

Establishing a therapeutic index for the inhaled corticosteroids: Part I.

Pharmacokinetic/pharmacodynamic comparison of the inhaled corticosteroids

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The inhaled corticosteroids contain physicochemical differences that alter both glucocorticoid receptor-binding characteristics and the pharmacokinetic variables of these drugs. Differences in receptor-binding affinity translate into differences in potency for different drugs. Differences in pharmacokinetics, however, determine the topical effect to systemic effect ratio, or the "pulmonary targeting" of the drug. Beneficial pharmacokinetic properties that may improve pulmonary targeting include low oral bioavailability, rapid systemic clearance, and slow absorption from the lung. Delivery devices can produce clinically significant differences in topical activity by altering the dose deposited in the lung and, for orally absorbed drugs, the amount deposited in the oropharynx and swallowed. Clinical trials have confirmed that differences in potency or drug delivery of 2-fold or more can be detected in patients with asthma. However, because of the relatively flat nature of the dose-response curve for morning peak expiratory flow and forced expiratory volume in 1 second, the trials must be adequately powered and well controlled. The use of bronchial provocation measures are problematic because of the prolonged lag time for response. Study design flaws can lead to misinterpretation of results. Clinical studies have indicated the following relative potency differences: fluticasone propionate > budesonide = beclomethasone dipropionate > triamcinolone acetonide = flunisolide. Current evidence suggests that potency differences can be overcome by giving larger doses of the less potent drug. However, because of these potency differences, studies of systemic effects should not be done in isolation of adequate topical activity studies to define the pulmonary targeting of the drugs. (*J Allergy Clin Immunol* 1998;102:S36-S51)

Key words: Corticosteroids, pharmacokinetics, dose-response relationship, clearance, inhalers, clinical trials.

Corticosteroids are the most potent anti-inflammatories currently used to treat patients with asthma.¹ The inhaled corticosteroids (ICS) have been developed to provide a larger margin of safety for any level of therapeutic efficacy than the systemic corticosteroids. The physicochemical modifications of the basic steroid structure from 1 compound to the next confer differences in pharmacologic and pharmacoki-

Abbreviations used

BDP:	Beclomethasone dipropionate
BHR:	Bronchial hyperresponsiveness
BUD:	Budesonide
DPI:	Dry powder inhaler
FLU:	Flunisolide
FP:	Fluticasone propionate
GR:	Glucocorticoid receptor
ICS:	Inhaled corticosteroid(s)
MDI:	Metered-dose inhaler
PEF:	Peak expiratory flow
T _{1/2} :	Elimination half-life
TAA:	Triamcinolone acetonide
Vd:	Volume of distribution

netic properties that produce clinically significant differences. The purpose of developmental research is to discover new products with enhanced benefit-to-risk profiles.

Earlier published guidelines on the management of asthma have provided the dosing of the ICS agents for each level of asthma severity in either number of puffs from a metered-dose inhaler (MDI)² or micrograms.³ However, emerging data from comparative clinical trials indicate that in vitro potency differences of the molecules and differences between delivery devices can result in clinically apparent differences in antiasthmatic potency. Because of the need to assess equivalent dosing, the National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program Expert Panel Report 24 provided clinically comparable doses for each commercially available product listed in Table I.

The purpose of this report is to address the differences in the pharmacologic and pharmacokinetic properties of the ICS. Comparative laboratory and clinical trials are critically evaluated. Areas in which more information and research are required for understanding the disparities in different studies are also addressed.⁵⁻⁷

BASIC PHARMACOLOGIC CONCEPTS AND DEFINITIONS

The anti-inflammatory action of glucocorticosteroids is mediated through the glucocorticoid receptors (GRs). Once activated, the receptor complex translocates from the cytoplasm to the nucleus. It may act both directly to inhibit cytokine-induced production of proinflammatory proteins and indirectly by acting as a transcription factor, binding to specific glucocorticoid response elements, that

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TABLE I. The ICS products

ICS	Preparation (No. inhalations)	Dose* (μ g/actuation)	Average wholesale price (\$)	Cost (\$) per day of therapy for moderate asthma†
BDP	CFC-based MDI	42	38.27	6.12
	200		40.66	6.50
	CFC-based MDI	84	48.88	6.52
BUD	Turbuhaler DPI	200	107.00	2.14
	200			
FLU	CFC-based MDI	250	59.64	7.16
FP	100			
	CFC-based MDI	44	32.56	4.34
	60 & 120		43.40	2.89
	CFC-based MDI	110	53.29	1.78
	120			
	CFC-based MDI	220	83.52	1.39
	120			
	Diskhaler DPI	50	43.40	5.79
	60			
TAA	Diskhaler DPI	100	33.71	2.25
	60			
	Diskhaler DPI	250	55.96	1.86
	60			
	CFC-based MDI	100	47.28	6.30
	with spacer			
	240			

CFC, chlorofluorocarbon.

* Dose per actuation based on Food and Drug Administration labeling requirement of the dose that leaves the actuator for MDIs and the actuated dose or nominal dose for the DPIs.

† Estimated cost based on average wholesale price, giving the equivalent of BUD Turbuhaler 800 μ g/day and using the most conservative estimate of potency differences FP:BDP = BUD:FLU = TAA (1:2:4) and differences in delivery. Costs for different institutions will vary based on contract prices with the manufacturers.

leads to an increase or decrease in specific messenger ribonucleic acid production.⁸ This indirect action results in wide-ranging suppressive effects on the inflammatory system and production of anti-inflammatory mediators and proteins such as lipocortin-1 and β_2 -adrenergic receptors.

