; DPI = dry powder inhaler; FLU = flunisolide; FP = fluticasone propionate; MDI = metered dose inhaler.

* Micrograms producing an AUC CS of 10%, 20%, 30%, 40%, and 50%.

[†] Doses in micrograms.

[‡] Values in parentheses represent 95% confidence intervals.

could have proposed a design in which the doses were administered randomly with washout periods, we felt there were scientific and practical drawbacks to such a design. A random design would be subject to the possibility of significant carryover effects when a larger dose of ICS preceded a smaller dose of ICS. To eliminate such carryover effects, we would have to introduce a washout period long enough to assure that prior effects of the larger dose had waned and that the responsiveness of the hypothalamic-pituitary-adrenal axis had recovered. The appropriate duration of such a washout period has not been established. Using the classic escalating dose–response design minimizes these uncertainties. Further, we considered that even if a carryover effect did exist from prior use of a lower dose of ICS, it would be no greater than any effect that would occur when these medications were used as currently prescribed, namely for long-term, extended use. We recognize,

TABLE 5. MODEL-BASED RATIO OF CORTISOL SUPPRESSIVE DOSES AT A 10% SUPPRESSION

	Labeled Dose*	Emitted Dose	Fine Particle Dose
FLU-CFC MDI	1	1	1
TAA-CFC MDI	1.19:1 (0.80, 2.38)[†]	0.95:1 (0.64, 1.90)	2.27:1 (1:53, 4.54)
BDP-CFC MDI	1.69:1 (0.99, 6.25)	1.74:1 (1.02, 6.41)	2.34:1 (1.37, 8.64)
FP-DPI	2.08:1 (1.00, 100)	0.67:1 (0.32, 32.0)	4.72:1 (2.27, 227.0)
BUD-DPI	3.45:1 (2.17, 9.09)	1.80:1 (1.11, 4.64)	2.68:1 (1.68, 7.05)
FP-CFC MDI	8.33:1 (5.26, 20.0)	4.34:1 (2.67, 10.1)	3.91:1 (2.47, 9.38)

Definition of abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide; CFC = chlorofluorocarbon; DPI = dry powder inhaler; FLU = flunisolide; FP = fluticasone propionate; ICS = inhaled corticosteroid; MDI = metered dose inhaler; TAA = triamcinolone acetonide.

* FLU-CFC is assigned the arbitrary numeric order of 1 with progressive ordering of the different ICS for the labeled dose. The ratios change for the emitted dose and fine particle dose.

[†] Values in parentheses represent 95% confidence intervals.

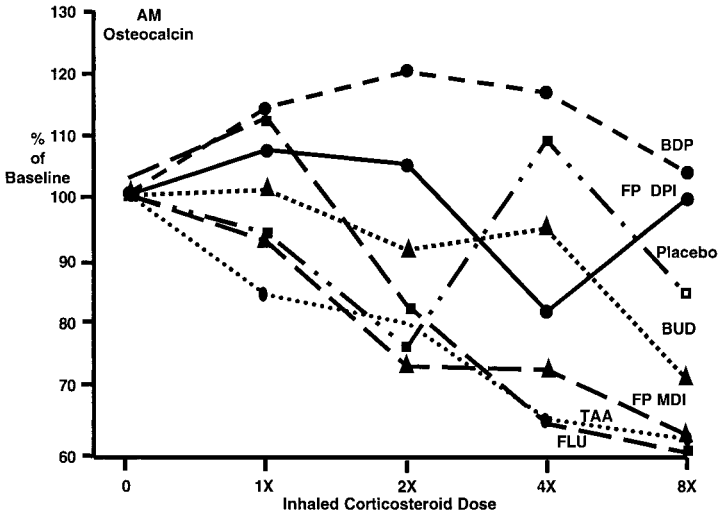

Figure 3. This figure demonstrates the dose–response of the ICS preparations for the morning blood osteocalcin. Dosing on the *horizontal axis* can be found in Table 2 for both labeled and emitted doses. There were significant dose–responses found for BUD DPI, FP-CFC MDI, TAA-CFC, and FLU-CFC. However, the variability of the test can be seen in the placebo group.

however, that further accumulation of effect might occur with steroids that have a slower rate of effect. For example, FP has an estimated half-life of 7.8 hours (24). Thus, steady state concentrations should theoretically be reached with 32 hours, i.e., four half-lives. However, slow absorption from the pulmonary site could extend the biologic half-life. An additional step would be to look at the time for maximum effect for each ICS.

