Systemic Effect Comparisons of Six Inhaled Corticosteroid Preparations


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 A.M. to 8 P.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 FEV1 following a β-2 agonist or a provocative concentration of methacholine needed to produce a 20% fall in FEV1 (PC20) of 8 mg/ml or less, and an FEV1 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 (adenocorticotropic 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; Respinorisons Health-Scan, 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.

(Received in original form May 3, 2001; accepted in final form February 12, 2002)

Supported by grants U10 HL-51810, U10 HL-51834, U10 HL-51831, U10 HL-51823, U10 HL-51845, U10 HL-51843, and U10 HL-56443 from the National Heart, Lung, and Blood Institute.

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This article has an online data supplement, which is accessible from this issue’s table of contents online at www.atsjournals.org


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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, actuating 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 Pharmacopeia 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 CS30, 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

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**TABLE 1. SUBJECT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Number</th>
<th>M/F (%)</th>
<th>Minority (%)</th>
<th>Age (Years, Mean ± SD)</th>
<th>FEV₁ (% Predicted, Mean ± SD)</th>
<th>Body Mass Index (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>156</td>
<td>90/66 (58/42)</td>
<td>48 (31)</td>
<td>30.1 ± 8.3</td>
<td>78.4 ± 6.9</td>
<td>25.5 ± 3.8</td>
</tr>
</tbody>
</table>

**TABLE 2. WEEKLY DOSE INCREMENTS OF INHALED CORTICOSTEROIDS**

<table>
<thead>
<tr>
<th>ICS</th>
<th>BDP-CFC MDI</th>
<th>BUD DPI</th>
<th>FLU-CFC MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing week</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Labeled dose</td>
<td>168</td>
<td>313</td>
<td>672</td>
</tr>
<tr>
<td>Emitted dose</td>
<td>52</td>
<td>103</td>
<td>206</td>
</tr>
<tr>
<td>Dosing week</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Labeled dose</td>
<td>100</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>Emitted dose</td>
<td>99</td>
<td>198</td>
<td>395</td>
</tr>
</tbody>
</table>

*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.
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.
MORNING FEV1

Although this was not an efficacy study, the morning laboratory FEV1 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 and the overnight collection 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.

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–response 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...
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 4. ESTIMATED CORISOL SUPPRESSIVE DOSES

<table>
<thead>
<tr>
<th>Labeled dose</th>
<th>CS&lt;sub&gt;10&lt;/sub&gt;*</th>
<th>CS&lt;sub&gt;20&lt;/sub&gt;*</th>
<th>CS&lt;sub&gt;30&lt;/sub&gt;*</th>
<th>CS&lt;sub&gt;40&lt;/sub&gt;*</th>
<th>CS&lt;sub&gt;50&lt;/sub&gt;*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLU-CFC</td>
<td>936†</td>
<td>1981</td>
<td>3167</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(484, 1387)‡</td>
<td>(1025, 2938)</td>
<td>(1639, 4695)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAA-CFC</td>
<td>787</td>
<td>1667</td>
<td>2664</td>
<td>3816</td>
<td>5178</td>
</tr>
<tr>
<td></td>
<td>(627, 947)</td>
<td>(1329, 2005)</td>
<td>(2124, 3204)</td>
<td>(3042, 4589)</td>
<td>(4128, 6227)</td>
</tr>
<tr>
<td>BDP-CFC</td>
<td>548</td>
<td>1161</td>
<td>234</td>
<td>375</td>
<td>537</td>
</tr>
<tr>
<td></td>
<td>(230, 866)</td>
<td>(487, 1835)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FP-DPI</td>
<td>445</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(0, 918)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FLU-DPI</td>
<td>268</td>
<td>567</td>
<td>907</td>
<td>2030</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(153, 383)</td>
<td>(323, 811)</td>
<td>(517, 1297)</td>
<td>(740, 1857)</td>
<td></td>
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<tr>
<td>TAA-DPI</td>
<td>309</td>
<td>653</td>
<td>1044</td>
<td>1496</td>
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</tr>
<tr>
<td></td>
<td>(246, 371)</td>
<td>(521, 786)</td>
<td>(833, 1256)</td>
<td>(1192, 1799)</td>
<td></td>
</tr>
<tr>
<td>BDP-DPI</td>
<td>168</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(71, 266)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLU-MDI</td>
<td>144</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(41, 95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAA-MDI</td>
<td>206</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(41, 154)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BDP-MDI</td>
<td>356</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(71, 266)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP-DPI</td>
<td>440</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(0, 907)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLU-DPI</td>
<td>164</td>
<td>348</td>
<td>556</td>
<td>796</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(94, 235)</td>
<td>(198, 497)</td>
<td>(317, 795)</td>
<td>(453, 1138)</td>
<td></td>
</tr>
<tr>
<td>TAA-DPI</td>
<td>68</td>
<td>144</td>
<td>230</td>
<td>329</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(41, 95)</td>
<td>(87, 201)</td>
<td>(139, 321)</td>
<td>(200, 459)</td>
<td></td>
</tr>
<tr>
<td>BDP-DPI</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td>(0, 99)</td>
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<td></td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Labeled Dose*</th>
<th>Emitted Dose</th>
<th>Fine Particle Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLU-CFC MDI</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TAA-CFC MDI</td>
<td>1.19:1 (0.80, 2.38)†</td>
<td>0.95:1 (0.64, 1.90)</td>
</tr>
<tr>
<td>BDP-CFC MDI</td>
<td>1.69:1 (0.99, 6.25)</td>
<td>1.74:1 (1.02, 6.41)</td>
</tr>
<tr>
<td>FP-DPI</td>
<td>2.08:1 (1.00, 100)</td>
<td>0.67:1 (0.32, 3.20)</td>
</tr>
<tr>
<td>BUD-DPI</td>
<td>3.45:1 (2.17, 9.09)</td>
<td>1.80:1 (1.11, 4.64)</td>
</tr>
<tr>
<td>FP-CFC MDI</td>
<td>8.33:1 (5.26, 20.0)</td>
<td>4.34:1 (2.67, 10.1)</td>
</tr>
</tbody>
</table>

**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.

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; 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 ratio change for the emitted dose and fine particle dose.

