Pharmacokinetic/Pharmacodynamic Aspects of Aerosol Therapy using Glucocorticoids as a Model

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Glucocorticoids are predominantly prescribed in asthma therapy as aerosols to achieve high pulmonary effects with reduced systemic spill-over and pronounced pulmonary selectivity. A variety of pharmacokinetic parameters are potentially important for determining pulmonary selectivity. The intent of this article, is to provide a practice-relevant theoretical approach to put the importance of these parameters on pulmonary targeting using pharmacokinetic/pharmacodynamic modeling as a tool in perspective. The applied pulmonary pharmacokinetic/pharmacodynamic model revealed that, in addition to recognized parameters such as systemic clearance, oral bioavailability, and efficiency of pulmonary deposition, other factors, such as the pulmonary release (dissolution) rate and dose, are relevant. However, the volume of distribution (for effect parameters not undergoing a diurnal rhythm) and the receptor affinity of a given glucocorticoid are not important for achieving lung targeting. J Clin Pharmacol 1997:37:881–892.

With the recognition of asthma as a relapsing inflammatory process, inhaled glucocorticoids have become the first-line treatment in the therapy of chronic asthma.[1–3]

Inhaled glucocorticoids are not free from systemic side effects when markers such as 24- hour plasma cortisol are monitored. [4,5] The extent of potentially undesirable systemic side effects represents only half of the problem, however, because the assessment of lung selectivity requires the evaluation of both local pulmonary and systemic effects. Although there is no question that inhaled glucocorticoids are effective in the treatment of asthma, pulmonary "efficacy" is difficult to quantify in humans. New inhaled glucocorticoids, with different pharmacokinetic and pharmacodynamic properties and improved delivery systems (such as dry powder inhalers) with improved pulmonary deposition, have been introduced on the market. Differences in their properties (including physicochemical factors potentially affecting the pulmonary residence time) will affect pulmonary targeting by determining the pulmonary and systemic availability of the drug. The goal with this article, is to provide an applied framework to evaluate the importance of these factors on pulmonary selectivity through use of a theoretical model. This model provides a novel approach by integrating physiologic aspects of pulmonary inhalation with pharmacokinetic and pharmacodynamic drug properties for the prediction of pulmonary and systemic effects. Receptor occupancy was selected as a surrogate marker because early work in cell systems found a close correlation between the extent of receptor occupancy and the extent of the biological response.[6–9] In addition, a direct relation between the receptor affinity of a glucocorticoid and the activity at the site of action (e.g., the skin blanching activity) has been demonstrated.[10,11] Contrary to a number of drug classes, pharmacologic desired and adverse effects of glucocorticoids are induced by the same receptors. Consequently, pulmonary selectivity has been defined in this study by the degree in which the occupancies of pulmonary and systemic receptors differ.

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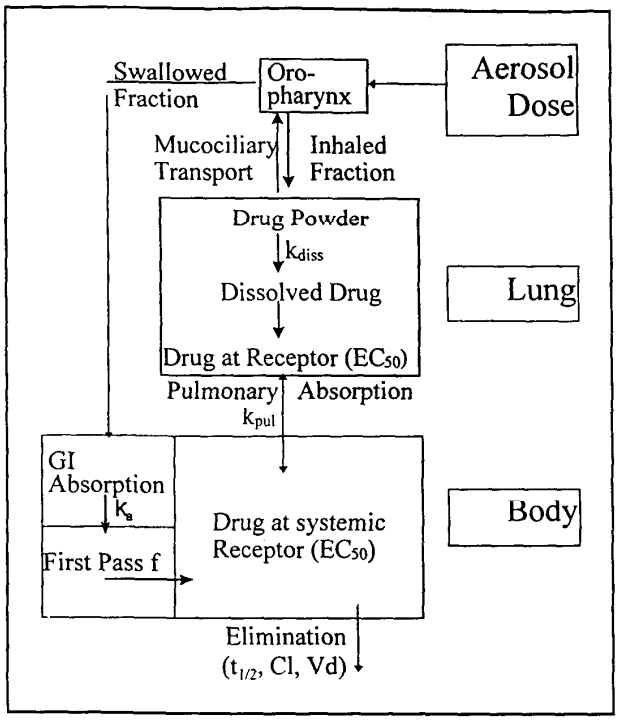

Figure 1. PK/PD Model for describing pulmonary targeting (see Methodological Aspects for more information).

