

Pharmacokinetics and pharmacodynamics of inhaled corticosteroids

H. Derendorf, PhD,^a G. Hochhaus, PhD,^a B. Meibohm, PhD,^a H. Möllmann, MD,^b
and J. Barth, MD^b Gainesville, Fla., and Bochum, Germany

There are significant differences in the pharmacokinetic properties of inhaled corticosteroids currently used in medical practice. All are rapidly cleared from the body but they show varying levels of oral bioavailability and more importantly variation in the rate of absorption after inhalation. Oral bioavailability is lowest for fluticasone propionate, indicating a low potential for unwanted systemic corticosteroid effects. Mathematical modeling has shown pulmonary residence times to be longest for fluticasone propionate and triamcinolone acetonide but shortest for budesonide and flunisolide. These properties appear to relate to pulmonary solubility, which appears to be the rate-limiting step in the absorption process. (*J Allergy Clin Immunol* 1998;101:S440-6.)

Key words: *Inhaled corticosteroids, pharmacokinetics, pharmacodynamics, safety, mathematical modeling*

During recent years, the treatment of asthma has been significantly improved as a result of the introduction of modern corticosteroids with improved therapeutic ratios. This improvement is mainly due to optimized pharmacokinetic properties. It is the goal of all inhaled corticosteroids to (1) produce long-lasting therapeutic effects at the pulmonary target site, (2) minimize oral bioavailability, and (3) minimize systemic side effects by rapid clearance of absorbed drug.

At present there are five compounds used to varying degrees in different countries for corticosteroid inhalation treatment: triamcinolone acetonide, flunisolide, beclomethasone dipropionate, budesonide, and fluticasone propionate. Of these compounds, FP and BUD are the latest developments, both becoming available in the United States last year. The available inhaled corticosteroids have very different pharmacokinetic properties and also differ in their pharmacodynamic potencies (Table I).

PRODRUGS VERSUS ACTIVE DRUGS

Most inhaled corticosteroids, including FP and BUD, are used in their pharmacologically active form. However, BDP is very different because it is a prodrug that first needs to be activated by hydrolysis. The active form of BDP is the respective monoester, beclomethasone-17-monopropionate.

Abbreviations used

BDP:	Beclomethasone dipropionate
17-BMP:	Beclomethasone-17-monopropionate
BUD:	Budesonide
FLU:	Flunisolide
FP:	Fluticasone propionate
RRA:	Relative receptor affinity relative to dexamethasone (RRA = 100)
TAA:	Triamcinolone acetonide

RELATIVE RECEPTOR AFFINITY

With respect to their receptor affinity relative to dexamethasone (RRA = 100), FP has the highest affinity (RRA = 1800) followed by 17-BMP (RRA = 1345), BUD (RRA = 935), TAA (RRA = 233), and FLU (RRA = 180).¹ In practical terms, this means that a 10-fold higher unbound concentration of FLU at the receptor site is needed to produce the same degree of receptor occupancy as FP. This fact also makes clear why inhaled corticosteroids should never be compared on the basis of equal weight doses but only in terms of their equipotent doses.

PLASMA PROTEIN BINDING

Because only the free, unbound drug is able to interact with the corticosteroid receptor, it is important to convert measured plasma or serum concentrations to the respective unbound concentrations. All inhaled corticosteroids show moderate to high levels of protein binding. TAA has the lowest plasma protein binding (71%)² followed by FLU (80%),^{3,4} BUD (88%),⁵ and FP (90%).⁶ BDP has been reported to be 87% bound to plasma proteins,⁷ but no data are available for 17-BMP.

ORAL BIOAVAILABILITY

Inhaled corticosteroids are intended to provide localized therapy with immediate drug activity at the site of delivery in the lungs. However, it is well known that the greater part of an inhaled dose is swallowed and therefore available for undesired oral absorption, resulting in unwanted systemic corticosteroid effects. Hence an ideal inhaled corticosteroid should have minimum oral bioavailability. This goal has been achieved in the case of FP, which has an oral bioavailability of <1%.⁸ The absorbed fraction of the other inhaled corticosteroids after oral intake is greater: 11% for BUD,⁵ 20% for FLU,⁹ and 23% for TAA.¹⁰ No reliable data are available for BDP.