Glucocorticoid Receptor-binding Affinities

Glucocorticoid receptors are widespread throughout many tissues and regulate numerous metabolic functions, producing a wide variety of effects in addition to the reduction of inflammation. Of interest is that GRs from different tissues and even from differing species are essentially the same.⁹⁻¹¹ Glucocorticoids with increased receptor-binding affinities for lung GRs will also have similarly increased receptor-binding affinities for GRs in other tissues or cellular systems.¹¹ This property of GRs facilitates the establishment of correlations between relative receptor-binding affinities and various in vitro and in vivo pharmacologic activities (Table II).¹²⁻¹⁷ A relatively simple noninvasive model such as skin blanching from vasoconstriction can be used as a means of comparing the in vivo potencies of the glucocorticoids.¹⁸⁻²⁰

The relative lipophilicity of the ICS agents is listed in Table II. A direct relationship exists between lipophilicity and glucocorticoid receptor-binding affinity. However,

as can be seen with beclomethasone dipropionate (BDP) and its more polar (less lipophilic) active metabolite, beclomethasone monopropionate, an absolute correlation does not exist. Brattsand¹³ has suggested that an optimal range of lipophilicity for ICS exists (3.5 to 4.5), beyond which further increases result in increased receptor-binding affinity but decreased activity. The lipophilicity of an ICS therefore appears to be an important property governing the pharmacodynamic characteristics of each drug in this class.^{12,13}

ICS: Potency Versus Efficacy

Differences in receptor-binding affinity also correspond to functional activity. It should be noted, however, that receptor antagonists can also bind to receptors and not produce functional activity. There appears to be a direct correlation between increased receptor-binding affinity and increased topical skin blanching potency of the inhaled steroids studied (Table II). The development of more specific tests of pharmacologic activity associated with asthmatic inflammation such as regulation of gene transcription¹³ or inhibition of T-cell proliferation²¹ may in the future provide more clinically relevant information than skin blanching.

The concentration-response curves depicted in Fig 1 are useful in understanding the relation between potency and

clinical efficacy. These curves represent 3 different drugs in the same pharmacologic class. Curves A and B represent 2 drugs of equal efficacy but of different potencies; curve C represents a drug with both a different potency and a different efficacy. Potency differences can be overcome by administering equipotent doses of the drugs, whereas the drug represented by curve C could never achieve the same maximal effect as either drug A or B.

Existing evidence suggests that the available ICS agents differ only in potency and not in efficacy.^{14,16,17} Although potency differences may not affect efficacy, it is essential that differences in potency be considered when evaluating clinical comparisons of the corticosteroids. As can be seen from the dose-response curves in Fig 1, it is much more difficult to determine potency differences between products if responses are evaluated at the top of the dose-response curve, as each product reaches the maximal possible effect. This point was illustrated in a recent dose-response comparison of skin blanching between fluticasone propionate (FP) and budesonide (BUD), where the differences in potency were apparent in the middle of the dose-response curve but not at the lowest and highest concentrations.²²

It is very difficult to provide a table that compares the absolute potencies of the ICS agents, because few investigators have compared all the available agents in the same studies.¹² Values are determined in terms of relative potency, particularly the vasoconstriction test that is compared with a laboratory standard. Thus differing "absolute" relative potencies are reported from different laboratories¹⁷ and, even within studies, the 95% confidence intervals for relative potency can often exceed 2-fold. For instance, BUD has been found to be 1.1 to 2.4 and 1.7 to 5 times more potent than BDP and flunisolide (FLU), respectively.²³ Although it is not possible to establish absolute potency differences between the ICS agents, it is perhaps useful to know that the order of relative potencies across the studies is remarkably consistent. A compilation of existing in vivo and in vitro measures of functional activity of the available ICS agents suggests the following relative potencies: FP > BUD = BDP (beclomethasone monopropionate) > triamcinolone acetonide [TAA] = FLU. More specifically, BDP is approximately twice as potent as TAA and FLU on a molar basis and is one half to three fourths as potent as BUD, which is approximately one half as potent as FP. Thus the relative potency ratio for these inhalational steroids is 1:2:2 to 4:8:8, respectively, with FP being the most potent as a value of 1. Several other factors may affect the apparent clinical potency of the ICS, however.

Of interest is whether the more potent ICS may have an improved efficacy in the face of severe asthmatic inflammation. Increasing evidence suggests that inflammation in the airways of asthmatics can alter glucocorticoid receptor-binding affinities and that this is mediated in part by the cytokines IL-2 and IL-4.^{24,25} This phenomenon may play a role in steroid-resistant asthma

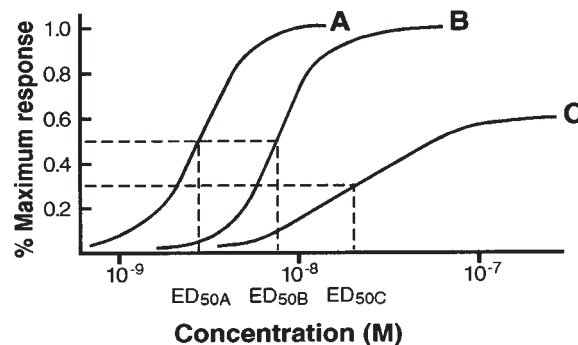


FIG 1. Concentration-response curves of 3 different drugs in same pharmacologic class. Curves A and B, 2 drugs of equal efficacy but different potencies; curve C, drug with different efficacy and different potency. ED_{50} , Median effective dose.

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FIG 2. Systemic glucocorticoids: integrated pharmacodynamic model. AUC, Area under time-concentration curve; mRNA, messenger ribonucleic acid. Reproduced with permission from Jusko WJ. Corticosteroid pharmacodynamics: models for a broad array of receptor-mediated pharmacologic effects. J Clin Pharmacol 1990;30:303-10.

reported in a small number of patients.²⁶ It is interesting that the decreased binding affinity can be reversed by a course of high-dose corticosteroids.²⁵ The reversal of steroid-resistant asthma by high-dose corticosteroids has implications in therapy, supporting 1 of the Expert Panel Report-2 recommendations (ie, start with high-dose therapy and step down) and for the design of ICS comparative trials (ie, the utility of dose back-titration protocols). More research in this area is required.

