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Optimized therapeutic ratio of inhaled corticosteroids using retrometabolism

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During recent years, the treatment of pulmonary diseases could be significantly improved due to the introduction of modern retrometabolism-based corticosteroids with improved therapeutic ratio. It is the goal of all inhaled corticosteroids to produce long lasting therapeutic effects at the pulmonary target site and to minimize systemic side effects by rapid clearance of the absorbed drug and low oral bioavailability. The development of PK/PD models allows predictions of drug effects based on the administered dose. For example, the cumulative suppression of endogenous cortisol release (CCS) as one of the major systemic side effects of inhaled corticosteroid therapy can be described with an integrated E_{max} based PK/PD model. In order to assess the predictive power of this model, a study was conducted to compare the PK/PD-based predictions with CCS data obtained from actual clinical trials for flunisolide, fluticasone propionate, budesonide and triamcinolone acetonide. CCS was predicted for different single doses from different inhaler devices for each drug and a good correlation was observed. Thus, the presented PK/PD model proved to be a valid tool for predicting CCS of inhaled corticosteroids. By fully understanding the underlying mechanisms it will be possible to further improve their therapeutic index.

1. Introduction

During recent years, the treatment of pulmonary diseases has been significantly improved due to the introduction of modern retrometabolism-based corticosteroids with improved therapeutic ratio. This improvement is mainly due to optimized pharmacokinetic properties. It is the goal of all inhaled corticosteroids to produce long-lasting therapeutic effects at the pulmonary target site, minimize oral bioavailability, and 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 (TA), flunisolide (FLU), beclomethasone dipropionate (BDP), budesonide (BUD), and fluticasone propionate (FP). The available inhaled corticosteroids (ICS) have very different pharmacokinetic properties and also differ in their pharmacodynamic potencies [1]. All the drugs except BDP are used in their pharmacologically active form. BDP is a prodrug that first needs to be activated by hydrolysis. The active form of BDP is the respective monoester, beclomethasone-17-monopropionate (BMP).

One of the major systemic side effects of inhaled corticosteroid therapy is the suppression of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a decrease in the release of endogenous cortisol [2, 3]. Since endogenous cortisol plasma concentration is an easily accessible parameter for quantification and monitoring, alterations in cortisol plasma levels as a consequence of modulation of cortisol release have been used as a surrogate marker to quantify overall systemic corticosteroid activity. The two-part review by Chrousos et al. further reinstates the fact that 24-hour integrated serial plasma cortisol concentrations provide the most sensitive and accurate estimates of adrenal suppression before the appearance of clinical effects [4, 5].

Several pharmacokinetic/pharmacodynamic-(PK/PD)-modeling approaches have been launched to describe the daily rhythm in the plasma concentration-time course of endogenous cortisol and its suppression after administration of exogenous corticosteroids [6–12]. A clinically valuable, integrated, E_{max}-based PK/PD model has been developed to describe the cumulative suppression of endogenous cortisol release (CCS) caused by exogenous corticosteroids [13].

In order to assess the predictive power of this model, a study was conducted to compare the PK/PD based predictions with CCS data from the literature involving actual clinical trials for FLU, BUD, TA and FP. BDP, although a commonly used drug, was not included in the study due to lack of reliable PK/PD data on BMP.

2. Investigations, results and discussion

2.1. Pharmacokinetic-pharmacodynamic model

The circadian pattern of endogenous cortisol plasma concentrations is generated by a complex pulsatile release of cortisol [14]. Time and amplitude of cortisol secretion bursts are controlled by the activity of the hypothalamic-pituitary-adrenal system via ACTH. In the absence of additional exogenous stimuli, this complex cortisol release function can be simplified to a previously reported linear release model [6–9], which describes the daily cortisol release (R_c in concentration/time) at baseline situation with two straight lines. For the time between the maximum cortisol release (t_{max}) and the minimum cortisol release (t_{min}), R_C decreases in a linear fashion from the maximum release rate (R_{max} in amount/time) at time t_{max} to approximately 0 at time t_{min} (Eq. 1).

$$R_C = \frac{R_{max}}{Vd^{Cort} \cdot (t_{max} - t_{min} - 24)} \cdot t - \frac{R_{max} \cdot t_{min}}{Vd^{Cort} \cdot (t_{max} - t_{min} - 24)} \quad (1)$$

where Vd^{Cort} is the volume of distribution of cortisol and t is the time after cortisol monitoring was initiated ($t_0 = 8$ a.m.).