From ^athe University of Florida, Gainesville; and ^bthe University of Bochum, Bochum, Germany.

Reprint requests: H. Derendorf, PhD, Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL 32610.

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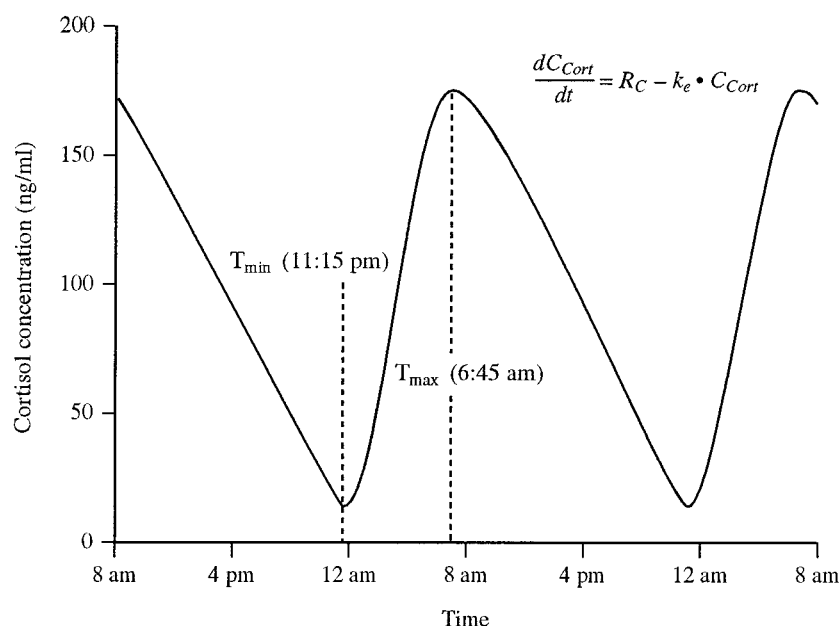


FIG. 1. Baseline plasma cortisol profile and linear release rate model based on cortisol concentration (C_{cort}), cortisol release rate (R_c), cortisol elimination rate constant (k_e), and time (t). T_{min} and T_{max} are the time points of minimum and maximum cortisol concentrations.

TABLE I. Pharmacodynamic and pharmacokinetic parameters of inhaled corticosteroids

Drug	RRA	f_u (%)	CL (L/h)	Vd_{ss} (L)	Vd_{β} (L)	$t_{1/2}$ (h)	F_{oral} (%)	F_{inh} (%)
Flunisolide	180	20	58	96	134	1.6	20	39
Triamcinolone acetonide	233	29	37	103	107	2.0	23	22
Budesonide	935	12	84	183	339	2.8	11	28
Beclomethasone dipropionate	53	13	230	...	167	0.1-0.2	...	...
Beclomethasone monopropionate	1345	...	...	...	...	...	...	...
Fluticasone propionate	1800	10	69	318	776	7.8	<1	16

RRA, relative receptor affinity compared with dexamethasone (RRA = 100); f_u , unbound fraction of the drug in plasma; CL, total body clearance; Vd_{ss} , apparent volume of distribution at steady state; Vd_{β} , volume of distribution during the elimination phase; $t_{1/2}$, plasma elimination half-life; F_{oral} , oral bioavailability; F_{inh} , inhalation bioavailability.

PULMONARY BIOAVAILABILITY

In general, corticosteroids are absorbed well from the lungs. Indeed it can be assumed that all the drug available at the receptor site in the lungs will be absorbed systemically. Corticosteroids administered by inhalation can therefore be detected in the blood, although the blood corticosteroid concentration represents the sum of pulmonary and orally absorbed fractions. For this reason it is difficult to separately assess the pulmonary bioavailability of those inhaled corticosteroids that also undergo significant oral absorption. Oral absorption of FP, however, is negligible, and its pulmonary bioavailability can be calculated with greater confidence. Indeed the pulmonary bioavailability of this drug has been calculated to range between 16% and 30%, depending on the inhalation device used.¹¹ Reported pulmonary bioavailabilities for other inhaled corticosteroids are 22% for TAA,¹⁰ 28% for BUD,¹² and

39% for FLU.¹³ Again, no reliable data are available for BDP.