† Values in parentheses represent 95% confidence intervals.
Table 6. Urine Cortisol as a Percent of Baseline

<table>
<thead>
<tr>
<th>ICS</th>
<th>Times</th>
<th>1× Dose</th>
<th>2× Dose</th>
<th>4× Dose</th>
<th>8× Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8 A.M.–8 P.M.</td>
<td>132a (77)a</td>
<td>134 (138)</td>
<td>97 (144)</td>
<td>104 (147)</td>
</tr>
<tr>
<td></td>
<td>8 P.M.–8 A.M.</td>
<td>74 (84)</td>
<td>105 (138)</td>
<td>80 (170)</td>
<td>100 (126)</td>
</tr>
<tr>
<td>BDP-CFC</td>
<td>8 A.M.–8 P.M.</td>
<td>112 (130)</td>
<td>53 (112)</td>
<td>86 (125)</td>
<td>73 (108)</td>
</tr>
<tr>
<td></td>
<td>8 P.M.–8 A.M.</td>
<td>88 (129)</td>
<td>73 (114)</td>
<td>81 (93)</td>
<td>79 (132)</td>
</tr>
<tr>
<td>BUD-DPI</td>
<td>8 A.M.–8 P.M.</td>
<td>68 (131)</td>
<td>63 (113)</td>
<td>39 (131)</td>
<td>48 (147)</td>
</tr>
<tr>
<td></td>
<td>8 P.M.–8 A.M.</td>
<td>77 (103)</td>
<td>54 (161)</td>
<td>43 (130)</td>
<td>37 (129)</td>
</tr>
<tr>
<td>FLU-CFC</td>
<td>8 A.M.–8 P.M.</td>
<td>70 (98)</td>
<td>75 (114)</td>
<td>71 (129)</td>
<td>67 (128)</td>
</tr>
<tr>
<td></td>
<td>8 P.M.–8 A.M.</td>
<td>92 (89)</td>
<td>77 (112)</td>
<td>76 (102)</td>
<td>79 (146)</td>
</tr>
<tr>
<td>FP-DPI</td>
<td>8 A.M.–8 P.M.</td>
<td>120 (85)</td>
<td>121 (111)</td>
<td>73 (82)</td>
<td>82 (127)</td>
</tr>
<tr>
<td></td>
<td>8 P.M.–8 A.M.</td>
<td>84 (73)</td>
<td>95 (120)</td>
<td>86 (115)</td>
<td>78 (130)</td>
</tr>
<tr>
<td>FP-CFC MDI</td>
<td>8 A.M.–8 P.M.</td>
<td>92 (70)</td>
<td>75 (81)</td>
<td>72 (102)</td>
<td>91 (97)</td>
</tr>
<tr>
<td></td>
<td>8 P.M.–8 A.M.</td>
<td>78 (84)</td>
<td>111 (88)</td>
<td>66 (115)</td>
<td>76 (104)</td>
</tr>
<tr>
<td>TAA-CFC</td>
<td>8 A.M.–8 P.M.</td>
<td>82 (116)</td>
<td>68 (112)</td>
<td>103 (141)</td>
<td>86 (145)</td>
</tr>
<tr>
<td></td>
<td>8 P.M.–8 A.M.</td>
<td>87 (135)</td>
<td>72 (147)</td>
<td>54 (130)</td>
<td>64 (141)</td>
</tr>
<tr>
<td></td>
<td>24-hour</td>
<td>102 (147)</td>
<td>78 (131)</td>
<td>98 (116)</td>
<td>86 (147)</td>
</tr>
</tbody>
</table>

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.

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.

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.
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.

Acknowledgment: The authors wish to deeply thank all the clinical coordinators at each center for their invaluable help in bringing this study to completion: J. Burke, RN, E. Freeman, L. Mazzella, C. Connolly, E. Snyder, C. Hong, J. Chang, J. Oliviero (Boston); J. Brandorff, J. Derbort, J. Pak (Denver); M. Love-Partron, RN, B. Miller, RN, R. Kelley, A. Sexton, MPH (Madison); D. DeGraffinreidt, E. Gilbert (New York); P. Ilves-Corressel, RN, C. Czajka, RN, S. Dodds, RN, C. Mitchell, M. Whislet, D. Campbell, M. Satchell, M. Police, RN, A. Haztie, Ph.D. (Philadelphia); L. Musumeci, RN, T. Ward, RN (San Francisco). They also thank Mary Peterson for manuscript production and R. Rhen for performing the particle sizing measurements. Drugs were supplied by AstraZeneca, Aventis, Forest, GlaxoSmithKline, and Schering; Opti-Chamber was supplied by Respironics.

References

12. Clark DJ, Grove A, Cargill RI, Lipworth BJ. Comparative adrenal suppression with inhaled budesonide and fluticasone propionate in adult asthmatics. Thorax 1996;51:262–266.