Pharmacokinetic Comparison of ICS

Jusko⁹ proposed the integrated pharmacodynamic model illustrated in Fig 2 for systemic glucocorticoids. When this model is functionally applied to the ICS, it can be seen that only pharmacokinetic differences are capable of altering the therapeutic index (pulmonary activity/systemic activity) of the glucocorticoids.¹⁵ Table III provides a comparison of the pertinent pharmacokinetic properties of the ICS.^{16,27-39} Ideally, an ICS would have a prolonged residence time in the lung after inhalation

TABLE II. Relative equivalency of ICS

ICS	Relative lipophilicity ¹³	Receptor complex half-life (hr) ¹⁴	Receptor-binding affinity*	Topical skin blanching potency†
FLU	3.4	3.5	1.8	330
TAA	3.4	3.9	3.6	330
BDP	4.9	NA	0.4	600
BMP	4.3	7.5	13.5	450
BUD	3.6	5.1	9.4	980
(22S)-BUD		NA	4.2	NA
(22R)-BUD		NA	11.2	NA
FP	4.5	10.5	18.0	1200

BMP, Beclomethasone monopropionate; NA, not available.

* Relative binding affinities with dexamethasone equal to 1.^{15,16}

† Relative to dexamethasone equal to 1.¹⁷

TABLE III. Pharmacokinetic variables of ICS

ICS	Oral F (%)	Systemic clearance (L/hr)	Vd _{ss} (L)	IV T _{1/2} (hr)	Inhaled T _{1/2} (hr)	Inhaled F (%)
BDP	15-20	230	NA	0.5 ²⁷	0.1 ²⁸	25
BMP	NA	NA	NA	0.6 ^{27,29}	1.5 ²⁹ -6.5 ²⁸	NA
BUD	11 ^{30*}	84 ^{30*†}	301 ^{30*†}	2.8 ^{30*†}	2.0 ^{30*†}	SD
		55 ^{31*}	196 ^{31*}	2.5 ^{31*}	NA	NA
	13 ³²	80.4 (56-119) ³²	183 ³²	2.3 (1.7-3.4) ³²	NA	26 MDI ³² 38 DPI ³²
(22S)-BUD	NA	67	245	2.7	NA	NA
(22R)-BUD ³³	NA	117	425	2.7	NA	NA
FLU	20 ^{34*}	58 ^{34*}	138 ^{34*}	1.6 ^{34*}	1.6 ^{34*}	39 ^{34*}
	NA				1.3-1.7 ³⁵	
FP	NA	66 ³⁶	318 ³⁶	7.8 ³⁶	NA	NA
	1 ³⁷	NA	NA	NA	14.4 ³⁷	16 DPI ³⁷ 30 MDI ¹⁶
TAA	NA	45-69 ³⁸	100-148 ³⁸	1.4-1.5 ³⁸	NA	NA
	23 ³⁹	37 ³⁹	103 ³⁹	2.0 ³⁹	3.6 ³⁹	22 ³⁹

F, Fraction absorbed (bioavailability); Vd_{ss}, volume of distribution at steady-state; IV, intravenous; SD, spacer device; BMP, beclomethasone 17-monopropionate; NA, not available.

*Radiolabeled.

†Tube spacer for inhalation.

and be completely inactivated once absorbed into the systemic circulation, thereby avoiding any systemic glucocorticoid activity. Therefore slow absorption from the lung tissue and a rapid systemic clearance are properties that will enhance the therapeutic index of an ICS.^{7,15} It is possible, however, that ICS can produce systemic activity from drug absorbed orally and from drug absorbed by way of the lung (Fig 3).¹

Oral Bioavailability

Oral bioavailability, which depends on both gastrointestinal absorption and first-pass liver metabolism, differs among the ICS (Table III). The differences in bioavailability result in variable effects of the ICS on systemic activity, which can be altered by the use of spacer devices with an MDI and by mouth rinsing and spitting after administration by a dry powder inhaler (DPI).⁴⁰⁻⁴² More specifically, the percentage of systemic activity produced by a drug that has a 20% pulmonary delivery with 1% oral bioavailability versus an ICS with 20% pulmonary delivery and 20% oral bioavailability would range from 3.8% to 44.4%, respectively.¹⁵

Clearance

Clearance is defined as the volume of blood or plasma that is completely cleared of drug over a unit of time; it generally correlates with the lipophilicity of the compound. All of the ICS are rapidly extracted and cleared from the plasma. The clearance rates reported in Table III are those observed after intravenous administration of the drugs. Because of the lipophilicity and high extraction ratios of ICS, their clearance is primarily determined by hepatic blood flow and is therefore unlikely to be influenced by drugs that alter metabolic activity. Clearance and dose are the determinants of systemic or plasma steady-state concentration of a drug during continuous dosing, as illustrated by the following equation:

$$\text{plasma concentration at steady state} = \text{dosing rate/clearance.}$$

Thus clearance is the principal pharmacokinetic parameter that determines the therapeutic index of the ICS. For the ICS the rapid clearance serves the dual purpose of both decreasing oral bioavailability and rapidly elimi-

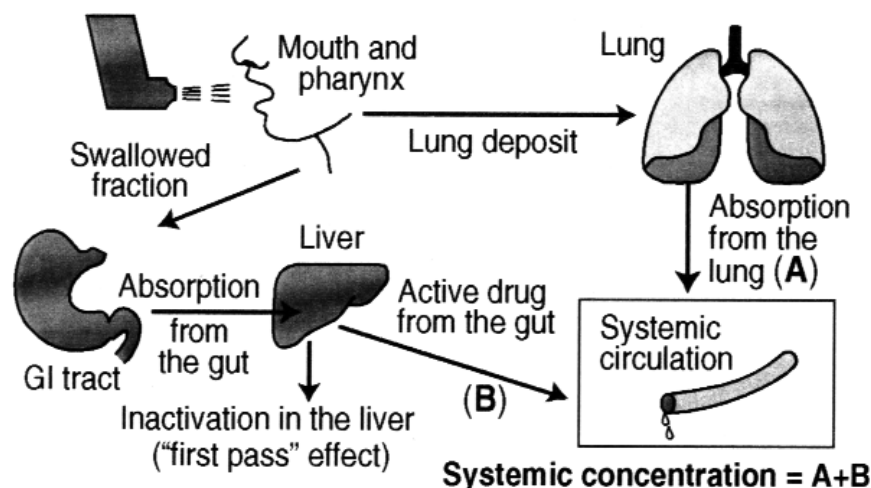


FIG 3. Systemic concentration of ICS is determined by oral bioavailability of swallowed fraction and by absorption from lung (inhaled fraction). Adapted with permission from Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med* 1995;332:868-75. Copyright © 1995, 1998 Massachusetts Medical Society. All rights reserved.

nating the drug to maintain a low plasma concentration at steady state with chronic dosing, thereby minimizing the potential for systemic effects.