SYSTEMIC CLEARANCE

One of the most important properties of inhaled corticosteroids is their rapid clearance after absorption, which minimizes systemic side effects (giving rise to the term "soft steroids"). In theory, the faster the systemic clearance, the higher the therapeutic index.

All of the currently used inhaled corticosteroids show a rapid systemic clearance that is of similar magnitude: systemic clearance was reported to be 84 L/h for BUD,⁵ 69 L/h for FP,¹⁴ 58 L/h for FLU,⁹ and 37 L/h for TAA.¹⁰ These values are approximately the same as the rate of hepatic blood flow, which would be the maximum clearance rate possible for hepatically metabolized drugs. Indeed even with an increased hepatic extraction efficiency, this value could not be increased because the

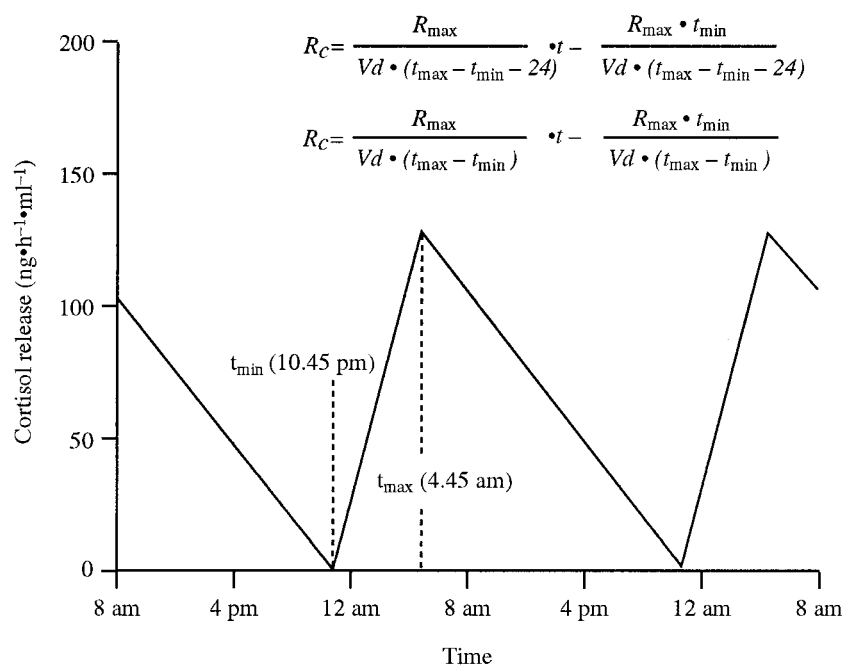


FIG. 2. Cortisol release profile, modeled by a set of two straight line equations with cortisol release rate in conc/time (R_c), maximum cortisol release in amount/time (R_{max}), cortisol volume of distribution (Vd), and time of maximum (t_{max}) and minimum (t_{min}) cortisol release.

maximum clearance rate would be achieved when all of the drug supplied by liver blood flow was removed. In this scenario, these so called “high-extraction drugs” are removed by the liver at a rate that is equivalent to hepatic blood flow. Only BDP was reported to have a systemic clearance greater than hepatic blood flow (230 L/h), indicating extrahepatic metabolism.¹⁵ However, in this case the metabolic reaction does not result in the formation of an inactive metabolite and therefore termination of systemic activity; it results in the formation of the extremely potent metabolite 17-BMP. The clearance rate of 17-BMP has not been reported.

VOLUME OF DISTRIBUTION

The volume of distribution is a pharmacokinetic parameter that allows quantification of tissue distribution. The larger its value, the greater the amount of drug located inside the peripheral body compartments. However, a large volume of distribution does not necessarily indicate higher pharmacologic activity in the peripheral body compartments because most of the drug is present in its pharmacologically inactive, bound form. Indeed the active, unbound drug concentration at steady state is independent of volume and depends only on clearance and degree of protein binding. Since there are different ways of calculating volume of distribution, comparison of literature values must be done with great care. The volume of distribution at steady state (Vd_{ss}) for FP was reported to be 318 L.¹⁴ This is far greater than the distribution values of other currently available inhaled

corticosteroids and is in agreement with the high lipophilicity of the drug. Vd_{ss} was reported to be 183 L for BUD,¹⁶ 103 L for TAA,¹⁰ and 96 L for FLU.³ Again, no reliable data are available for BDP or 17-BMP.