For the time between t_{min} and t_{max}, R_C increases according to Eq. 2.

$$R_C = \frac{R_{max}}{Vd^{Cort} \cdot (t_{max} - t_{min})} \cdot t - \frac{R_{max} \cdot t_{min}}{Vd^{Cort} \cdot (t_{max} - t_{min})} \quad (2)$$

The resulting change in cortisol plasma concentrations (C_{Cort}) at baseline situation can then be described by Eq. 3, where k_e^{Cort} is the first order elimination rate constant for cortisol.

$$\frac{dC_{Cort}}{dt} = R_C - k_e^{Cort} \cdot C_{Cort} \quad (3)$$

Based on Eq. 3, an indirect response model can be deducted to characterize the suppression of endogenous cortisol concentrations during exogenous corticosteroid therapy [9, 11, 15], thereby relating the corticosteroid concentrations to the effect on cortisol release according to Eq. 4.

$$\frac{dC_{Cort}}{dt} = R_C \cdot \left(1 - \frac{E_{max} \cdot C}{EC_{50} + C}\right) - k_e^{Cort} \cdot C_{Cort} \qquad (4)$$

E_{max} is the maximum suppressive effect, EC_{50} is the corticosteroid plasma concentration that produces half of E_{max}, and C is the plasma concentration of the exogenous corticosteroid. Since the maximum possible effect is complete suppression of cortisol release, E_{max} is fixed at 1. The approach assumes that the exogenous corticosteroid exhibits linear plasma protein binding. Otherwise, free, pharmacologically active rather than total corticosteroid concentrations have to be used [16].

2.2. Cumulative cortisol suppression

2.2.1. Amount of suppressed cortisol

According to the described linear release model, the amount of endogenous cortisol released at baseline situation A_C^{Base} can be calculated as the integral of cortisol release R_C (concentration/time) times volume of distribution of cortisol Vd^{Cort} from time t_0 to time t_1 (Eq. 5).

$$A_C^{Base} = \int_{t_0}^{t_1} Vd^{Cort} \cdot R_c dt = Vd^{Cort} \cdot \int_{t_0}^{t_1} R_c dt \qquad (5)$$

Based on Eq. 5, the amount of cortisol release during corticosteroid therapy $A_C^{Therapy}$ can then be determined with a similar integral, which considers the release suppression by the exogenous corticosteroid (Eq. 6).

$$A_C^{Therapy} = \int_{t_0}^{t_1} Vd^{Cort} \cdot R_c \cdot \left(1 - \frac{E_{max} \cdot C}{EC_{50} + C}\right) dt \qquad (6)$$

Eq. 6 can be rearranged to give Eq. 7.

$$A_C^{Therapy} = Vd^{Cort} \cdot \int_{t_0}^{t_1} R_c dt - Vd^{Cort} \cdot \int_{t_0}^{t_1} \left(R_c \cdot \frac{E_{max} \cdot C}{EC_{50} + C}\right) dt \qquad (7)$$

Since $A_C^{Therapy}$ is the difference between A_C^{Base} and A_C^{Supp}, the amount of cortisol whose release is suppressed during corticosteroid therapy, Eq. 8 follows from Eq. 7 and Eq. 5.

$$A_C^{Supp} = Vd^{Cort} \cdot \int_{t_0}^{t_1} \left(R_c \cdot \frac{E_{max} \cdot C}{EC_{50} + C}\right) dt \qquad (8)$$