Elimination Rate

The elimination half-life ($T_{1/2}$) of a drug is dependent on both of the physiologically defined pharmacokinetic variables of volume of distribution (Vd) and clearance, as follows:

$$\frac{\text{clearance (organ function)}}{\text{Vd (physiologic status)}} = \frac{0.693}{T_{1/2}} = \text{elimination rate constant}$$

where 0.693 is the natural log constant and the elimination rate constant is the slope of the log concentration-time curve. In humans a strong correlation exists between relative lipophilicity and the Vd of glucocorticoids.¹³ It is important to understand that although changes in Vd can affect $T_{1/2}$, only changes in Cl can affect steady-state serum concentrations. The $T_{1/2}$ determines how long it takes to reach steady-state, not what the final steady-state concentration will be. The pharmacokinetic/pharmacodynamic model nicely illustrates how differences in Vd would be expected to have a minimal effect on the therapeutic index compared with differences in clearance.¹⁵

Lung Residence Time

Increasing attention is being directed to lung retention of the ICS.^{7,13,16} Slow absorption from the lung and prolonged exposure of the ICS to the airway GRs enhances the desired anti-inflammatory effect without a concomitant increase in systemic glucocorticoid activity (Fig 2).^{9,15} This effect may be particularly important in lung tissue with a high degree of inflammation in which decreased binding affinities may require prolonged corti-

costeroid exposure.²⁶ Although slow dissolution in the lung fluids leading to delayed absorption does not necessarily guarantee an enhanced pharmacologic response, animal studies with liposomes suggest that slowed dissolution and prolonged exposure improve pulmonary targeting.^{43,44} One method of assessing pulmonary retention is by comparing the $T_{1/2}$ of the ICS after intravenous administration with that after inhalation (Table III). A longer $T_{1/2}$ for beclomethasone monopropionate, FP, and TAA after inhaled administration compared with intravenous administration suggests that slow absorption from the lung is the rate-limiting step for elimination. Lipophilicity is not necessarily a prerequisite for slower absorption.

As a result of its high lipophilicity, BDP has a slower dissolution time in human bronchial fluids (5 hours) than BUD (6 minutes).^{12,13} This difference may partially explain why, despite an apparently greater molar potency of BUD, BDP and BUD have been shown in comparative clinical trials to have equivalent efficacy on a microgram for microgram basis.⁴⁵ More research is required to determine the relative contribution of dissolution rate of the ICS in the bronchial mucosa to the antiasthmatic effect. In summary, from a pharmacokinetic viewpoint improved pulmonary targeting (ie, increased benefit to risk ratio) is achieved by increasing systemic clearance, reducing oral absorption, and increasing lung residence time. Changes in either Vd or $T_{1/2}$ would not produce a significant effect on pulmonary targeting.

The ICS Delivery Devices

A primary determinant of both effectiveness and systemic activity of ICS is the delivery.⁴⁶⁻⁴⁸ Both airway and oral delivery of ICS are device- and patient-dependent (Fig 3). Each device, whether an MDI or a DPI, requires

TABLE IV. Lung deposition from in vivo studies of ICS in healthy adults

ICS Agent	MDI (%)	MDI + Spacer (%)	DPI (%)
BDP	NA		NA
BUD	15 (3-47) ^{32*}		32 (16-59) ^{32*} 28 (15-42) ^{51‡}
FLU	32 ^{50†}		
FP	26 ^{52§}		15 (13-18) ³⁷
TAA		22 ± 12 ^{39¶}	

* Geometric mean and ranges (% of metered dose).

† Mean systemic availability compared to intravenous dose and after inhalation with mouthwash and rinse.

‡ Mean and (range) of ^{99m}Tc-labelled BUD with inspiratory flow of 60 L/min.

§ Mean systemic availability compared with intravenous dose. Percent from canister dose equivalent to 30% from dose leaving actuator.

||Mean compared with intravenous dose.

¶Mean ± SD without mouthwash or oral charcoal block. Percent of 100 µg dose (ie, that leaving actuator/spacer) equivalent to 11% of canister dose.

TABLE V. Factors determining comparative clinical effectiveness of ICS

Potency	Efficacy	Clinical effectiveness
Receptor-binding affinity	Potency	Dose
Intrinsic agonist activity	Duration at receptor site	Delivery device
Distribution	Delivery to receptor site	Therapeutic index (risk: benefit)
Inflammation?		Compliance

specific inhalational techniques for optimal intrapulmonary drug delivery.⁵ Although early investigations with radiolabeled particles suggested that 7% to 15% of the nominal dose (that leaving the canister) from an MDI reaches the lungs of patients,⁴⁹ more recent data show greater airway delivery from certain products (Table IV).^{32,37,39,50-52} In addition, the devices have proven to be sufficiently different such that delivery characteristics of one should not be extrapolated to other products.⁴⁸ Delivery characteristics of an MDI are determined by the formulation including the excipients and propellants and the drugs (solutions vs micronized suspensions).⁵³ In addition, the concentration of drug in each actuation may result in a different amount of drug in the respirable range so that 5 inhalations of 50 µg/actuation may deliver more drug than 1 inhalation of 250 µg/actuation.⁵⁴ Increased potency may have a beneficial advantage for formulation of drug for inhalation from an MDI by allowing a lower mass of delivered drug.