ELIMINATION HALF-LIFE

The elimination half-life of any drug is a secondary pharmacokinetic parameter that is dependent on the rate of systemic clearance and the volume of distribution. The elimination half-life quantifies how rapidly the plasma concentration changes but does not indicate the magnitude of this concentration. As a result of its large volume of distribution, FP has the longest elimination half-life of 7 to 8 hours, as measured after intravenous administration.¹⁴ The elimination half-life of BUD is 2.8 hours,⁵ of TAA is 2.0 hours,¹⁰ and of FLU is 1.6 hours.^{4, 13} The elimination half-life of BDP was recently reported to be only 0.1-0.2 hours,¹⁷ but no data are available for the monopropionate. A sufficiently high analytic sensitivity is a prerequisite for an accurate determination of half-life.

TERMINAL HALF-LIFE AFTER INHALATION

The terminal half-life after inhalation can differ from the true elimination half-life after intravenous administration if absorption is slow and if it is the overall rate-limiting step (“flip-flop pharmacokinetics”). Hence a slower terminal elimination half-life after inhalation than after intravenous administration indicates slow absorption. This may be the case for FP because terminal half-life values of >10 hours have been reported

after inhalation of this drug. Since FP is absorbed only from the lungs, this indicates a relatively long pulmonary residence time at the site of action. Similar findings have been reported for TAA since the terminal half-life after inhalation was found to be longer (3.6 hours) than after intravenous administration.¹⁰ Terminal half-life of BUD and FLU remains short after inhalation, indicating rapid absorption from both the lungs and the gastrointestinal tract.^{4,5} The terminal half-life of 17-BMP is reported to be 6.5 hours¹⁷; however, no reliable intravenous data are available to determine whether this value is limited by absorption.

ACCUMULATION

Accumulation is the term used to describe the increase in plasma drug concentration that may occur during multiple-dose administration until steady state is reached. The accumulation time is a function of the terminal elimination half-life of the drug. As a general rule, it takes approximately five terminal half-lives to reach steady state. In the case of FP, this is equivalent to about 2 days. Steady state is reached in about half a day in the case of BUD and TAA and within 8 hours for FLU (i.e., after the first dose). In contrast, the extent of accumulation, that is, the magnitude of the steady-state plasma drug level, is independent of the half-life of the drug and is only a function of clearance. Hence in the case of FP, it will take longer to reach steady state than, for example, BUD; however, for equal amounts of drug absorbed, the resulting steady-state concentrations will be quite similar. Once steady state is reached, these concentrations will remain the same and will not increase further.

CORTISOL SUPPRESSION

Cortisol suppression is the most frequently used surrogate marker for corticosteroid systemic activity. However, because of the circadian rhythm of cortisol release, analysis of cortisol suppression is complex. With the use of deconvolution methods, it is possible to convert the cortisol concentrations (Fig. 1) into the respective cortisol release rates that can be well described by a set of two straight line equations (Fig. 2).¹⁸ This linear release rate model is able to describe cortisol baseline data (Fig. 3). Furthermore, the model is able to account for cortisol suppression by exogenous corticosteroids with the equation

$$\frac{dC_{\text{Cort}}}{dt} = R_c \cdot \left(1 - \frac{E_{\text{max}} \cdot C_f}{EC_{50} + C_f} \right) - k_e \cdot C_{\text{Cort}}$$

where C_{cort} is the cortisol concentration, R_c is the cortisol release rate [conc/time], E_{max} is the maximum possible effect (usually 1), EC_{50} is the unbound concentration of the exogenous corticosteroid that produces 50% of the maximum effect, k_e is the elimination rate constant of cortisol, and t is time.¹⁸ This model allows very good characterization of plasma cortisol concentrations after inhalation of various corticosteroids. Fig. 4

