Impact of Study Design on the Evaluation of Inhaled and Intranasal Corticosteroids' Effect on Hypothalamic–Pituitary–Adrenal Axis Function, Part I: General Overview of HPA Axis Study Design

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ABSTRACT: Inhaled and intranasal corticosteroids (ICS and INS) are among the mainstays of the treatment for asthma and allergic rhinitis, respectively, and also carry the potential to suppress the hypothalamic–pituitary–adrenal (HPA) axis. Several important factors affect the interpretability of trials investigating the impact of ICS and INS on the HPA axis. This paper reviews 106 published clinical trials, peer-reviewed articles, and New Drug Application reviews of approved ICS and INS, using MEDLINE and Drugs@FDA database. The trials included in this review evaluated the potential impact on HPA axis function of eight approved single-ingredient ICS and INS (beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, flucticasone propionate, mometasone furoate, and triamcinolone acetonide) and combination products containing these ingredients. The most commonly utilized design was blinded, placebo controlled, and short term (<6 weeks) for adult trials and blinded, placebo controlled, and long term (≥6 weeks) for pediatric trials. Factors potentially affecting trial results include the choice of dose, dosing duration, assay sensitivity, statistical methodology, and the study population evaluated (patients or healthy volunteers). All of these factors have the potential to affect the level of adrenal suppression detected. In conclusion, to be informative, a HPA axis study should be well designed and carefully implemented to minimize variability in results and improve the overall interpretability of data obtained. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3513–3527, 2013

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INTRODUCTION

Inhaled corticosteroids (ICS)[1] are the preferred treatment for persistent asthma.[2] Asthma is a chronic inflammatory disease of the airways, and ICS are among the most effective anti-inflammatory medications available. Clinical studies have shown that ICS significantly reduce airway inflammation and hyperresponsiveness, improve lung function, decrease symptom severity, and effectively prevent or reduce the occurrence of acute asthma exacerbations.[3] National and international guidelines for asthma management currently recommend low-dose ICS as first-line therapy for patients with mild persistent asthma, which may be stepped up to medium-dose or high-dose ICS and/or combined with other agents (e.g., long-acting β2-agonists or leukotriene receptor antagonist) as needed.[2,4]

Allergic rhinitis (AR) is the most prevalent chronic allergic disease, affecting up to 10% of adults and 40% of children in the United States.[5] The use of intranasal corticosteroids (INS) is well established in the treatment of moderate-to-severe seasonal and perennial AR. The *Allergic Rhinitis and its Impact on Asthma (ARIA)* guideline considers INS to be "the most effective drugs for the treatment of allergic rhinitis."[6] INS are highly effective in preventing and relieving nasal symptoms associated with both early- and late-phase allergic responses.[7] In general, they relieve nasal congestion and itching, rhinorrhea, and sneezing, and in some studies, they almost completely prevent late-phase symptoms.[8,9]

Both ICS and INS are considered to be safer than oral corticosteroids, as the route of administration delivers the drug directly to the lung and nasal mucosa, where it acts locally, minimizing the systemic exposure. However, there is the potential to produce systemic adverse effects, especially when recommended therapeutic doses are exceeded. A systemically bioavailable ICS or INS may lead to suppression of the hypothalamic–pituitary–adrenal (HPA) axis, as well as reductions in growth velocity in children and bone mineral density in adults, although the latter is not as well documented in long-term controlled studies.[10]

Abbreviations used ICS, inhaled corticosteroids; INS, intranasal corticosteroids; HPA axis, hypothalamic–pituitary–adrenal axis; ARIA, allergic rhinitis and its impact on asthma; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone (corticotropin); AUC, area under the curve; PC, plasma cortisol; SC, serum cortisol; UC, urinary free cortisol; UCC, urinary free cortisol corrected for creatinine; BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; FF, fluticasone furoate; FLN, flunisolide; FP, flucticasone propionate; MF, mometasone furoate; TAA, triamcinolone acetonide; PK, pharmacokinetic; PD, pharmacodynamic; AR, allergic rhinitis; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; MDI, metered-dose inhaler; NS, nasal spray; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CI, confidence interval; ITT, intent-to-treat; PEF, peak expiratory flow.

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The HPA axis is under circadian regulation and operates in a negative-feedback-loop to regulate stress response and cortisol secretion within the body.[11–13] Corticotropin-releasing hormone (CRH) is released by the hypothalamus in response to a stimulus derived from brain, with peak levels being produced in the morning (around 6–8 a.m.). CRH then stimulates the release of corticotropin, also known as adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then stimulates the adrenal glands to secrete cortisol. Endogenous cortisol binds to receptors on the hypothalamus and adrenal glands, suppressing the secretion of CRH and ACTH and, which in turn, lead to reduced production and secretion of cortisol.[11–13] Exogenous glucocorticoids in the blood exert negative feedback in the same manner as endogenous cortisol, leading to the suppression of endogenous cortisol production, thereby disrupting the normal function of the HPA axis.[13,14] HPA axis suppression becomes clinically relevant in corticosteroid-treated patients if exogenous corticosteroid treatment is abruptly stopped, or if stressful conditions occur, because the adrenal glands are unable to increase endogenous cortisol production.[15,16] Short-term disruptions in cortisol secretion may lead to acute adrenal insufficiency. This is of particular concern with prolonged exposure to high doses of exogenous ICS and INS.[17,18] Therefore, it is important to monitor the HPA axis function for the safety profile of corticosteroids.

When evaluating the HPA axis function in clinical studies, many factors should be considered. Some of these relate to the nature of the drug molecule [pharmacokinetic/pharmacodynamic (PK/PD) properties], the mode of administration (type of device and aerosol formulation), and the type and severity of the disease condition. Other factors relate to the nature of the study design, which includes such elements as dosing, treatment controls, sample size, duration of treatment, methods of data analysis, and choice of HPA axis function test.[19,20] A number of studies reviewing the HPA axis suppressive effects of ICS or INS have been published. It is not surprising to see inconsistent or even conflicting results among these studies, as there is considerable variation in the study designs utilized. To our knowledge, there have been no comprehensive examinations of the impact of study design on the outcome of HPA axis studies to date. Moreover, HPA axis study design is only briefly discussed in the United States Food and Drug Administration (FDA) draft guidances "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action"[21] and "Allergic rhinitis: clinical development programs for drug products."[22] These documents are not dedicated to the topic and provide only limited information from the study design perspective. Further exploration of the impact of study design on the results of HPA axis investigations is therefore warranted.

This review article provides an overview of the different study design types employed in the evaluation of HPA axis function in the context of ICS and INS use, with a focus on drug products developed over the past decade. It is not intended to be a systemic review or a meta-analysis of the results from HPA axis studies, as this has been published in detail elsewhere.[23–26] Rather, the objective is to identify factors of study design that may be associated with the outcomes observed in these studies. Such information may be useful to both investigators and regulators involved in the design and evaluation of HPA axis studies relevant to drug development.