The ICS are currently available as chlorofluorocarbon-propelled MDIs and breath-activated DPIs (Table I). The newer hydrofluoroalkane-propelled MDIs under investigation appear to have different performance characteristics^{7,53} than the standard chlorofluorocarbon-propelled MDIs. The use of spacer devices can alter the amount of drug in the respirable range and decrease the amount of drug deposited in the oropharynx and swallowed, thus altering both therapeutic efficacy and the potential for systemic effects.^{5,53}

Table IV suggests that significant differences in delivery among MDIs exist. These differences in delivery are likely to produce clinically significant differences in effect.^{48,53} Preliminary reports indicate that the newer hydrofluoroalkane-propelled BDP MDIs may increase lung deposition to 50% to 60% of the actuated dose, pro-

ducing a concomitant increase in efficacy.⁵⁵⁻⁵⁸ Other factors that determine delivery from MDIs include the patient's ability to coordinate actuation and inhalation and the rate of inhalation.⁵³ The values provided in Table IV are under optimal conditions.

The DPIs present unique challenges to the patient. Optimal lung delivery from available DPIs (Diskhaler, Diskus, Rotahaler, and Turbuhaler) requires a forceful deep inhalation.^{48,53} An inspiratory flow of 60 L/min is considered optimal to help break up the aggregates of the micronized powders into respirable particles (<5 µm diameter).^{48,53,59} However, the high inspiratory flow can increase impaction of even respirable particles in the oropharynx and larger airways. What effect this more central deposition might have on clinical efficacy is only speculative, because clinical comparisons among DPIs and their corresponding MDIs with or without spacers have not adequately explored this issue.⁵³ Although the Turbuhaler has the highest mean lung deposition (Table IV), it has a greater flow dependency^{60,61} and higher variability than the Diskhaler and Diskus.^{53,61} The lung deposition of BUD is reduced by half to 15% at an inspiratory flow of 36 L/min.⁵¹ The flow dependency of Turbuhaler produced clinically significant differences in bronchodilation from terbutaline in children younger than age 6 years.⁶² More recently, Devadason et al⁶³ reported a significant correlation between lung deposition of radiolabeled BUD and peak inspiratory flow through the Turbuhaler in children ages 3 to 16 years with clinically stable cystic fibrosis and normal lung function. Children ages 6 to 12 years received approximately one half the dose of those older than 12 years, whereas children younger than 6 years received one quarter of the dose; however, when the "lung dose" was corrected for body weight,

TABLE VI. Summary of clinical trials comparing efficacy of ICS with sufficient statistical power and design to determine

Study (no. patients)	Drugs/dosages	Study design/Duration
Svendsen 1992 ¹⁰² (37 adults)	BDP MDI 750 µg twice daily BUD MDI + spacer 800 µg twice daily	Randomized, double-blinded, double dummy, crossover trial; 6 wk
Selroos 1994 ¹⁰⁰ (102 adults)	BDP MDI + spacer BUD DPI	Randomized, open, parallel, dose reduction trial
Gustafsson 1993 ⁸⁵ (398 children)	BDP MDI + spacer 200 mg twice daily FP MDI + spacer 100 µg twice daily	Randomized, double-blinded, multicenter, parallel trial; 6-wk with 2-wk run-in period
Fabbri 1993 ¹⁰³ (274 adults)	BDP MDI 750 µg twice daily FP MDI 750 µg twice daily with or without spacer; could increase to 1000 µg twice daily if needed	Randomized, double-blinded, multicenter, parallel trial; 1 yr with 2-wk run-in period
Lundback 1993 ⁸⁷ (585 adults)	BDP MDI 500 µg twice daily FP MDI 250 µg twice daily FP DPI 250 µg twice daily	Randomized, double-blinded, double dummy, multicenter, parallel trial; 6 wk with 2-wk run-in period and 46-wk open label follow-up
Barnes 1993 ⁸⁹ (154 adults)	BDP MDI 1000 µg twice daily FP MDI 500 µg twice daily	Randomized, double-blinded, multicenter, parallel trial; 6 wk with 2-wk run-in period
Dahl 1993 ⁸² (672 adults)	BDP MDI 200 µg twice daily FP MDI 50 µg, 100 µg, 200 µg, 400 µg twice daily	Randomized, double-blinded, multicenter, parallel trial; 4-wk dose-ranging study
Leblanc 1994 ⁸⁴ (261 adults)	BDP MDI 200 µg twice daily FP MDI 100 µg twice daily with or without spacer	Randomized, double-blinded, multicenter, parallel trial; 4 wk with 2-wk run-in period
Pauwels 1995 ^{86*} (306 adults)	BDP MDI 500, 750, 1000 µg twice daily FP MDI 250, 325, 500 µg twice daily	Randomized, double-blinded, crossover, multicenter, parallel trial; 6 months with 4-wk run-in period

Outcome measures	Comments
FEV ₁ : BDP = BUD FVC: BDP = BUD AM PEF: BDP = BUD β ₂ -agonist: BDP = BUD SS: BDP = BUD BHR: BDP > baseline	Both drugs improved PEF over baseline.
Final dose required for asthma control based on PEF, SS, and β ₂ -agonist use: BUD = 600 µg day BDP = 1000 µg day	Dose reduction period (2 yr) sufficiently long to prevent carryover effect. Groups unequal (26 BDP, 76 BUD).
FEV ₁ : FP = BDP AM PEF: FP > BDP β ₂ -agonist: FP > BDP SS: FP = BDP	Power of 99% to detect 3% difference in PEF. Patients required at least 400 µg day BDP for optimal asthma control.
FEV ₁ : FP > BDP AM PEF: FP > BDP PM PEF: FP > BDP β ₂ -agonist: FP > BDP SS: FP = BDP	Asthma exacerbations less with FP; β ₂ -agonist use less with FP in wks 5–8 only. Patients had to be receiving at least 1000 µg BDP or BUD daily to qualify.
FEV ₁ : FP = BDP AM PEF: FP = BDP PM PEF: FP = BDP PM-AM PEF: FP DPI > BDP β ₂ -agonist: FP = BDP SS: FP > BDP nighttime FP < BDP daytime	Differences favoring a specific therapy small and likely insignificant.
FEV ₁ : FP = BDP AM PEF: FP = BDP PM PEF: FP = BDP PM-AM PEF: FP > BDP β ₂ -agonist: FP = BDP SS: FP = BDP % predicted PEF: FP > BDP	FEV ₁ , PEF all improved over baseline. Patients required 1–2 mg BDP or BUD to qualify.
PEF showed linear increase with FP dose. FP 200 µg daily = BDP 400 µg daily. Asthma exacerbations: FP 400 µg > BDP FP 800 µg > BDP	FEV ₁ also showed dose-response improvement with FP. AM PEF increased 4.3 L/min per doubling dose of FP.
FEV ₁ : FP = BDP AM PEF: FP = BDP PM PEF: FP = BDP β ₂ -agonist: FP = BDP SS: FP = BDP	Power of 90% to detect 17 L/min PEF. Mild to moderate disease.
FEV ₁ : FP = BDP AM PEF: FP > BDP PM PEF: FP = BDP β ₂ -agonist: FP = BDP SS: FP = BDP	All measures improved over baseline for both drugs. Inhaled steroid-dependent patients receiving 800–2000 µg daily to qualify. Placed on salmeterol during 1-month run-in. Study drug dose was based on run-in inhaled steroid dose.