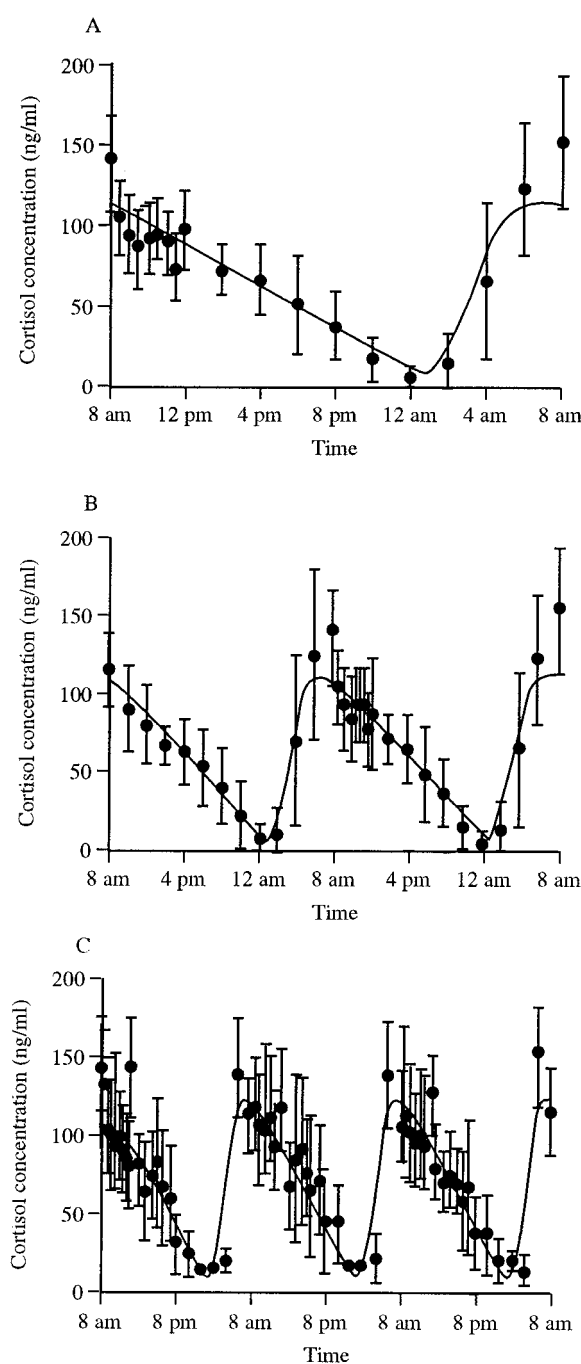


FIG. 3. Measured plasma cortisol concentrations (mean $\pm$ SD) over (A) day 1, (B) day 2, and (C) day 3 fitted with the described linear release rate model.

shows the average plasma cortisol concentrations and the measured and fitted cortisol concentrations after pulmonary administration of FLU, TAA, and FP.^{2,4,11} The cumulative extent of suppression can then be expressed as the area between the baseline and the suppressed cortisol concentrations (Fig. 5).¹⁹ It should be