2.2.2. Cumulative cortisol suppression after single dosing

Based on the determination of A_C^{Supp}, the CCS can be expressed as the absolute amount or as percent compared to the baseline condition. After a single corticosteroid dose the total amount of suppressed cortisol from the time of administration t_0 until infinity ($A_C^{Supp,\infty}$) can be determined according to Eq. 9.

$$A_C^{Supp,\infty} = Vd^{Cort} \cdot \int_{t_0}^{\infty} \left(R_c \cdot \frac{E_{max} \cdot C}{EC_{50} + C}\right) dt \qquad (9)$$

$A_C^{Supp,\infty}$ is the most accurate way of quantifying CCS, since cortisol suppression is completely registered over time. However, $A_C^{Supp,\infty}$ might be of limited clinical value because it lacks information regarding the time frame within CCS occurs.

A clinically more valuable way of estimating CCS might be the comparison between the amount of suppressed cortisol A_C^{Supp} and the amount of cortisol released under baseline conditions A_C^{Base} within a certain time interval. The resulting cumulative cortisol suppression in percent (%CCS) is usually determined over 24 h following administration of the dose at time t_0 (Eq. 10)

$$\%CCS = \frac{A_C^{Supp,\,24}}{A_C^{Base,\,24}} \qquad (10)$$

$A_C^{Base,\,24}$, the amount of cortisol released at baseline condition, is equal to the area under the release-time curve over 24 h that is described by the cortisol linear release model at baseline condition. According to Eq. 1 and Eq. 2, this area has the shape of a triangle with the base 24 h and the height R_{max}. Hence, $A_C^{Base,\,24}$ can simply be calculated by Eq. 11 (h stands for the unit hours).

$$A_C^{Base,\,24} = \frac{1}{2} \cdot 24\,h \cdot R_{max} = 12\,h \cdot R_{max} \qquad (11)$$

Substituting Eq. 8 and Eq. 11 in Eq. 10 yields Eq. 12 as an expression to quantify %CCS.

$$\%CCS = \frac{Vd^{Cort} \cdot \int_{t_0}^{t_0+24\,h} R_c \cdot \frac{E_{max} \cdot C}{EC_{50}+C}\, dt}{12hr \cdot R_{max}} \qquad (12)$$

It should be noticed that the obtained results for %CCS after a single dose are thoroughly influenced by the regarded time interval (in this case 24 h). A too short interval might miss part of the CCS of a corticosteroid with prolonged effect, whereas a too long interval might underestimate the CCS of a short acting corticosteroid.

2.2.3. Relationship between A_C and AUC^{Cort}

In analogy to the known pharmacokinetic relationship between dose, clearance (CL) and area under the plasma concentration-time curve (AUC), the amount of released cortisol (A_C) is proportional to the area under the cortisol plasma concentration-time curve (AUC^{Cort}), with the clearance of cortisol (CL^{Cort}) as proportionality factor (Eq. 13).

$$A_C = CL^{Cort} \cdot AUC^{Cort} \qquad (13)$$

Thus, Eq. 10 is equivalent to Eq. 14.

$$\%CCS = \frac{AUC^{Supp,\,24}}{AUC^{Base,\,24}} = \frac{AUC^{Base,\,24} - AUC^{Therapy,\,24}}{AUC^{Base,\,24}} \qquad (14)$$

where $AUC^{Supp,\,24}$ is the difference between the area under the cortisol plasma concentration-time curves at baseline ($AUC^{Base,\,24}$) and during therapy ($AUC^{Therapy,\,24}$), all quantified over 24 hours. Fig.1 shows the $AUC^{Supp,\,\infty}$ and $AUC^{Supp,\,24}$ corresponding to $A_C^{Supp,\,\infty}$ and $A_C^{Supp,\,24}$ for single doses.