When is an HPA Axis Study Performed?

Evaluations of the systemic effects of ICS and INS, particularly on the HPA axis, are an important element in the evaluation of safety for these drug products. These studies may be conducted as part of a drug's development program or as part of a postmarketing program. Typically for new formulations of ICS, if the new formulation results in a higher systemic exposure to the drug substance than other formulations already marketed or under development for which an adequate assessment of HPA axis effects has been conducted, or if PK data for these other formulations are unavailable, an evaluation of the effect of the new formulation on the HPA axis is strongly recommended.[22]

Measures of HPA Axis Function

Measurements of basal HPA axis function [e.g., area under the curve (AUC) or morning blood cortisol levels or urinary cortisol excretion] and dynamic stimulation tests (e.g., CRH and ACTH stimulation) are recognized methods for assessing systemic exposure and adrenal integrity, respectively.

Among these, serum cortisol measurements (AUC or morning cortisol levels), urinary free cortisol (UC) excretion, and the high-dose (250 μg) and low-dose (0.5–1.0 μg) ACTH stimulation test are considered standard measures. Other methods, such as the CRH stimulation test, the insulin tolerance test, the metapyrone test, and measures of urinary cortisol metabolites and salivary cortisol, have all been found to be relatively insensitive methods for HPA axis evaluation in previous publications.[16,27]

The measurement of plasma cortisol at a single time point can be used for screening individual patients, considering that there are large interindividual variations in the circadian secretion of cortisol. Another approach is to measure integrated serial plasma or serum cortisol levels, expressed as AUC during a 24-h period. Additional sampling of blood or urine over time produces highly reproducible results and minimizes interindividual variations in diurnal rhythm at single time points. The measurement of cortisol excreted in the urine over certain period of time is both noninvasive and highly sensitive in assessing dose-related HPA axis suppression. However, measurements of urinary cortisol must be carefully monitored and corrected for creatinine excretion to ensure accuracy in the sample collection.

The conventional high-dose ACTH stimulation test is useful in determining severe adrenocortical insufficiency. However, it has been found inadequate for detecting mild or short-term adrenal gland suppression or for detecting isolated central adrenal insufficiency.[28–30] Lower-dose (0.5–1.0 μg) ACTH stimulation roughly mimics the normal physiologic response to stress and is more sensitive than the conventional high-dose stimulation test in detecting evolving or partial adrenal suppression.[28]

This review will only focus on studies employing at least one of the following testing methods: measurements of plasma cortisol concentration (morning or integrated), measurements of integrated UC levels, and the ACTH stimulation test.

Currently Approved ICS and INS

Among the available ICS and INS, eight corticosteroids for inhalation and intranasal route of administration were selected: beclomethasone dipropionate (BDP), budesonide (BUD),

Table 1. Currently Approved Inhaled Corticosteroids and Recommended Dosages

Generic Name	Brand Name (Delivery Device)	Approval Date	Strength	Indication (Age Range)	Recommended Dosing[a], Adults and Adolescents (≥12 yrs) (Age Range): Starting; Highest	Recommended Dosing[a], Pediatric (≤12 yrs) (Age Range): Starting; Highest
BDP	QVAR (HFA MDI)	9/15/2000	40; 80 μg/inhalation	Asthma (≥5 yrs)	40–160 μg b.i.d.; 320 μg b.i.d.	(5–11 yrs): 40 μg b.i.d.; 80 μg b.i.d.
	BECONASE AQ (NS)	8/27/1987	42 μg/spray	SAR, PAR or NAR/VM	84–168 μg b.i.d.	(6–12 yrs): 84 μg b.i.d.; 168 μg b.i.d.
BUD	PULMICORT TURBUHALER (DPI)	6/24/1997	160 μg/inhalation	Asthma (≥6 yrs)	200–800 μg b.i.d.; 800 μg b.i.d.	(6–17 yrs): 200–400 μg b.i.d.; 400 μg b.i.d.
	PULMICORT FLEXHALER (DPI)	7/12/2006	80; 160 μg/inhalation	Asthma (≥6 yrs)	(18 yrs and older): 180–360 μg b.i.d.; 720 μg b.i.d.	(6–17 yrs): 180–360 μg b.i.d.; 360 μg b.i.d.
	PULMICORT RESPULES [Inhalation suspension (Jet Nebulizer)]	8/8/2000	250; 500; 1000 μg/2 mL	Asthma (12 months to 8 yrs)	N/A	(12 months to 8 yrs): 0.5–1 mg/d (q.d. or b.i.d.); 1 mg/d
	RHINOCORT (NS)	10/1/1999	32 μg/inhalation	SAR, PAR (≥6 yrs)	64 μg q.d.; 256 μg q.d.	(6–12 yrs): 64 μg q.d.; 128 μg q.d.
BUD; formoterol	SYMBICORT (HFA MDI)	7/21/2006	80/4.5; 160/4.5 μg/inhalation	• Asthma (≥12 yrs) • COPD	160/9 or 320/9 μg b.i.d.; 320/9 μg b.i.d.	320/9 μg b.i.d.; 320/9 μg b.i.d.
CIC	ALVESCO (HFA MDI)	1/10/2008	80; 160 μg/inhalation	Asthma (≥12 yrs)	80 μg b.i.d.; 160–320 μg b.i.d.	Not approved
	OMNARIS (NS)	10/20/2006	50 μg/spray	SAR (≥6 yrs), PAR (≥12 yrs)	200 μg q.d.	200 μg q.d.
	OMNARIS (NS)	11/21/2007	50 μg	SAR (≥6 yrs), PAR (≥12 yrs)	200 μg q.d.	200 μg q.d.
FLN	AEROSPAN HFA (HFA MDI)	1/27/2006	80 μg/inhalation	Asthma (≥6 yrs)	160 μg b.i.d.; 320 μg b.i.d.	(6–11 yrs): 80 μg b.i.d.; 160 μg b.i.d.
FF	VERAMYST (NS)	4/27/2007	27.5 μg/inhalation	SAR, PAR (≥2 yrs)	110 μg q.d.	(2–11 yrs): 55 μg q.d.
FP	FLOVENT DISKUS (DPI)	9/29/2000	100; 250; 50 μg/inhalation	Asthma (≥4 yrs)	100–1000 μg b.i.d.; 1000 μg b.i.d.	(4–11 yrs): 50 μg b.i.d.; 100 μg b.i.d.
	FLOVENT HFA (HFA MDI)	5/14/2004	220; 110; 44 μg/inhalation	Asthma (≥4 yrs)	88–440 μg b.i.d.; 880 μg b.i.d.	(4–11 yrs): 88 μg b.i.d.
	FLONASE (NS)	10/19/1994	50 μg/spray	SAR, PAR (≥4 yrs)	(≥18 yrs): 200 μg q.d.	(4–17 yrs): 100 μg q.d.; 200 μg q.d.
FP; salmeterol	ADVAIR DISKUS (DISKUS DPI)	8/24/2000	100/50; 250/50; 500/50 μg/inhalation	Asthma (≥4 yrs) COPD	100/50, 250/50, or 500/50 μg b.i.d.	(4–11 yrs): 100/50 μg b.i.d.
	ADVAIR HFA (HFA MDI)	6/8/2006	45/21; 115/21; 230/21 μg/inhalation	Asthma (≥12 yrs)	Two inhalations b.i.d.	Not approved
MF	ASMANEX TWISTHALER (DPI)	3/30/2005	220; 110 μg/inhalation	Asthma (≥4 yrs)	220–440 μg q.d. p.m.; 880 μg/d	(4–11 yrs): 110 μg q.d. p.m.; 110 μg/d
	NASONEX (NS)	10/1/1997	50 μg/spray	AR (≥2 yrs) SAR(≥2 yrs) Nasal Polyps (≥18 yrs)	200 μg q.d. to 200 μg b.i.d.	(2–11 yrs): 100 μg q.d.