METHODS

A pharmacokinetic/pharmacodynamic (PK/PD) modeling approach (Fig. 1) is used to demonstrate key features of pulmonary targeting. The applied PK/PD model is an extension of Byron's and Gonda's pharmacokinetic pulmonary models.[12,13] The model presented here predicts the time course of occupied systemic and pulmonary glucocorticoid receptors as surrogate markers of the effect (see introduction for the rationale) upon inhalation of a glucocorticoid by considering both physico-chemical aspects relevant to lung absorption and pharmacokinetic and pharmacodynamic properties of a given glucocorticoid. This model takes into consideration the oral bioavailability, as determined by the hepatic first pass effect, total clearance, volume of distribution, pulmonary aspects such as the drug release (dissolution), pulmonary absorption rate, and the receptor binding affinity.

When the drug is inhaled, it is either deposited in the oropharynx and swallowed, or it is deposited in the lung. The amount of drug deposited in the lung will dissolve as determined by its dissolution rate k_{diss}. The dissolved drug will enter pulmonary cells, where it will be able to interact with pulmonary receptors. The number of occupied receptors (see introduction for the rationale of selecting the receptor occupancy as a surrogate marker of the effect) is determined by the concentration of the drug in the pulmonary cells and its receptor binding affinity (EC_{50}). The drug will then be absorbed into the systemic circulation (k_{pul}). In addition, the solid portion of the drug (that has not been dissolved) can be cleared from the lung by expulsion from the airways through the mucociliary escalator into the oropharynx where it will be swallowed. This part of the model represents a simplification, because the lung was not divided into superficial and deep lung compartments (the latter not showing mucociliary transport). However, this simplification is not important for most of the simulations because the impact of mucociliary transport is insignificant for drugs dissolving with half-life much shorter than the half-life of the mucociliary transporter (the model used a dissolution half-life of 0.3 hours compared with a mucociliary transport half-life of 4 hours. In the results section, we highlight when simulations are being affected by this simplification).

Drugs reaching the gastrointestinal tract (directly deposited or transported into the gastrointestinal tract through mucociliary transport) will be absorbed systemically with the gastrointestinal absorption rate, k_a. The degree of oral absorption depends on oral bioavailability (f) (Figure 1), and is determined predominantly by its hepatic first pass effect. The model assumes that the drug fraction metabolized during first pass is pharmacologically inactive and will not induce systemic effects. Once absorbed, the oral fraction of intact drug, combined with the drug entering the systemic circulation through the lung, will induce systemic side effects by interacting with systemic glucocorticoid receptors (including those of the lung [see also introduction for the rationale for selecting the receptor occupancy as a surrogate marker of systemic effect]). As indicated by the reverse direction arrow in Figure 1, the model allowed for an immediate diffusion of the systemic drug into the lung. The drug will finally be eliminated from the systemic circulation according to its pharmacokinetic properties (clearance and volume of distribution). In the model, predictions were performed by solving the differential equations describing the drug concentrations in the systemic circulation and in the lung as a function of time. These concentrations were linked to an E_{max} model to calculate the degree of receptor occupancy in the systemic circulation and the lung. A concentration gradient between lung areas close to the solid drug, and pulmonary cells close to the pulmonary absorption site, were incor-

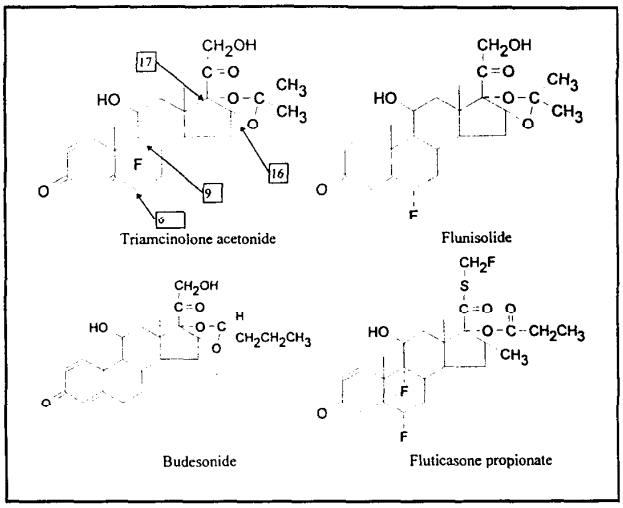

Figure 2. Chemical structures of commercially available glucocorticoids

TABLE I

Relative Binding Affinities of Commercially Available Glucocorticoids to the Glucocorticoid Receptor