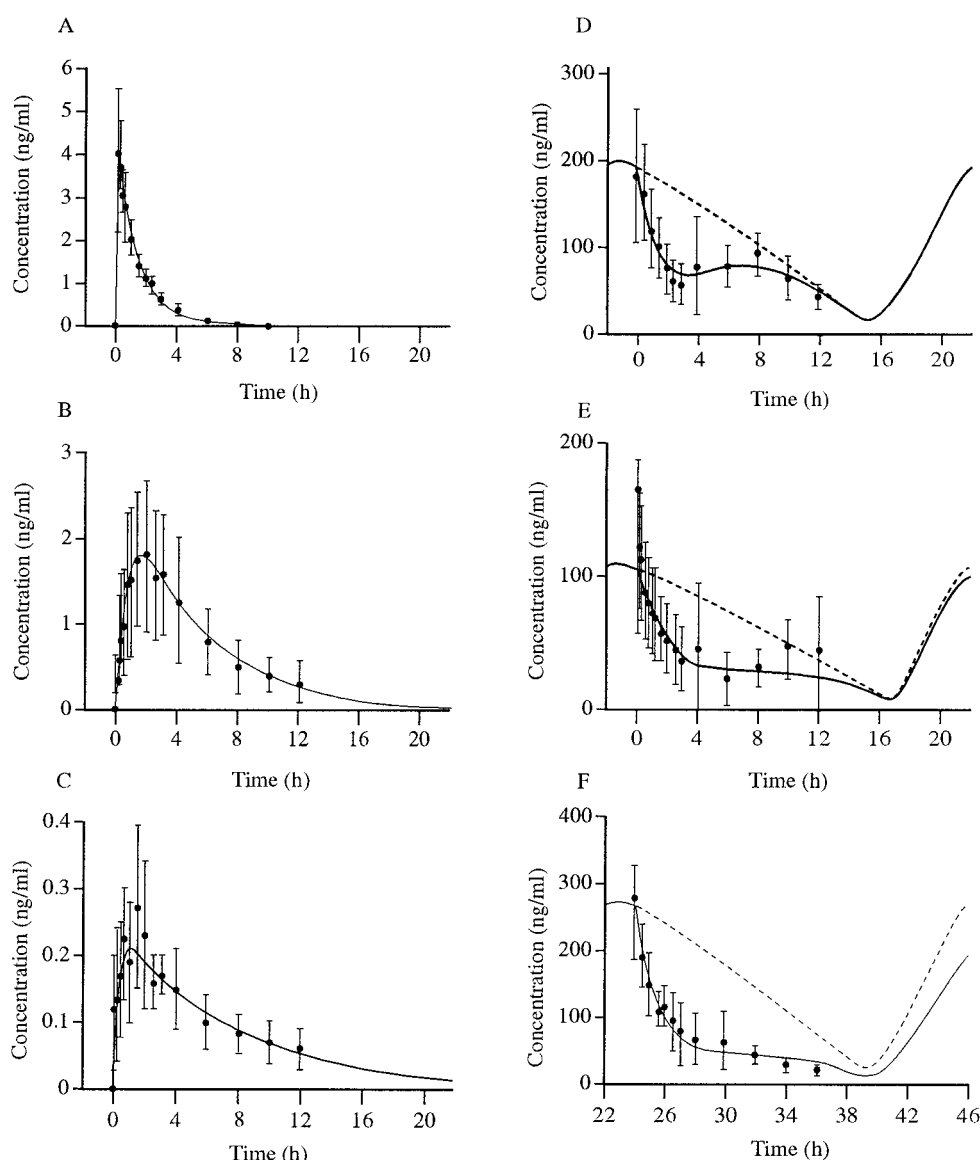


FIG. 4. Plasma drug concentrations (mean $\pm$ SD, **A** through **C**) and respective cortisol concentrations (mean $\pm$ SD, **D** through **F**) after inhalation of 1 mg flunisolide (**A**, **D**), 2 mg triamcinolone acetonide (**B**, **E**) and 1 mg fluticasone propionate (**C**, **F**). Also shown is the respective cortisol baseline profile (dotted line, **D** through **F**).

noted, however, that the total physiologic glucocorticoid requirement is not exceeded at low to medium doses of inhaled steroids. This pharmacokinetic/pharmacodynamic model allows good prediction of cumulative cortisol suppression reported in several published studies (Fig. 6).¹⁹ Hence the model is suitable to predict the expected cortisol suppression for various dosing regimens. As a result of the circadian rhythm of cortisol release, it is important to consider the time of dosing in these comparisons.²⁰ Fig. 7 shows a comparison of calculated cumulative cortisol suppressions after different dosing regimens of inhaled corticosteroids. As can be seen for a drug with a short elimination half-life such

as FLU or BUD, dosing at 10 PM will produce much less cortisol suppression than dosing at 8 AM, whereas for a drug with a longer elimination half-life there is no significant difference whether it is administered in the morning or evening. It is extremely important, therefore, to critically examine the study design and drug administration time when evaluating study results and when comparing results from different studies.

CONCLUSIONS

A comparison of the pharmacokinetic and pharmacodynamic properties of inhaled corticosteroids currently used in medical practice clearly reveals significant dif-