TABLE VI CONT'D. Summary of clinical trials comparing efficacy of ICS with sufficient statistical power and design to determine

Study (no. patients)	Drugs/dosages	Study design/Duration
Ayres 1995 ¹⁰⁴ (671 adults)	BUD MDI 800 µg twice daily FP MDI 500 µg, 1000 µg twice daily with or without spacers	Randomized, double-blinded, double dummy, multicenter, parallel trial; 6 wk with 2-wk run-in period
Ringdal 1996 ⁹⁶ (518 adults)	BUD DPI 800 µg twice daily FP DPI 400 µg twice daily	Randomized, double-blinded, double dummy, multicenter, parallel trial; 12 wk with 2-wk run-in period
Hoekx 1996 ¹⁰⁵ (229 children)	BUD DPI 200 µg twice daily FP DPI 200 µg twice daily	Randomized, double-blinded, double dummy, parallel, multicenter trial; 8 wk with 2-wk run-in period
Anderson 1998 [†] (321 adults)	TAA MDI 400 µg twice daily BDP MDI 200 µg twice daily	Randomized, double-blinded, double dummy, placebo-controlled, multicenter, parallel trial; 8 wk
Aaronson 1998 [†] (313 adults)	TAA MDI 400 µg twice daily BDP MDI 200 µg twice daily	Randomized, double-blinded, double dummy, placebo-controlled, multicenter, parallel trial; 8 wk
Condemni 1997 ^{106*} (291 adults)	TAA MDI 200 µg four times daily FP DPI 250 µg twice daily	Randomized, double-blinded, double dummy, placebo-controlled, multicenter, parallel trial; 24 wk with 3-wk run-in period

FVC, forced vital capacity; SS, subjective symptoms; BHR, bronchial hyper-responsiveness; P, placebo.

* Abstract only.

† Unpublished data, Schering/Key and the Food and Drug Administration.

only the very young children received a lower dose on a per-kilogram basis.

In summary, the delivery system is a significant determinant of both efficacy and safety. It is clear that both interdevice and intradevice delivery cannot be extrapolated from one device to another.

COMPARATIVE CLINICAL TRIALS

The preceding overview demonstrates that a number of inter-related factors are involved in determining the comparative clinical effectiveness of the various ICS (Table V). From a purely pharmacologic approach, potency differences are relatively insignificant unless those differences can be translated into improved effectiveness. The understanding of potency differences, however, prevents the misinterpretation of inappropriately designed comparative trials and aids the clinician in accurately assessing product-specific and disease-specific data. For example, studies comparing adrenal suppression from equivalent microgram doses of the ICS in

nonasthmatic healthy volunteers are solely evaluations of potency differences and provide no information on relative clinical efficacy and safety, which are required for establishing relative clinical effectiveness. Both pharmacokinetic and delivery system differences have a significantly greater impact on clinical effectiveness than potency differences, yet most of the comparative clinical trials have been designed to establish potency differences. Comparative clinical trials establishing antiasthmatic potency differences are required. In addition, cost comparisons and formulary decisions cannot be accurately made without this appropriate comparative information. The comparative trials have been completed primarily in BDP, BUD, and FP. Therefore the lack of information on both FLU and TAA is due to the paucity of clinical trials with these agents.

Establishing dose-response studies for comparing clinical effectiveness of the ICS has been difficult and is somewhat controversial. The difficulties have been extensively reviewed^{6,7,17} and relate to the lack of an

Outcome measures	Comments
FEV ₁ : FP > BUD AM PEF: FP > BUD PM PEF: 2 mg FP > BUD β_2 -agonist: FP = BUD SS: FP = BUD	All measures improved over baseline for both drugs. Severe patients who required a minimum of 800 μ g day of BUD or BDP. Stratified on entry to oral steroid use. Power of 90% to detect 13 L/min difference in PEF.
FEV ₁ : FP > BUD AM PEF: FP > BUD β_2 -agonist: FP = BUD SS: FP = BUD	All measures improved over baseline for both drugs. Power of 80% to detect 15 L/min difference in PEF. Difference was 17.6 L/min. All patients previously receiving ICS.
FEV ₁ : FP = BUD AM PEF: FP > BUD PM PEF: FP > BUD β_2 -agonist: FP = BUD SS: FP = BUD	All measures improved over baseline for both drugs. Difference for AM PEF was 7 L/min or 3% of predicted.
FEV ₁ : BDP = TAA > P AM PEF: BDP = TAA > P β_2 -agonist: BDP = TAA > P SS: BDP = TAA > P	FEV ₁ was the primary efficacy measure.
FEV ₁ : BDP > TAA > P AM PEF: BDP = TAA > P β_2 -agonist: BDP = TAA > P SS: BDP = TAA > P	
FEV ₁ : FP > TAA > P am PEF: FP > TAA > P β_2 -agonist: FP > TAA > P Withdrew from lack of efficacy: BDP > TAA > P	Patients previously receiving 8–12 inhalations daily of ICS.

acceptable direct measure of airway inflammation, the natural variability of asthma, and the highly inconstant rate of response to ICS. Measurements of asthma severity include FEV₁ by spirometry, symptom scores, nocturnal awakening, morning and evening peak expiratory flow (PEF), PEF variability, frequency of rescue β_2 -agonist therapy, and nonspecific bronchial hyper-responsiveness (BHR). The disadvantage of these measurements is that they are downstream events from the pharmacologic effect and thus are only surrogate markers of anti-inflammatory activity.