Continued

Table 1. Continued

Generic Name	Brand Name (Delivery Device)	Approval Date	Strength	Indication (Age Range)	Recommended Dosing[a], Adults and Adolescents (≥12 yrs) (Age Range): Starting; Highest	Recommended Dosing[a], Pediatric (≤12 yrs) (Age Range): Starting; Highest
MF; Formoterol Fumarate	DULERA (HFA MDI)	6/22/2010	100/5; 200/5 μg/inhalation	Asthma (≥18 yrs)	200–400 μg/10 μg b.i.d.; 400–800 μg/20 μg/d	Not approved
TAA	AZMACORT (CFC MDI)	4/23/1982	100 μg/inhalation	Asthma	150 μg tid or qid/ 300 μg b.i.d.; 1200–1600 μg/d	(6–12 yrs): 75–150 μg tid or qid / 150–300 μg b.i.d.; 900 μg/d
	NASACORT AQ (NS)	5/20/1996	55 μg/spray	SAR, PAR (≥2 yrs)	220 μg q.d.	(6–12 yrs): 110 μg q.d.; 220 μg/d (2–5 yrs): 110 μg q.d.

[a]In many cases, dosing recommendations depend on a patient's previous therapy; see a product's associated Prescribing Information for full details.
BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; FF, fluticasone furoate; FLN, flunisolide; FP, fluticasone propionate; MF, mometasone furoate; TAA, triamcinolone acetonide; DPI, dry powder inhaler; MDI, metered-dose inhaler; NS, nasal spray; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; NAR/VM, nonallergic rhinitis/vasomotor rhinitis; q.d., once daily; b.i.d., twice daily; yrs, years.

Figure 1. Flow of study identification and selection.

ciclesonide (CIC), flunisolide (FLN), fluticasone propionate (FP), fluticasone furoate (FF), mometasone furoate (MF), and triamcinolone acetonide (TAA). Table 1 summarizes the generic names, brand names, approval date, dosage forms, labeled indications, strengths, and recommended dosage for the selected corticosteroids.

DATA SOURCE AND STUDY SELECTION

Searches were performed using MEDLINE and the Drugs@FDA databases, covering the period from January 1990 to the present, to identify studies that include an evaluation of the clinical safety and systemic effects of the aforementioned ICS and INS. The literature search covered all English-language studies published during this time frame. Only primary reports were sought (review articles were excluded), and drug dosing and HPA axis testing methodology had to be clearly described. Of 176 reports identified by this process, 34 were eliminated because they were case reports, pilot or single-dose studies. Of the remaining 142 reports, 17 studies assessing HPA function were rejected because they did not employ any of the testing methods of interest: response to ACTH stimulation test, measurements of plasma cortisol concentration (morning or integrated), and measurements of integrated UC levels. When other tests were also performed in addition to the methods of interest, the corresponding data are noted and presented for purposes of completeness and comparison. In addition to the exclusions noted above, 19 studies were excluded because of the lack of detailed description of design or results. In total, 106 studies were included in this review. The process of study exclusion is summarized and illustrated in Figure 1.

For each study included, the following characteristics of design were extracted: year, duration, control arms, blinding,

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dosing regimen, dosage form, sample size, subject disease type [asthma/AR/healthy/chronic obstructive pulmonary disease (COPD)], gender, age, previous steroid dependency, compliance, statistical analysis method, HPA axis function test/endpoint and evaluation timing, in addition to study results.

RESULTS

Ten design categories describing the four key characteristics of study design (blinding, control arms, parallel/crossover design, and duration) identified from current FDA draft guidance documents[21,22] were defined for the studies under review. A list of the definitions for the 10 categories and the numbers of studies assigned to each category is provided in Table 2 and Figure 2, respectively, for both adults and adolescents (age > 12 years) and children (age ≤ 12 years). A general overview of design trends over the past decade is given in Figure 3.

Hypothalamic–pituitary–adrenal axis evaluation may be conducted as a part of larger trial, or in a stand-alone (dedicated) investigation. In both cases, the general methods used to evaluate HPA axis function are similar. Compared with the overall number of studies that included an evaluation of HPA axis function, the proportion of dedicated HPA axis trials is relatively low: 34 studies (53%) in adults and adolescents, and nine studies (23%) in children. For studies evaluating adults and adolescents, the most common design types were B, E, and F, which are blinded, placebo-controlled, or placebo and active-controlled, and short-term (<6 weeks) studies (see Table 2). For pediatric studies (children <12 years of age), however, the most common design type was found to be category D: blinded, placebo controlled, and long term (≥6 weeks).

The frequencies of studies following most design categories were evenly distributed from the year of 1991 to 2010 (Fig. 3). For adult and adolescent studies, the peak of studies conducted in design categories A, B, and I occurred around 1998–2000; whereas for pediatric studies, the peak of the most common design category D occurred in 2000 and 2006 (Fig. 3).

Table 3 is a brief summary of the various study design types used in the evaluation of the ICS and INS products. What is notable is the amount of variability in study design, even among trials for the same formulation of a specific drug. For example, 11 studies of the BDP MDI formulation in adults and adolescents can be differentiated into seven design categories.