Glucocorticoids	RBA
Fluticasone propionate	1800*
Beclomethasone monopropionate	1022
Budesonide	935†
Triamcinolone acetonide	233
Flunisolide	190
Dexamethasone	100

*Relative binding affinities[22], * [23],† [6].*
RBA, relative binding affinities.
RBA of dexamethasone set as 100.

porated into the model by simulating passage compartments with increased volume of distributions (1.9 L total). This was done to mimic the existing difference between high drug concentration in the near vicinity to deposited particles and lower drug concentrations in lung areas close to the absorption site (with the average receptor occupancies representing the overall lung effect). The model did not consider an exhaled fraction of the dose because only pulmonary and systemically deposited drugs are relevant for the degree of targeting.

Unless otherwise stated, representative pharmacokinetic properties of inhaled glucocorticoids or pulmonary physiologic properties were used in the model. They represent: a 100 μg dose; administration interval of 8 hrs, oral bioavailability of 10%, pulmonary deposition of 10% (inhaled fraction of dose

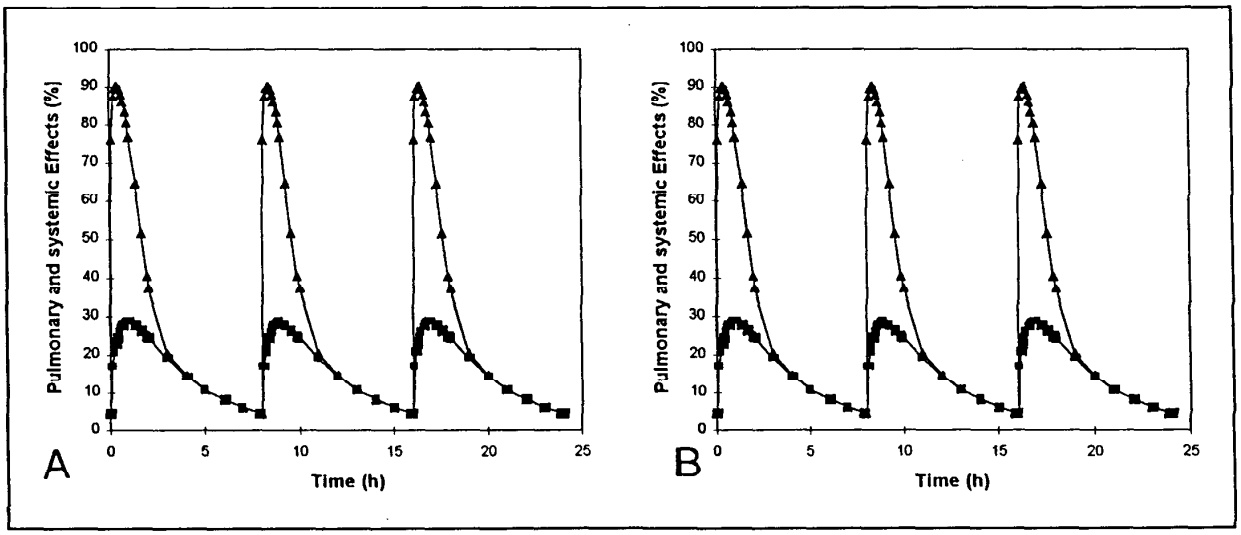

*Figure 3. Effect of receptor-binding affinity on model-predicted pulmonary and systemic effects after inhalation of two hypothetical drugs that differ in their receptor binding affinity, given as EC_{50} (concentration necessary to achieve 50% of receptor occupancy). Systemic (■) and pulmonary (▲) effects are plotted as a function of time. Drugs were assumed to be inhaled every 8 hours. Doses were adjusted for differences in the receptor binding affinity. The difference between pulmonary and systemic effects indicates the degree of pulmonary targeting. See Scheme 1 for more information. **A**: EC_{50} = 0.24 ng/mL, Dose = 100μg; **B**: EC_{50} = 2.4 ng/mL, Dose = 1000μg.*