The response rates of these surrogate measures to ICS agents follow different time courses,^{64–66} which may vary with ICS dose, severity of asthma at initiation of therapy, and exposure to allergen(s) and viral infections during the study period. In addition, a direct connection between any 1 of these surrogate markers and degree of airway inflammation has eluded researchers.^{67,68} The advantage is that they measure control of asthma, the desired end point. However, the

clinical markers show only a weak correlation to each other, so some authors suggest that they be used in conglomerate because each marker (airway obstruction, BHR, and symptoms) may represent different aspects of disease severity.^{64,67} At present, no comparative studies present both clinical markers of response to treatment and laboratory examinations demonstrating decreased inflammation. Because of the relative disconnect between specific markers of airway inflammation and the clinical expression of asthma, the clinical markers should be considered the best measure of anti-asthmatic activity for comparing the ICS.

Establishing a Dose Response to ICS

A number of clinical studies, but not all, have established dose-response curves for various measures of clinical efficacy to ICS.^{5,6,69} Reasons for the disparity involve differences in study design including outcome measurements, patient selection, patient numbers, and study duration.

Image not available

FIG 4. Difference with 95% confidence interval in mean improvement in morning PEF for FP and BDP. *DH*, Diskhaler; *PEFR*, peak expiratory flow rate. Reproduced from Barnes NC, Hallett C, Harris TAJ. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;92:95-104, by permission of the publisher WB Saunders Company Limited, London.

Image not available

FIG 5. Difference with 95% CI in mean improvement in morning PEF for FP and BUD. *PEFR*, peak expiratory flow rate. Reproduced from Barnes NC, Hallett C, Harris TAJ. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;92:95-104, by permission of the publisher WB Saunders Company Limited, London.

The best method or test for evaluating potency or for determining dose-response with a single ICS has not been established. Some studies suggest that BHR is the more sensitive indicator, particularly in patients with near-normal spirometry values.^{65,70,71} However, the longer time course for change limits its utility. Toogood⁷² suggested the lowest daily PEF was more sensitive than diurnal variation in PEF. Morning PEF appears to be the more sensitive measure for determining dose-response effects of the ICS, particularly in a parallel-group study

design. The poor correlation between symptoms, FEV₁, PEF, and measurement of BHR suggests that all should be included when dose effects are evaluated.⁶⁴

Crossover studies are a problem because of possible carryover from previous therapy, particularly if initial therapy was the higher dose.⁷² In a study by Haahtela et al,⁷³ 18 of 37 patients with newly diagnosed mild asthma were discontinued from 2 years of ICS treatment with BUD (1200 µg/day). Asthma symptom scores and morning PEF values took 6 weeks to return to precortico-

steroid levels, and BHR fell significantly only after 28 weeks. Juniper et al⁷⁴ reported that BHR could be maintained for 3 months after discontinuation or halving of the ICS dose after 1 year of therapy but that increased symptoms and deterioration in FEV₁ occurred by that time. The fact that most measurements show continued improvement over a 4- to 12-week period is a limitation for short-term dose escalation studies and for crossover and "survival" study designs. It is possible that the higher steroid dose at the beginning of the study can decrease the inflammation, changing the dose-response to the lower doses during the down-titration.^{25,75} If this change occurs, significantly lower doses of steroid can maintain control of symptoms and lung function than are required to improve lung function and symptoms.^{73,76,77} Because of this finding, down-titration design from a dose of ICS that controls asthma may be unable to detect true potency differences.⁷⁸⁻⁸¹

Investigators have attempted to enhance the sensitivity of parallel comparisons by incorporating an initial back-titration phase and including only those patients unable to tolerate a further reduction in dose, establishing a minimal effective dose.⁷⁸ With this method BUD administered by Turbuhaler at one half the dose of BUD administered by MDI plus a Nebuhaler spacer in children produced the same therapeutic effect as measured by FEV₁, PEF, and exercise challenge. However, with a parallel, escalating-dose study design in adults, the BUD Turbuhaler and BUD MDI plus Nebuhaler were found to be equally effective on a microgram basis. Whether these conflicting results are due to delivery differences between children and adults for the BUD MDI plus Nebuhaler spacer or to study design is unknown.

It is yet to be determined whether the "survival" model or incorporating an initial back-titration phase before enrollment provides any advantage over large-group, double-blind, parallel comparisons to determine clinical potency differences.^{6,7,17} Although morning PEF values appear to be the most sensitive indicator and have the advantage of partially assessing both airway obstruction and BHR, it is not the most sensitive indicator of either variable.⁶⁴ In addition, the expected change in morning PEF per doubling dose is small, giving a relatively flat dose response.^{82,83} Because of the variability of morning PEF and the small incremental differences, large numbers of patients are required to ensure that the study is adequately powered. For example, a double-blind, placebo-controlled, parallel comparison was unable to determine a significant difference between a 2-fold dosage of BUD (200 µg daily vs 400 µg daily) in a group of adults with mild asthma despite 11 L/min and 32 L/min improvements over placebo, respectively. These results were likely influenced by the small number of patients (32 to 38 per treatment group). Only the high-dose group achieved statistically significant improvements in daytime symptom scores and morning PEF values compared with placebo. In patients with mild to moderate asthma, it is difficult to show a dose response.