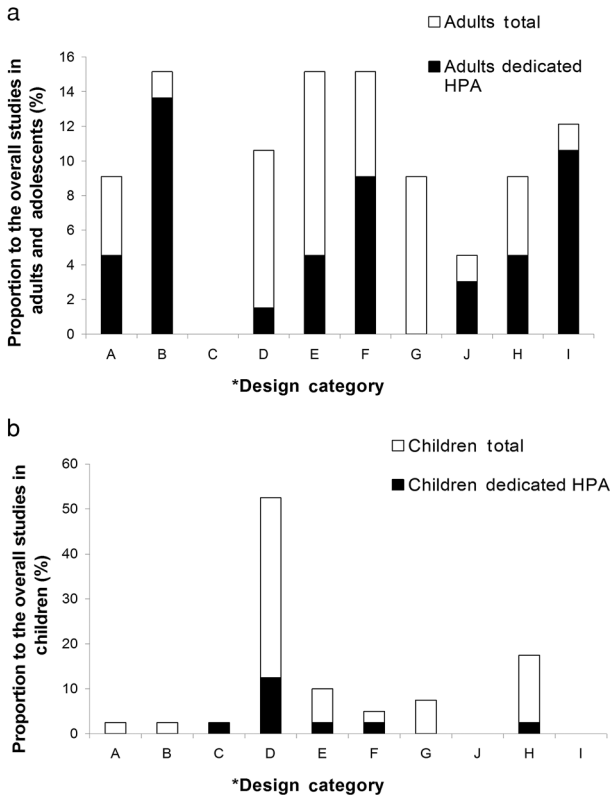

Figure 2. Percentage proportion of design categories to the overall number of studies in (a) adults and adolescents and (b) children. *: Refer Table 2 for definition of design categories.

Similarly, seven studies evaluating the MF DPI formulation in adults and adolescents can be assigned to six different categories.

Besides the four basic aspects of study design previously described, there are many other sources of variability both within and among trials. These include dose and duration of treatment, the testing method sensitivity, methods of analysis, and the study population. All of these factors have the potential to affect the level of adrenal suppression detected and may be considered when evaluating the effect of ICS/INS on the HPA axis.

Table 2. Summary of HPA Axis Study Design Categories

Design Category	Masking	Control Arms	Design	Duration (weeks)	# of Study in Adults and Adolescents (≥12 years)		# of Study in Children (<12 years)	
					Total	Dedicated HPA	Total	Dedicated HPA
A	Blinding	Placebo and Positive	Parallel	≥6	6	3	1	0
B	Blinding	Placebo and Positive	Parallel	<6	10	9	1	0
C	Blinding	Placebo and Positive	Crossover	<6	0	0	1	1
D	Blinding	Placebo	Parallel	≥6	7	1	21	5
E	Blinding	Placebo	Parallel	<6	10	3	4	1
F	Blinding	Placebo	Crossover	<6	10	6	2	1
G	Blinding	No placebo		≥6	6	0	3	0
H	Blinding	No placebo		<6	3	2	0	0
I	Open label			≥6	6	3	7	1
J	Open label			<6	8	7	0	0
Total					66	34	40	9

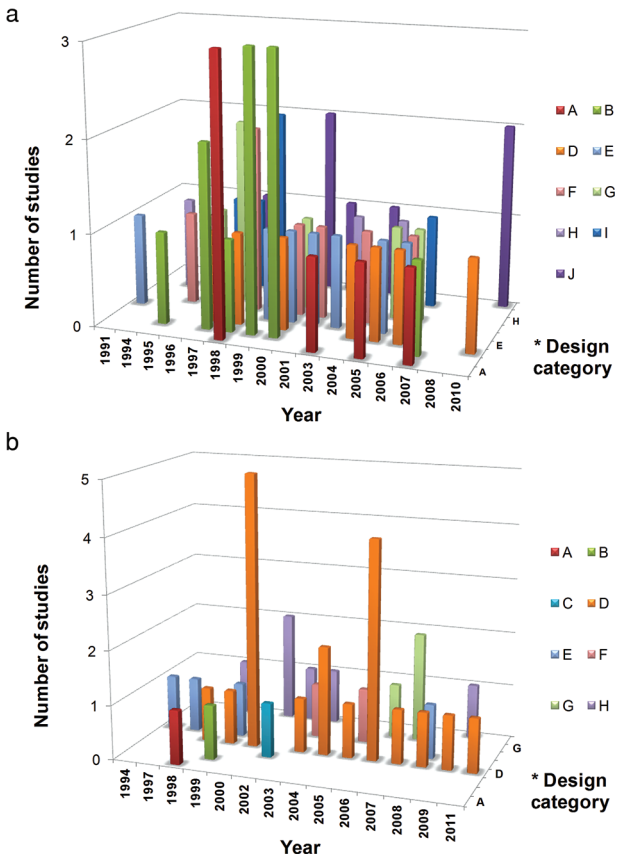

Figure 3. Design trend for (a) adult and adolescent HPA axis studies; (b) pediatric HPA axis studies. *: Refer Table 2 for definition of design categories.

DISCUSSION

The systemic effects of ICS and INS have been studied extensively over the past decade. These studies vary greatly in their designs. It is important to consider the elements of design when interpreting the results of a HPA axis study, including study dosing, duration, susceptibility of the study population, test sensitivity, dosing comparisons, and compliance issues. Other practices that may impact results include the titration of corticosteroid dose, the use of oral corticosteroids as rescue medication. Measurement error and the missing data also have the potential to complicate analyses. Therefore, an optimal HPA axis study should be well designed and carefully implemented, taking into account many factors that may affect the final outcomes. As discussed in this manuscript, for best practices there are several factors that need to be considered for design and conduct of HPA axis studies. These range from selecting appropriate study population, sample size, dose studied, randomization, blinding versus open label, placebo control versus positive control to PK parameters of the drug being evaluated to the length of trial. Pros and cons of these specific considerations have been included in each specific sub headings.

Dose

Generally, studies evaluating the potential HPA axis effect of a specific ICS or INS should be conducted at the highest dose proposed for marketing to maximize study sensitivity. In the FDA draft guidance (2003) "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action,"[21] it is recommended that the HPA axis study would be conducted at the maximum labeled adult dose to maximize study sensitivity. It is also mentioned that "the study design would be based on an understanding that the maximum labeled dose over a 6-week period may not result in detectable adrenal suppression by T (test) and R (reference)," which indicates that the maximum labeled dose may results in undetectable adrenal suppression. However, it is not discussed further for dose determination of the particular drug in the draft guidance and recommended sponsors submit a protocol before the conduct of the study.[21]

For comparisons between drugs, clinically equivalent dosages should be used, accounting for differences in potency and receptor binding affinity. It is noted that studies in the literature often fail to compare clinically equivalent dosages or to test drugs within their recommended dose range, which may limit the usefulness of the data generated. For example, suppression of UC levels was reported in a comparison of BDP, FP, BUD, and TAA not only on a microgram per microgram basis but also in total doses of up to 2000 μg/day, which greatly exceeds the recommended dosage for these drugs.[15] On the contrary, an earlier study found no significant differences between BUD and FP with respect to suppression of UCC excretion with more reasonable and clinically relevant dosages.[31]

For the dosing regimen, the PK profile and in particular, the elimination half-life needs to be considered, as this will determine the degree of drug accumulation after steady state dosing. Because of high lipophilicity, FP has a considerably longer elimination half-life (7–8 h) than that of other corticosteroids. Thus, with a 12-h dosing interval for FP, the average plasma concentration at steady state is approximately 1.7 times higher after repeated dosing than that with single dosing.[32] This degree of steady-state accumulation with FP is associated with a twofold increase in adrenal suppression between single- and repeated-dose administration.[33,34] This demonstrates that performance of comparative studies at the steady state is needed, as the HPA axis effects of single dosing will be much less for a drug with long elimination half-life.