TABLE II

% of Systemic Activity of an Inhaled Glucocorticoid Dose Absorbed Via the G I Tract (% of Absorbed Drug Stemming From Swallowed Component)

Oral Bioavailability (%)	10% Pulmonary Delivery	20% Pulmonary Delivery	30% Pulmonary Delivery
1	8.3	3.8	2.3
10	47.4	28.6	18.9
20	64.3	44.4	31.8
30	73.0	54.5	41.2
90	89.0	78.3	67.7

from meter dose inhalers), pulmonary dissolution half-life of 0.3 hrs (equivalent to k_{diss}), elimination half-life of 2.1 hrs (equivalent to k_e), volume of distribution of 150 L, pulmonary volume of distribution of 1.9 L (an educated guess, animal experiments are needed), clearance of 50 L/hr, EC_{50} of 0.24 ng/mL, rate constants describing lung gradient of 10 hrs^{-1} (not indicated in Scheme 1), pulmonary absorption rate of 10 hrs^{-1}, mucociliary transport rate of 0.167 hrs^{-1} [13], and GI absorption rate of 10 to 32 hrs^{-1}.

RESULTS AND DISCUSSION

It is recognized that the success of an inhaled glucocorticoid depends on certain pharmacokinetic and pharmacodynamic key features that will determine the pulmonary selectivity. In the following sections, relevant factors will be discussed using the PK/PD model described in the Methods section. Although purely theoretically, recently published animal experiments strongly support the validity of this model.[14]

Pharmacodynamic Properties

It is well established that the majority of effects of glucocorticoids are mediated through cytosolic receptors. The binding of a glucocorticoid ligand to the receptor will result in activated receptor dimers which are transported into the nucleus. Binding of the receptor dimer to the glucocorticoid response elements of DNA is responsible for the induction of the synthesis of certain proteins such as lipocortin or the inhibition of the synthesis of factors such as cytokines. Other mechanisms may involve the direct interaction of the receptor with factors such as AP1 or nuclear-kappa B.[15]

Independent of the mechanism, the degree of effects and side effects is directly related to the number of activated receptors in the target cells.[6–9] This suggests that, for both effects and side effects, the relative receptor binding affinities determined in *in vitro* tests are highly suitable for describing the activity of a glucocorticoid at the site of action. Glucocorticoids with higher receptor binding affinity (such as budesonide, beclomethasone monopropionate, and fluticasone propionate, see Figure 2, Table I) are, however, not automatically the "better" drugs. This is demonstrated in Figure 1 for two hypothetical glucocorticoids. The two drugs differ in their glucocorticoid receptor binding affinity by a factor of 10 (here expressed as EC_{50}: concentration to achieve 50% of maximum receptor occupancy) but otherwise exhibit identical physicochemical and pharmacokinetic properties. The drug with the lower receptor binding affinity (EC_{50} = 2.4 ng/mL) is delivered through inha-

TABLE III

Pharmacokinetic Parameters of Commercially Available Glucocorticoids

	Cl (L/hr)	Vd_{ss} (L)	$t_{1/2}$ (hrs)	Oral Bioavailability (%)	Plasma Binding (%)	Dissolution Rate*
Hydrocortisone[24]	18.0	34	1.6	96	75–95[24]	
Methylprednisolone[25]	21.0	66	2.6	99[26]	77[27]	
Dexamethasone*	16.8	100	4.5	80[28]	77[29]	
Triamcinolone acetonide[30]	37	103	2.0	23[30]	71[30]	slow
Flunisolide[31,32]	58	96	1.6	20	80	fast
Budesonide[18,33]	84	183	2.8	11[33]	88[33]	fast
Fluticasone propionate[34]	69	318	7.8	<1[35]	90	slow

* *Unpublished results.*
Cl, clearance; Vd_{ss}, volume of distribution at steady state; $t_{1/2}$, half-life.