The doses selected for each ICS were based on anticipated suppression from previously published results from normal individuals and subjects with asthma (8–15). It should be noted that ICS doses exceeded the recommended doses for clinical use for several of the ICS. This was done to produce the desired doses for cortisol suppression. We acknowledge that it is difficult to extrapolate from normal subjects to asthmatic subjects, as absorption of ICS may be affected by airway disease (25). However, our predictions of cortisol suppression were fairly accurate for BUD DPI, FLU-CFC, FP-CFC MDI, and TAA-CFC. We slightly underdosed for BDP-CFC but still achieved a significant dose–response. The only ICS preparation that did not achieve a significant dose–response for cortisol suppression was FP DPI. The adherence check measurements were equal to those observed in the other groups. Furthermore, the in-laboratory morning FEV_1 improvement at the 4-week time interval was equivalent to that with FP-CFC MDI, which demonstrated the predicted cortisol suppression. Because FP has approximately 99% first pass liver metabolism, the main systemic effect is due to lung absorption. This then would be related to the FPD, i.e., the dose of the ICS delivered to the lung. The FPD for the FP-CFC MDI used with OptiChamber is about four times greater than that for FP DPI (Table 3), which could be the main factor contributing to the difference in cortisol suppression between these same compounds. This relationship of FP-CFC MDI versus DPI cortisol suppression was demonstrated in healthy volunteers using both 8 A.M. serum cortisol and overnight urinary cortisol (26).

Our study design allows for determination of doses that produce equisystemic effect, that is, the microgram dose at which each ICS produces an equivalent degree of cortisol suppression. Because FP-DPI reached a cortisol suppression of 10%, but not quite 20%, all the ICS could be compared only at doses causing 10% suppression, although most could be compared at doses causing higher percentages of suppression (Table 4). With this study, as with others, the coefficients of variation are large. Thus, comparing increments of 10% suppression is not feasible unless sample sizes are increased substantially, but 20 to 30% increments can be compared. It is notable that the rank order of systemic effect (Table 5) was very similar to that found by Lipworth in a large meta-analysis (27).

The ICS formulations used in this study were the ones available at the time of study initiation. Presently and in the near future there are and will be newer formulations and delivery devices. The hydrofluoroalkane ICS will need to be individually tested as particle size and delivery device will be different among these ICS. This may lead to different pulmonary and systemic distribution. The same can be stated for different delivery devices for a formulation that has been evaluated in this study, i.e., FP DPI. At study initiation, only the Rotodisk FP DPI was available to us, whereas presently the Diskus is the delivery system of choice for this drug. For BUD, the Turbuhaler II will supersede the Turbuhaler. However, the methods developed in this study aid in planning future studies and allow analyzing newer ICS and corresponding delivery devices.

TABLE 6. URINE CORTISOL AS A PERCENT OF BASELINE

ICS	Times	1× Dose	2× Dose	4× Dose	8× Dose
Placebo	8 A.M.–8 P.M.	132* (77)†	134 (138)	97 (144)	104 (147)
	8 P.M.–8 A.M.	74 (84)	105 (138)	80 (170)	100 (126)
	24-hour	108 (62)	140 (117)	90 (160)	121 (143)
BDP-CFC	8 A.M.–8 P.M.	112 (130)	53 (112)	86 (125)	73 (108)
	8 P.M.–8 A.M.	88 (129)	73 (114)	81 (93)	79 (132)
	24-hour	108 (90)	82 (99)	92 (109)	88 (109)
BUD-DPI	8 A.M.–8 P.M.‡	68 (131)	63 (113)	39 (131)	48 (147)
	8 P.M.–8 A.M.‡	77 (103)	54 (161)	43 (130)	37 (129)
	24-hour‡	71 (58)	44 (123)	35 (131)	38 (116)
FLU-CFC	8 A.M.–8 P.M.	70 (98)	75 (114)	71 (129)	67 (128)
	8 P.M.–8 A.M.	92 (89)	77 (112)	76 (102)	79 (146)
	24-hour	72 (85)	77 (88)	70 (90)	81 (112)
FP-DPI	8 A.M.–8 P.M.‡	120 (85)	121 (111)	73 (82)	82 (127)
	8 P.M.–8 A.M.	84 (73)	95 (120)	86 (115)	78 (130)
	24-hour	109 (61)	104 (80)	73 (77)	81 (114)
FP-CFC MDI	8 A.M.–8 P.M.	92 (70)	75 (81)	72 (102)	91 (97)
	8 P.M.–8 A.M.‡	78 (84)	111 (88)	66 (115)	56 (104)
	24-hour	74 (67)	93 (70)	57 (112)	78 (98)
TAA-CFC	8 A.M.–8 P.M.	82 (116)	68 (112)	103 (141)	86 (145)
	8 P.M.–8 A.M.	87 (135)	72 (147)	54 (130)	64 (141)
	24-hour	102 (147)	78 (131)	98 (116)	86 (147)

For definition of abbreviations, *see* Table 5.
* Percent of baseline area under the curve.
† Value in parentheses is the coefficient of variation.
‡ Significant dose response, $p < 0.05$.

In summary, the ACRN has developed a method to compare and contrast ICS preparations in regard to one systemic effect, i.e., cortisol suppression, an effect that occurs more rapidly than other systemic effects. Although an overnight in-laboratory evaluation with sampling for plasma cortisol every hour or every 2 hours was required, it was clearly the most reliable test to evaluate suppression in our study population. This systemic analysis of suppression is the base for future ACRN studies of the efficacy of doses of different ICS preparations selected based on equisystemic effect (cortisol suppression) and not on microgram comparisons.

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