Duration

In a 1998 article, Dluhy[35] recommends that the clinical relevance of ICS treatment at a defined dose be viewed in the context of HPA axis suppression after long-term ICS use (months rather than days) as adrenocortical atrophy usually requires weeks or months of exogenous glucocorticoid exposure. The author also states that although unexpected adrenal responses may occur at moderate doses of corticosteroids, clinically relevant HPA axis suppression should only occur after high-dose, long-term treatment in a subset of patients. For the definition of long-term, a 6-week HPA axis study is generally recommended in the FDA draft guidance (FDA draft guidance (2003) "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action" and FDA draft guidance (2000) "Allergic Rhinitis: Clinical development programs for drug products") for ICS and INS.[21,22]

The findings from studies under review support Dluhy's assertion, as adrenal suppression was more evident when ICS and INS were used at higher doses and in long-term therapy. Among 25 studies that indicated significant cortisol suppression, 21 studies (84%) were conducted at doses higher than the highest approved dose of the particular drug. Three out of the

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Table 3. Brief Summary of HPA Axis Studies and Design Categories for Each Inhaled and Intranasal Corticosteroid

		Adults and Adolescents (≥12 Years)		Children (<12 Years)	
Drug	Dosage Form	# of Study	# Design	# of Study	# Design
BDP	MDI	12	7	2	2
	NS	3	3	1	1
BUD	Inhalation suspension (jet nebulizer)	Not approved	5	2	
	DPI	5	4	5	2
	NS	0	0	1	1
CIC	MDI	5	4	3	3
	NS	1	1	3	1
FLN	MDI	4	4	2	2
FF	NS	3	3	2	1
FP	DPI	2	2	1	1
	MDI	6	4	1	1
	NS	4	3	3	3
MF	DPI	7	6	3	2
	MDI	1	1	0	0
	NS	4	3	4	3
TAA	MDI (CFC)	4	2		
	NS	2	1	2	2
BUD/Formoterol	MDI (SYMBICORT)	2	2	2	2
FP/Salmeterol	DPI (ADVAIR DISKUS)	4	3	0	0
FP/Salmeterol	MDI (ADVAIR HFA)	1	1	1	1
MF/Formoterol	HFA MDI (DULERA)	2	1	0	0

BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; FF, fluticasone furoate; FLN, flunisolide; FP, flucticasone propionate; MF, mometasone furoate; TAA, triamcinolone acetonide; DPI, dry powder inhaler; MDI, metered-dose inhaler; NS, nasal spray; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane.

remaining four were long-term studies. In addition, considering that therapy for asthma is generally long-term, the monitoring for potential HPA axis suppression should be of sufficient duration to be informative for a product intended for chronic use. Nevertheless, it is the authors' opinion that monitoring adrenal suppression during short-term therapy and at lower doses is still of value to ascertain a lower limit for an ICS's safety profile.

Among the studies included in this review, long-term trials comprise 80% of the studies in children, but only 38% of the studies in adults and adolescents. This difference may be due to a greater level of concern about the susceptibility of children to the long-term side effects of systemic corticosteroids (e.g., growth, bone turnover) as compared with that for adults.

Blinding

Randomization can ensure that the test treatment and the control groups are similar at the beginning of the trial. Blinding is, on the other hand, to make sure that the two groups are treated similarly during the course of the trial.

In the FDA draft guidance 2003 "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action," "double-blind" study design is recommended.[21]

In our survey, approximately 80% of the HPA axis studies under review employed blinding in the study design. Forms of blinding vary, and include single-blinded, double-blinded, and triple-blinded designs. Bias derived from preconceptions and subjective judgment in reporting, evaluation, data processing, and statistical analysis should be minimized in these studies.

In contrast, for open-label studies, a serious bias might occur as patients may psychologically react according to the treatments they receive when they are aware of the identity of the treatments. Especially for HPA axis studies, endogenous cortisol secretion is highly susceptible to the emotional stress level of the subjects, which may be influenced by knowing the treatment they are given.

Several studies were conducted using a "double-dummy" or "triple-dummy" design to allow assurance of blinding.[36–39] This technique is employed when two or more active treatments, which cannot be made identical in appearance, are under evaluation. The blind is maintained by including in the trial two or more placebos, each of which matches a corresponding active treatment. A given patient receives a single active treatment, and placebo(s) matching the alternative treatment(s).

Control Arms (Placebo/Positive)

The purpose of using a control group in a clinical trial is to allow discrimination of subject outcomes caused by the active treatment from outcomes caused by other factors.

In the FDA draft guidance 2003 "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action," the placebo and positive control arm were recommended in the section VIII "PD or clinical studies for systemic absorption," section C "clinical BE study designs and subject inclusion criteria."[21] The dose and dosing regimen of the positive control was discussed in the same draft guidance, but in the section A "general information."[21] It does not provide specific recommendations, and recommend the sponsors submit a protocol before the conduct of the study.

Most studies in this review are well controlled with a corresponding placebo. In studies without a placebo arm, that is, either open-label studies or comparisons between different corticosteroids, results appear to be difficult to interpret. For example, a 6.9% reduction from baseline in 24-h UC was