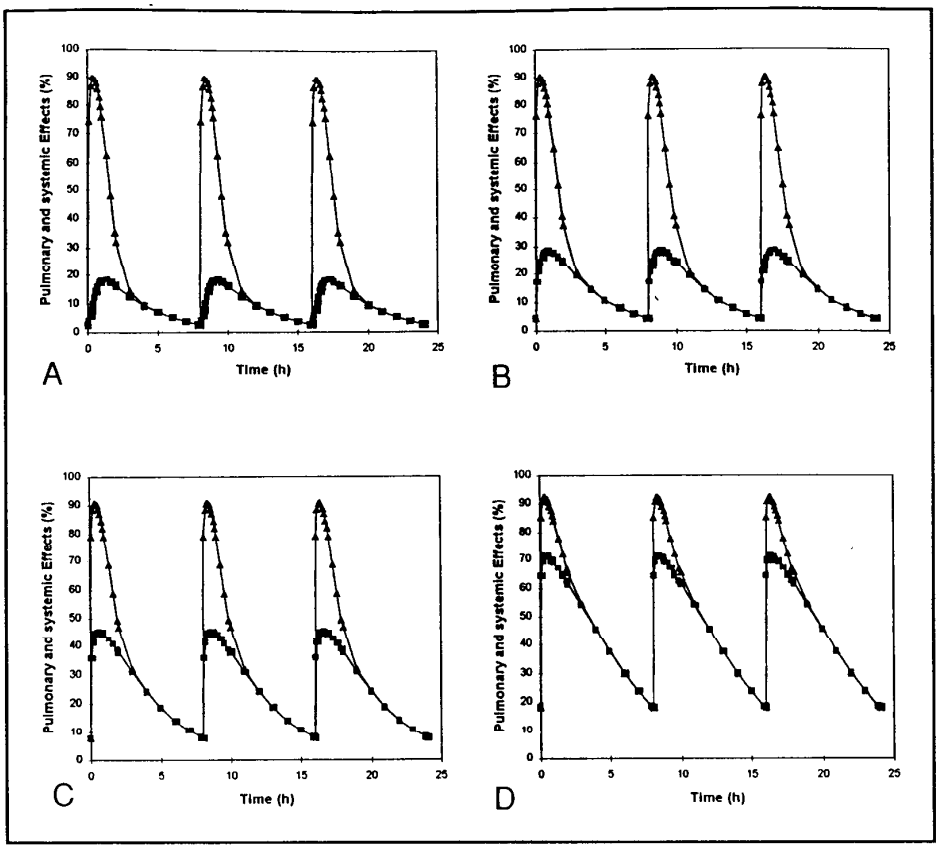

*Figure 4. Effect of oral bioavailability on model-predicted pulmonary and systemic effects. Systemic (■) and pulmonary (▲) effects are plotted as a function of time. Hypothetical drugs were assumed to be inhaled every 8 hours. The difference between pulmonary and systemic effects indicates the degree of pulmonary targeting. See Scheme 1 for more information. **A:** 1% oral bioavailability; **B:** 10% oral bioavailability; **C:** 30% oral bioavailability; **D:** 100% oral bioavailability.*

lation at a 10 times higher dose. The identical pulmonary and systemic effect profiles (Figure 1) show that a low receptor binding affinity can be compensated by an increase in dose, assuming that the required dose can be delivered through inhalation. It further indicates that pharmacodynamic properties of glucocorticoids will have no direct effect on the extent of pulmonary targeting.

Oral Bioavailability

Only a portion of the drug delivered by metered dose inhalers or dry powder inhalers is deposited in the lung. The majority of the inhaled drug (70%–90%) is deposited in the oropharynx and subject to swallowing, and to systemic absorption through the gastrointestinal tract. Glucocorticoids absorbed through the gastrointestinal tract will be systemically available. The percentage of systemically available drug stemming from oral absorption depends on the oral bioavailability (f) of the glucocorticoid (Table II); a parameter that differs among the commercially available glucocorticoids (Table III). Pulmonary targeting will be lost with increasing oral bioavailability (Figure 4A–D) because the orally absorbed fraction is not able to induce local lung effects. For inhalation purposes, an "ideal" glucocorticoid will consequently exhibit a zero percentage of oral bioavailability. However, even these glucocorticoids are not necessarily without any systemic side effects (see Figure 4A), because the pulmonary deposited drug will also enter the systemic circulation and induce systemic side effects.

Effects of the Delivery Device

Inhaled glucocorticoids are administered through nebulizers, metered-dose inhalers with or without spacers, and dry powder inhalers, all of which differ in pulmonary deposition efficiency. It is now well established that the use of spacer devices in conjunction with metered dose inhalers reduces the orally deposited fraction. [16–17] Studies on dry powder inha-

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