Estimation of %CCS by Eq. 14 has been performed in clinical studies by using the trapezoidal rule to estimate AUC^{Cort} from multiple cortisol plasma concentration measurements [17, 18]. From Eq. 13 follows, that estimating AUC^{Supp} with the trapezoidal rule as well as calculating A_C^{Supp} with the PK/PD-model will both result in the same values for %CCS, thereby allowing comparisons be-

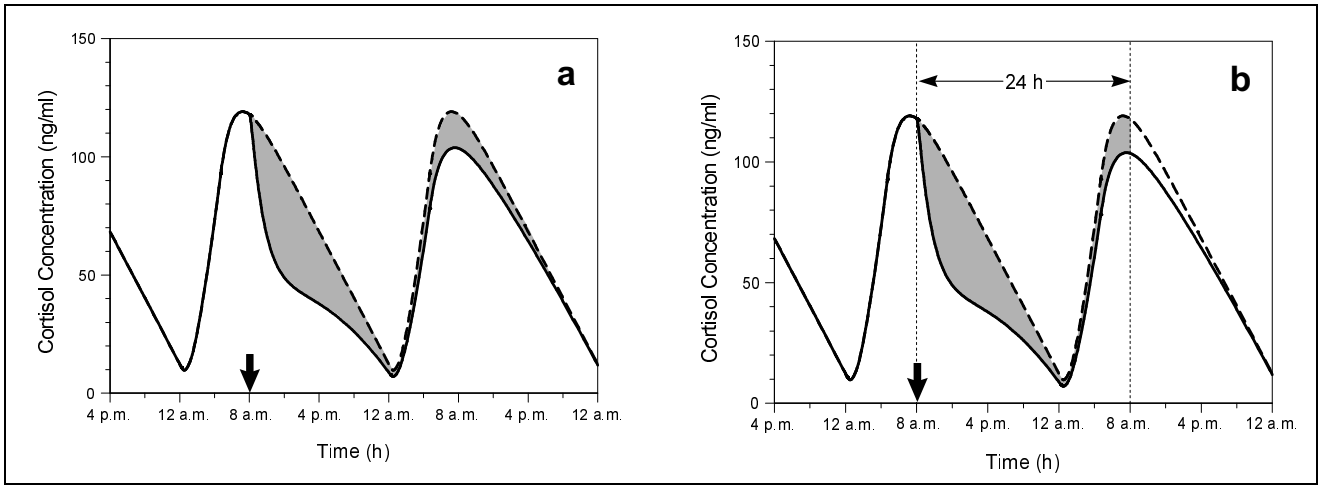

Fig. 1: Area (shaded) between the plasma concentration-time profiles of endogenous cortisol at baseline (- - - - -) and after exogenous corticosteroid administration (——), that corresponds to (a) the total amount of suppressed cortisol ( ) $A_C^{Supp,\infty}$ after a single dose (↓), and (b) the amount of suppressed cortisol $A_C^{Supp,24}$ within 24 h after a single dose

tween %CCS values measured in clinical studies and those simulated with the PK/PD-procedure. However, the PK/PD-based approach provides the advantage that it is not limited to clinically determined data but allows predictions beyond the existing data set for other dosing regimens.

2.3. Simulation of cumulative cortisol suppression for ICS

A total of 29 CCS observations from 8 reports of actual clinical trials were used to evaluate the predictive power of the PK/PD model. Table 1 lists the studies that reported the suppressive effects of ICS after a single inhalation.