Table 4. Summary of Positive Control Usage inHPA Axis Studies

Positive Control/ Active Comparator	Dosage	Duration	Population	Placebo Control Inclusion	Suppression Effect
PRD	PRD po 10 mg q.d.[46]	36 wks	Asthma, 18–50 yr	Yes	Sig. cortisol ↓
	PRD po 10 mg q.d.[47]	36 days	AR, 19–47 yr	Yes	Sig. cortisol ↓
	PRD po 10 mg q.d.[36]	6 wks	Asthma, 18–65 yr	Yes	Sig. cortisol ↓
	PRD po 10 mg q.d. a.m.[48]	Last 7 days/6 wks	PAR, 12–65 yr*	Yes	Sig. cortisol ↓
	PRD po 10 mg q.d.[39]	4 wks	Asthma, 18–50 yr	Yes	Sig. cortisol ↓
	PRD po 10 mg q.d.[38]	4 wks	Asthma, 18–51 yr	Yes	Sig. cortisol ↓
	PRD po 7.5 mg q.d. PRD po 15 mg q.d.[49]	4 wks	AR, 18–65 yr	Yes	Sig. cortisol ↓
	PRD po 7.5 mg q.d.[50]	3 wks	Asthma, 18–50 yr	Yes	Sig. cortisol ↓
	PRD po 10 mg q.d. a.m.[51]	4 wks	Asthma, 18–47 yr	Yes	Sig. cortisol ↓
	PRD po 10 mg q.d. a.m.[52]	5 wks	SAR, >18 yr	Yes	Sig. cortisol ↓
	PRD 10 mg po q.d. a.m.[52]	4 wks	Healthy, >18 yr	Yes	Sig. cortisol ↓
	Prednisolone po q.d. [2 mg/(kg d) for 4 days followed by 1 mg/(kg d) or half the original dose for 3 days.][45]	1 wk	Asthma, 5–15 yr	No	Sig. cortisol ↓
BDP	BDP MDI 672 μg b.i.d.[53,54]	52 wks	Asthma, 12–62 yr	No	Normal
	BDP NS 84 μg b.i.d.[55]	4 wks	SAR, 6–11 yr	No	Normal
	BDP CFC 400 μg b.i.d.[56]	2 wks	Asthma, 18–60 yr	Yes	Sig. cortisol ↓ only for UC24, normal for ACTH
	BDP CFC 800 μg q.d.[56]	12 wks	Asthma, 18–65 yr	Yes	Normal
BUD	BUD DPI 200 μg b.i.d.[57]	12 wks	Asthma, 12–75 yr	No	Sig. cortisol ↓ (from baseline)
	BUD NS 100 μg qid[58]	52 wks	PR, 18–69 yr	No	Normal
	BUD DPI 1600 μg q.d.[59]	12 wks	Asthma, 18–75yr	No	Normal
	BUD MDl 320 μg q.d.[60]	12 wks	Asthma, 16–79 yr	Yes	Normal
TAA	TAA NS 220 μg q.d. a.m.[52]	52 wks	PAR, 18–50 yr	No	Normal
FP	FP MDI 880 μg q.d.[61]	12 wks	Asthma, 18–80 yr	Yes	Sig. cortisol ↓
	FP MDI 440 μg b.i.d.; FP MDI 880 μg b.i.d.[61]	4 wks	Asthma, >18 yr	Yes	Sig. cortisol ↓ only in 880 μg b.i.d.
	FP MDI 880 μg b.i.d.[51]	4 wks	Asthma, 19–50 yr	Yes	Sig. cortisol ↓
	FP NS 200 μg q.d.[62]	2 wks	AR, 4–11 yr	Yes	Sig. cortisol ↓
FLN	CFC FLN 250 μg b.i.d.; CFC FLN 500 μg b.i.d.; CFC FLN 1000 μg b.i.d.[53,54]	12 wks	Asthma, 12–78 yr	Yes	Normal
Conventional therapy	Inhaled glucocorticosteroids, β2-agonists, methylxanthines, and/or nonsteroidal anti-inflammatory agents (e.g., cromolyn sodium), as judged by the investigator[63]	52 wks	Asthma, 6 months to 8 yr	No	Normal
		52 wks	Asthma, 4–8 yr	No	Normal

PRD, prednisone, BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; FF, fluticasone furoate; FLN, flunisolide; FP, flucticasone propionate; MF, mometasone furoate; TAA, triamcinolone acetonide; DPI, dry powder inhaler; MDI, metered-dose inhaler; NS, nasal spray; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; q.d., once daily; b.i.d., twice daily; Sig., significantly; wks, weeks; yr, years.

reported by treatment of 160 μg CIC once daily.[40] The decrease was considered statistically significant by the authors according to the large sample size, whereas the significance was not seen in previous study of CIC with the same dose.[41] Because no placebo control was included in the first study, the clinical relevance of the observed decrease from baseline to the end of the study cannot be evaluated conclusively. In long-term pediatric studies, use of a placebo arm for the entire period is avoided, given concerns over the ethics of such a design. For a 20-month growth study on FP and BDP, the placebo group was merged with the FP group at 10 weeks into the study.[42]

In addition to placebo control, many studies included a positive control or a corticosteroid comparator to establish assay sensitivity. A summary of the positive controls used in the reviewed studies is shown in Table 4. The positive control dose is generally of sufficient magnitude and the duration of treatment with positive control of sufficient length to produce a statistically significant response relative to placebo (whereas at the same time, short enough to avoid undue risk to subjects). The most common positive control employed is oral prednisone at 10 mg/day because it has been shown to have a relatively insignificant effect on asthma[43] and is viewed as being associated with minimal adverse effects.[44] However, as recommended in the FDA draft guidance 2000 "Allergic Rhinitis: Clinical development programs for drug products," because of ethical concerns about the use of oral prednisone as an active

comparator in adrenal response studies in children, inclusion of an oral prednisone arm in pediatric adrenal assessment studies is not recommended.[22] Among the 28 studies reviewed that employed active comparators, there was only one pediatric study. This study included prednisolone, an active metabolite of prednisone, as a positive control.[45] Prednisolone was administered to 5–15-year-old asthmatic children orally at 2 mg/(kg day) for 4 days followed by 1 mg/(kg day) or half the original dose for 3 days and was compared with 7 days of treatment with nebulized FP using the endpoints of 24-h UC excretion, systemic exposure, and safety. Nebulized FP (1 mg b.i.d. twice daily) was associated with significantly less suppression than was oral prednisolone ($p = 0.001$), whereas prednisolone caused a major reduction on 24-h UC levels (60.9% decline).

Determination of the optimum active control dose and dosing regimen may require further evaluation to establish the most appropriate duration of treatment with placebo and the number of subjects needed to yield informative differences between the results for active control versus placebo.

Sensitivity of HPA Axis Function Tests

The sensitivity of the test chosen to evaluate HPA axis function also has a major bearing on results. Higher sensitivity and precision can increase the power of the assay, reduce the likelihood of underestimating the HPA axis effect (a desirable feature for safety studies), as well as reduce sample size requirements.

The relative sensitivity of the four main measurements of HPA axis function appears to be: 24-h PC/SC AUC, 24-h UCC > PC/SC a.m., low-dose ACTH test > high-dose ACTH test. This relationship has been demonstrated in the studies included in this review. Overall, different tests may offer distinct advantages and deficiencies. The use of more than one method of measuring cortisol suppression is recommended, if feasible.

In the current draft guidance "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action," the timed urine or plasma samples for determination of 24-h UC or 24-h plasma cortisol levels were recommended to be collected.[21]

The measurement of the plasma cortisol in a single morning sample was the most common test in the trials reviewed, likely because of the convenience it offers. This method is limited, however, by its wide inter- or intrasubject variability, which renders it insensitive compared with other tests. For example, it has been reported that as many as 15% of cases of documented hypoadrenalism may be missed using this testing method.[64] The results of the current review reinforce these concerns. There was marked variability in the results obtained from this test between studies, indicating that a single measurement is not able to reliably capture the relative effects of various ICS and INS on cortisol secretion.