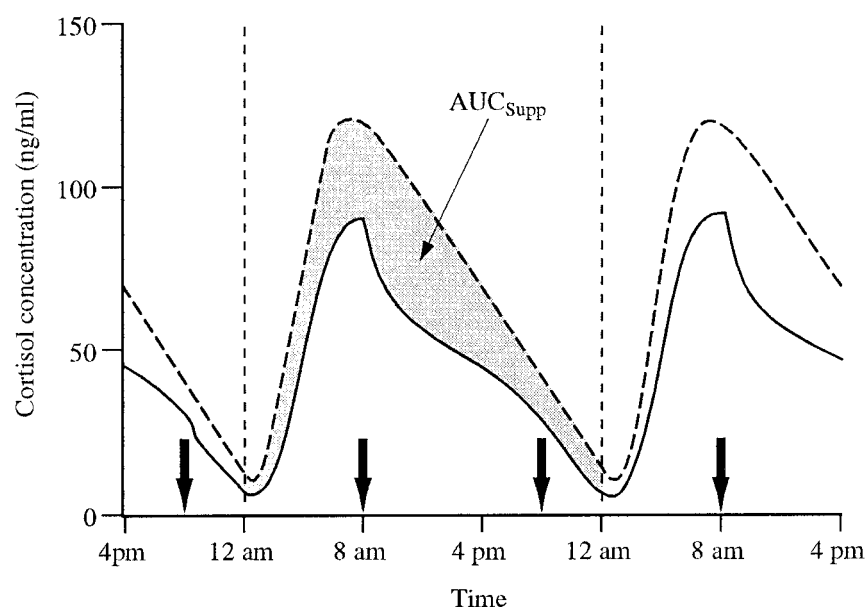


FIG. 5. Cortisol suppression after administration of an exogenous corticosteroid. Area under the curve (AUC_{Suppr} , shaded) is a cumulative parameter to quantitate the degree of suppression. Arrows indicate time of dose administration.

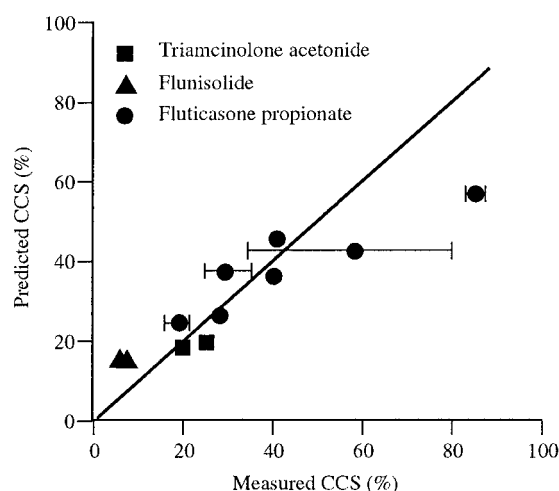


FIG. 6. Correlation between predicted cumulative cortisol suppression (CCS) as a percent of baseline and measured CCS in several clinical studies. Values are mean $\pm$ SD (where available).

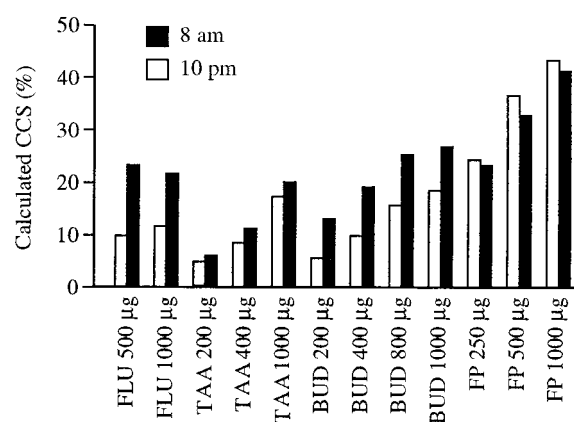


FIG. 7. Calculated cumulative cortisol suppression as a percent of baseline for several dosing regimens of inhaled corticosteroids (microgram equivalent doses, not therapeutically equivalent doses) administered at 8 AM versus 10 PM.

ferences between these compounds. Although all of these agents show rapid systemic clearance after absorption, there are differences in oral bioavailability and absorption rate after inhalation. The last parameter is probably the most relevant property because it reflects pulmonary residence time after inhalation and therefore duration of availability in the lungs.²¹ Initial attempts at mathematical deconvolution to estimate pulmonary residence time have resulted in significant differences be-

tween agents. Long residence times have been calculated for FP and TAA, but BUD and FLU appear to disappear rapidly.^{22,23} These properties appear to be related to pulmonary solubility, which appears to be the rate-limiting step in pulmonary absorption. The available inhaled corticosteroids have improved asthma therapy significantly. However, it seems that by fully understanding the underlying mechanisms and by building on this understanding it may be possible to improve the therapeutic index of these compounds even more in the future.

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