A recent meta-analysis of 14 comparative clinical trials between FP and either BDP^{82,84-89} or BUD⁹⁰⁻⁹⁶ concluded that FP at half the dose (or less) in micrograms was equally effective to BDP and more effective than BUD (Figs 4 and 5).⁹⁷ These findings are consistent with the relative receptor-binding affinities for these 3 ICS (Table II).¹³⁻¹⁷ Unfortunately, many of these studies were designed to prove a predetermined potency difference and were neither placebo-controlled (negative control) nor positively controlled by having an arm that received a known double or greater dose of one of the ICS being compared. For studies designed to show no difference, a positive control allows a more certain estimate that the 2 products used are equivalent and that the results are not influenced by the "ceiling effect,"^{6,98,99} where the maximum effect is produced by the lower dosed drug and administration of any higher doses is unlikely to produce a perceivable difference. If a statistically significant difference between predetermined equivalent dosages is found (Fig 5), then positive and negative controls are less important, except that the difference in apparent potency is not quantifiable. The Barnes meta-analysis,⁹⁷ although limited by the design of the studies, does demonstrate that FP at half the dose is numerically superior in all studies and statistically superior in 4 of the individual studies and for the pooled data. Furthermore the pooled data demonstrated a significant difference favoring FP for less effect on mean serum cortisol levels.

Results of the Comparative Trials

Most of the comparative clinical trials have been previously reviewed.^{7,17,45,97} Although there are some minor inconsistencies in the findings, most can be attributed to difficulties with study design (primarily inadequate sample power) or can be explained by differences in lung delivery. For example, a down-titration comparison of BUD by Turbuhaler and FP by Diskhaler in 217 children concluded that BUD and FP were equivalent on a microgram basis.⁸¹ Despite the difficulties with this particular study design, the results are consistent with a 2-times greater potency of FP on a microgram basis because of the differences in lung delivery from the 2 devices (Table IV).

The available clinical trial data generally confirm the potency differences as measured by relative receptor-binding affinities and topical skin blanching (Table II). The relative order of microgram potency for topical anti-asthmatic effect is FP > BDP = BUD > TAA = FLU. Although the exact ratio of comparative clinical potency is not currently possible to ascertain, it appears that a ratio of 1:2 to 4:4 to 8, with FP being the most potent at a value of 1, is consistent with the clinical trial data.^{7,17,45,97} Davies⁴⁵ reviewed 18 comparative trials of BUD versus BDP and concluded they were essentially equivalent on a microgram basis. Many of the studies were short-term, 2- to 4-week crossover trials in small patient populations (*n* range, 25 to 30), so the validity of the findings can be questioned.

Each of the comparison studies reviewed by Davies⁴⁵ used MDIs with or without spacer devices. More recently,

BUD by Turbuhaler has been compared with BDP by MDI plus spacer¹⁰⁰ and DPI (Rotahaler).¹⁰¹ In both studies using different designs, BUD by Turbuhaler was considered to be more potent on a microgram basis than either dosage form of BDP, likely the result of improved delivery.

Table VI lists the well-designed, sufficiently powered clinical comparisons of the ICS.^{82,84-87,89,96,100,102-106} Most of the clinical trials have been with BDP, BUD, and FP. A recent comparison of FP and BUD in their respective DPIs illustrates the difficulties of comparative trials. The drugs were administered in equivalent microgram doses (400 µg daily) in children (aged 4 to 12 years) who were already receiving ICS.¹⁰⁵ The primary outcome measure was daily morning PEF, which was at 98% (mean value) of predicted normal at baseline. Despite this finding, each therapy produced a statistically significant improvement in morning PEF over baseline; the difference in favor of FP was small (3% of predicted) but also statistically significant. Analysis of the rate of response indicated a more rapid response for the more potent FP. No significant difference was observed for the last 4 weeks of the 8-week treatment protocol. Thus this study compared delivery devices with different lung depositions in patients with mild asthma with minimal room for improvement. They demonstrated that FP is more potent (nonquantifiable) on a microgram basis than BUD.

Of the studies comparing FP and BUD, the most convincing evidence that a significant difference in topical antiasthmatic potency exists are the studies comparing them with their respective DPIs.^{81,92,93,96,104,105} The Diskhaler delivers approximately one half the amount of drug delivered by the Turbuhaler, yet the studies show that FP is equal to or more potent at equivalent microgram doses based on the nominal dose^{81,105} or that FP is more effective than BUD at one half the nominal dose.^{92,93,96,104}

The few recent trials comparing FP and BDP with TAA appear to confirm that BDP is approximately 2 times more potent than TAA on a microgram basis¹⁷ and that FP is more than 2 times more potent.¹⁰⁶ Preliminary reports (abstract only) of comparisons of FP with BDP, TAA, and FLU have also suggested that FP is approximately 4 times more potent than BDP, greater than 3 times more potent than TAA, and greater than 2 times more potent than FLU.¹⁰⁷⁻¹¹³

CONCLUSION

Numerous factors can influence the clinical effectiveness of ICS including potency, pharmacokinetics, and delivery systems. Enhanced clinical effectiveness can be achieved by giving an intrinsically more potent drug (FP), by giving more drug per inhalation dose (Turbuhaler 200 µg/dose), or by enhancing delivery (BDP HFA MDI formulations). Increased potency per se does not affect pulmonary targeting, so its primary advantage is the ability to give lower microgram dosages to achieve similar effectiveness. The more rapid response to more potent agents may also improve compliance but may be achievable with the use of higher doses of a low-potency drug initially and then stepping down therapy, as recommended by the Expert

Panel Report-2.⁴ Clinical comparisons clearly illustrate that in vitro potency differences are translated into clinical potency differences. Whether higher potency drugs will provide evidence of greater efficacy in steroid-dependent or steroid-resistant asthmatics has yet to be determined.

The issue of safety surrounds improvement in pulmonary targeting. Pulmonary targeting is enhanced by decreased oral bioavailability, increased systemic clearance of drug absorbed from the pulmonary tree, and retention of drug in the airways. Lipophilicity appears to benefit each of these factors. Because of known potency differences, studies comparing potential risks of the various ICS are not meaningful in isolation from clinical effectiveness. Given in high enough dosages, all ICS will produce systemic activity. Excess concern about risks are fueled by studies that use the high doses required to produce systemic effects. Risk-benefit analysis requires studies that assess risk at equivalent benefit; therefore the establishment of a therapeutic index is necessary.

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