Serum cortisol AUC (over 12–24 h) and urinary cortisol corrected for creatinine measurements, reflecting basal HPA axis function, are both considered to be sensitive and highly reproducible markers for assessing systemic activity of systemic corticosteroids.[27] It has been shown in many studies that 24-h UC excretion closely mirrored the results of 24-h SC concentration AUC, particularly when total timed urine collections are confirmed as accurate and comparable.

The conventional high-dose ACTH stimulation, however, is not generally accepted as a sensitive method to assess systemic effects on HPA axis function. Clinically, this test is useful in determining severe adrenocortical insufficiency but inadequate for detecting mild or short-term adrenal gland suppression. Low-dose (0.5-μg) ACTH stimulation test is found to be more sensitive than the conventional high-dose test in detecting evolving or partial adrenal suppression. Fewer false-negative results are reported with the low-dose ACTH stimulation test as well. For example, in a crossover study of asthmatic adults and children receiving long term inhaled BDP (median dose, 482 μg/day) or BUD (median dose, 507 μg/day), over 24% of the cases exhibited an insufficient cortisol response to 0.5-μg ACTH, but showed a normal cortisol response to 250-μg ACTH.[29]

For pediatric patients 2–5 years of age, the ACTH stimulation test, while not the preferred method to assess the HPA axis, may be the only assessment that is practical.[65] The collection of 12 or 24-h urine specimens may not be feasible in this age group. For one trial in children from 3 to 13 years of age, UC concentrations were not measured for the younger group (3–5 years) simply because it was not possible to obtain accurate 24-h urine samples from children who were not completely toilet trained.[66] In addition, although the measurement of serum cortisol levels is technically possible across the age spectrum, in some cases, the requirement for blood draws may be prohibitive.

Study Population

The study population selected for evaluation is also an important design factor. Cortisol suppression may be greater in healthy subjects exposed to ICS as compared with asthma patients because of their increased likelihood of having drug reach the peripheral airways, causing an increase in systemic circulation.[67] Differences in the lung absorption of healthy versus asthmatic patients, and patients with mild versus severe asthma make extrapolation of data on HPA axis suppression difficult.[13] It is therefore recommended that the HPA axis assessment be conducted among the population for which the product is indicated. This also allows for an assessment of efficacy, which can be a useful indicator of compliance with treatment.

Also important when choosing the study population for a HPA axis evaluation is the history of prior corticosteroid exposure, which may result in false negative results.[31] Subjects with a history of prior ICS or INS treatment may already have disturbed HPA axis function.

Sample Size

The inclusion of heterogeneous populations of patients (severe and mild asthma; allergic and non-AR; children and adults) in clinical trials would enhance the generalizability of the findings. However, the more heterogeneous the study population, the greater variation of the measured outcomes. Consequently, an increase in sample size is required to accurately capture any difference between treatments or to demonstrate that treatments are equivalent.

The larger a trial, the less likely it is to miss a real effect of treatment. A sample size larger than 35 per treatment group is recommended in the FDA draft guidance (2003) "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action."[21] Of all the studies under review, 43 (40%) studies met this recommended criteria, in which 20 were

conducted before the publication of this draft guidance. For most large trials, sample size is calculated based on a fixed power level (80%–90%); some studies did further calculation to compensate for predicted noncompliance rate or drop out cases. A pilot study may be useful in that it can provide an estimate of the number of subjects needed in the pivotal study to yield a statistically significant difference in the HPA axis endpoint between the active control and the test product placebo.[21]

Statistical Methods

A summary of the statistical methods employed in the studies under review is provided in Table 5. The key components including endpoint assessed, type of mean used, baseline adjusted or not, and the statistical test employed are presented respectively for each study.

In the FDA draft guidance (2003) "Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action," it is recommended that "the sensitivity analysis and efficacy analysis would be conducted as intent-to-treat (ITT) analysis,"[21] however, it does not go into any details in the draft guidance. The ITT population is most often used for analyses, and is typically defined as any subject who had received at least one dose of study medication. To normalize the distribution, data were sometimes logarithmically transformed before analysis. Data can be expressed as arithmetic mean, geometric mean, least squares mean, and adjusted mean depending on the purpose of test. For multiple comparisons among all treatment groups, analysis of covariance (ANCOVA) and analysis of variance (ANOVA) are commonly performed, adjusted for effects of possible covariates such as: baseline, age, sex, center, treatment, subject, and investigator. For pair wise comparisons, Dunnett's procedure was most often used to adjust for the comparisons of treatment groups with the placebo group.[46,47,52,91] Pair wise comparisons can also be constructed and adjusted using the Fisher's exact test,[49] Tukey–Kramer method,[100] and two-sided *t*-test.[85] For crossover studies, a comparison is often made with assess any carryover effect between the two treatment periods by comparing values for placebo and washout in order of sequence.[87,99]

For trials that researchers are interested in demonstrating the equivalence between treatments and placebo group, attention must be paid to the type II (β) error, which is the probability of falsely accepting the null hypothesis when a difference truly exists. "Negative" results with nonsignificant *p* values do not give any information about the type II error. Thus, many authors have suggested that presenting two-sided 95% confidence interval (CI) is a better approach.[101,102] Treatment ratios and a corresponding two-sided 95% CI were calculated for the difference. Noninferiority is determined when the lower limit of the two-sided 95% CI for the geometric mean treatment ratio was greater than the predefined value of 0.80.

Compliance

Compliance is an important issue that must be considered when assessing the effect of any long-term treatment. Even in the tightly controlled clinical trial setting, compliance may decrease over time. For example, in a study evaluating compliance with ICS, Milgrom et al.[103] found that although children between 8 and 12 years of age reported near 100% compliance with their medication regimen, actual compliance as determined by electronic metered-dose monitors was on average 58%, with more than 90% of subjects exaggerating their use of ICS. Furthermore, only 32% of those doses were actually received at the correct time. Similar findings were reported in a 5-week study in asthmatic patients. Despite an extensive educational program, which was conducted at the initiation of study for the self-management of asthma (video, face-to-face instruction, and written protocols), compliance with recommended treatment was only 40%.[104]

Therefore, it is critical to ensure monitoring of compliance throughout the treatment period. Various techniques have been employed among studies, including canister weight, daily record, interview, PK sampling, and the compliance ratio [number of puffs used (based on the dose counter) divided by the number of puffs that a patient supposed to take (based on the doctor's prescription)]. It should be noted, however, that diary data alone might be an unreliable assessment of compliance, especially in a pediatric population. A study was undertaken in asthmatic children (5–16 years) evaluating the compliance with peak expiratory flow (PEF) measurements twice daily for 4 weeks. The mean actual compliance assessed by an electronic meter (77.1%) was much lower than the mean reported compliance by written diary (95.7%). The percentage of correct PEF entries decreased from 56% to <50% from the first to the last study week, mainly as a result of an increase in self-invented PEF entries.[103,105] Compliance with electronic monitoring of PEF rate is preferred method to provide early identification of patients who do not comply.[104,106] However, it is not as accurate when the study is longer than 3 months or if patients are not motivated to do these measurements.[107]

Lack of compliance with use of study drugs could be a potential source of false-negative findings in long-term studies. Every effort should be made to maximize and document patient adherence to the use of the study drug. The reductions in compliance must be considered in both design of a trial and the final interpretation of results. Compliance may be used as a covariate in the data analysis.

CONCLUSIONS

The design and interpretation of clinical trials assessing the HPA axis effects of ICS and INS present multiple challenges. The study duration must be adequate (at least 6 weeks), as short-term observations do not accurately predict long-term effects. Dosing, population, sample size, blinding, choice of controls, and statistical analytic methods should be carefully considered. The testing method employed should be of sufficient sensitivity to predict of clinically relevant end points. Finally, compliance must be carefully monitored and the possibility of decreased compliance over time must be taken into account for both study design and interpretation of the results. Adherence to these recommendations may help to minimize the variability in results and improve the interpretability of the findings of HPA axis studies.

DISCLAIMER

Opinions expressed in this manuscript are those of the authors' and do not reflect the views or policies of the FDA.

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Table 5. Summary of Statistics Methods in HPA Axis Studies

Study	Endpoint for HPA Axis Function	Type of Mean Used	Baseline Tested	Means Adjusted for Baseline	Statistics Method
PC, SC, UC, UCC					
56[a]	PC a.m.	Adjusted	Yes	Yes	ANCOVA
68[b]	PC12; UC24				
45[b]	UCC24				
59	SC a.m.	Geometric	Yes	Yes	
69[b]	UCC12				
70	Mean SC24				
48[b]	Mean SC24				
71[b]	SC a.m.; Urinary total cortisol metabolites				
72[a]	UC24				
73[b]	UCC10; UC10; UCC a.m.; UC a.m.				
60[a, b]	PC a.m.; UC24				
74[b]	SC24	Arithmetic	Yes	No	
57	UCC 24				
75	SC12; UC24	Geometric; least squares	Yes	Yes	
74	UC24				
76[a,b]	PC24				
69[a]	SC a.m.	Least squares	Yes	Yes	
61[b]	SC24; UCC24,				
72	UC24				
77,78[a]	PC a.m.; UCC24; UC24				
48[b]	UC24				
70	UC24				
79	UCC12	Least squares	No	No	
66	PC a.m., UC24	Arithmetic	Yes	No	ANOVA
49b	PC a.m.; UC24				
80	PC a.m.; UCC24				
38[b]	PC8;				
39[b]	PC8; PC12				
81	SC; UC24				
50[b]	SC22; UCC24				
82[b]	SC24; UC24				
62[b]	UCC12				
83	PC a.m.				
84[b]	UCC9 (Overnight)	Arithmetic	No	No	
85[b]	PC a.m., UCC10	Geometric	Yes	No	
86[b]	SC a.m.; UCC a.m.	Geometric	No	No	
87[b]	PC a.m.; PC24				
88[b]	SC a.m.; SC24; UCC24	Least squares	Yes	Yes	
89	PC a.m.	Least squares	Yes	No	
90[b]	SC a.m.; UCC12	Least squares	No	No	
91	SC a.m.; UC24 and SC24	Arithmetic	No	No	ANOVA; Dunnett's test
52[a,b]	PC a.m.; UC24	Arithmetic	Yes	No	
92[b]	PC a.m.; UCC24	Arithmetic	Yes	No	ANOVAR
58	PC a.m.	Arithmetic	Yes	No	Paired *t*-test1
42	SC a.m.				
93	SC a.m.; SC20	Geometric	No	No	The equivalence: 90% CI for geometric mean ratio (test/reference) fall in 0.8–1.25
94[b]	UCC24	Arithmetic	Yes	No	Two-tailed student *t*-test
53,54[a]	UCC24	Arithmetic	Yes	No	Kruskal–Wallis tests
95	SC a.m.; UC24	Arithmetic	Yes	No	Wilcoxon two-sample test
96	SC a.m.	Arithmetic	Yes	No	Wilcoxon–Mann–Whitney test
40	UCC 24	Least squares	Yes	No	

Continued

Table 5. Continued

Study	Endpoint for HPA Axis Function	Type of Mean Used	Baseline Tested	Means Adjusted for Baseline	Statistics Method
ACTH test (SC, PC pre- and/or post-)					
65[a]	SC pre- and post-ACTH test	Adjusted	Yes	Yes	ANCOVA
97[b]	PC pre- and post-ACTH test				
98[b]	SC post-ACTH test; UC24				
98,53,54[a]	PC pre- and post-ACTH test	Least squares	Yes	Yes	
61[b]	SC pre- and post-ACTH test				
47[b]	PC post-ACTH test	Arithmetic	Yes	Yes	ANCOVA; Dunnett's test
46	PC pre- and post-ACTH test				
52[a]	UC24; SC pre- and post-ACTH test	Arithmetic	Yes	No	ANOVA
99[b]	SC pre- and post-ACTH test	Arithmetic	No	No	
36	PC a.m.; PC-post ACTH test	Adjusted	Yes	Yes	
84[b]	UC10 (Overnight); SC pre- and post-ACTH test	Geometric	No	No	
55	SC a.m.; PC pre- and post-ACTH test	Least squares	Yes	No	
100[b]	SC pre- and post-ACTH test; UC12 (Overnight)	Arithmetic	Yes	Yes	ANOVA; Tukey–Kramer method
96	SC pre- and post-ACTH test	Arithmetic	Yes	No	Mann–Whitney test
58	PC pre- and post-ACTH test	Arithmetic	Yes	No	Paired *t*-test
51[a]	PC post-ACTH test	Arithmetic	Yes	Yes	Two-sided tests
ACTH test (# of abnormal responders)					
63[a]	# of abnormal responders to ACTH test	Adjusted	Yes	Yes	ANOVA
53,54[a]		Arithmetic	Yes	No	χ^2 tests
38[b]		Arithmetic	Yes	No	Cochran–Mantel–Haenszel test
39[b]					
66		Arithmetic	Yes	No	Fisher's exact test
49[b]					

[a]Study data collected from Drugs@FDA databases.
[b]Dedicated HPA study.
ANOVA, analysis of variance; ANCOVA, analysis of covariance; ANOVAR, ANOVA for repeated measures; PC, plasma cortisol; SC, serum cortisol; UC, urinary free cortisol; UCC, urinary free cortisol corrected for creatinine; PC#, #-hour AUC of plasma cortisol; SC#, #-hour AUC of serum cortisol; UC#, #-hour urinary free cortisol; UCC#, #-hour urinary free cortisol corrected for creatinine; mean SC24, 24-h SC weighted mean, calculated by dividing the AUC during the 24-h period by the sample collection interval.

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