Table 1: Suppressive effects of inhaled corticosteroids (ICS) on the HPA axis

Study*	Regimen (%CCS)		Cortisol monitoring method and comment
Lönnebo et al. [28]			
(N = 25)	FP (DH)	BUD (TBH)	AUC (0–20 h)
(o, r, cr, w ≥ 7)	1 mg (25%)	0.8 mg (26%)	Cortisol measured after a single dose at 10 p.m.
Grahnen et al. [29]			
(N = 25)	FP (DH)	BUD (TBH)	AUC (0–20 h)
(Part 1: o, r, cr, w = 4	0.25 mg (8%)	0.8 mg (16%)	Cortisol measured after a single dose at 10 p.m.
Part 2: o, nr)	0.50 mg (19%)		
	1 mg (28%)		
Möllmann et al. [26]			
(N = 6)	FP (MDI with spacer)	0.5 mg (34%)	AUC (0–24 h); all doses taken with charcoal except 250 µg.
(o, r, cr, w ≥ 14)	0.25 mg (24%)	3 mg (74%)	Cortisol measured after a single dose at 8 a.m
	1 mg (51%)		
Corren et al [25]			
(N = 12)	FP (MDI)	BUD (MDI)	AUC (0–24 h)
(o, r, p)	1 mg (35%)	1 mg (17%)	Cortisol measured after a single dose at 10 p.m.
	FLU (MDI)	TA (MDI)	
	1 mg (9%)	1 mg (20%)	
Rohatagi et al [7]			
(N = 12)	FP (MDI)	1 mg (40%)	AUC (0–24 h)
(o, r, cr, w = 7)	0.5 mg (20%)		Cortisol measured after a single dose at 8 a.m
Möllmann et al. [26]			
(N = 18)	FLU (MDI with spacer)		AUC (0–24 h)
(o, r, cr, w = 14)	8 A.M.	10 P.M.	Cortisol measured after a single dose at 10 p.m. OR 8 a.m. all
	0.5 mg (20%)	0.5 mg (10%)	doses taken with charcoal except 500 µg.
	1 mg (22%)	1 mg (14%)	
	2 mg (30%)	2 mg (22%)	
	3 mg (36%)	3 mg (33%)	
Brus [31]			
(N = 12)	FP (MDI)	BUD (MDI)	AUC (0–24 h)
(o, r, p)	0.88 mg (35%)	0.9 mg (17%)	Cortisol measured after a single dose at 10 p.m.
	FLU (MDI)	TA (MDI)	
	1 mg (7%)	1 mg (19%)	
Thorsson et al. [27]			
(N = 12)	FP (DH)		AUC (0–24 h)
(o, pr, cr, w = 14)	1 mg (47%)		Cortisol measured after a single dose at 8 a.m

*-All the studies were carried out in healthy volunteers
Definition of Abbreviations: N-Number of subjects, o-open label, r-randomized, p-parallel group, cr-crossover, w-washout (all washout periods are in days), pr-partially randomized, nr-not randomized, %CCS-% cumulative cortisol suppression, DH-Diskhaler, TBH-Turbohaler, MDI-metered dose inhaler, AUC- area under the cortisol concentration time curve

The simulations were carried out using an Excel® macro designed to calculate the %CCS using the described PK/PD model. The input variables were name of the drug, drug dose, time of dosing (clock time) and inhalation device. The output variable was %CCS.

Total corticosteroid plasma concentrations were described with a one-compartment body model with first order absorption for TA (Eq. 15) and a two-compartment body model with first order absorption for FLU, BUD and FP (Eq. 16).

$$C = C_1 \cdot \left(e^{-\lambda_1 \cdot t} - e^{-\lambda_2 \cdot t}\right) \quad (15)$$

$$C = C_1 \cdot e^{-\lambda_1 \cdot t} + C_2 \cdot e^{-\lambda_2 \cdot t} - (C_1 + C_2) \cdot e^{-\lambda_3 \cdot t} \quad (16)$$

where C is the total corticosteroid concentration in plasma, C_1 , C_2 and λ_1, λ_2, λ_3 are hybrid constants.

The parameters used for simulating the PK/PD profiles for FLU, TA, BUD and FP were obtained from previous studies as study population means and are listed in Table 2. FP is available in metered-dose inhaler (MDI), and Diskhaler™ and Diskus™ dry powder devices (DPI). These devices differ significantly in their lung deposition capacities. It has been reported that the bioavailability of FP is highest (26.4%) with the MDI, whereas the Diskhaler™ and Diskus™ are comparable at 11.9 and 16.6%, respectively [19]. Similarly, BUD is available in MDI and Turbohaler™ dry powder device (DPI) with bioavailabilities of 26% and 38%, respectively [20]. TA and FLU are available in MDI with 22% and 39% bioavailabilities respectively [21, 22]. For the purposes of simulation, the pharmacokinetic parameters were extrapolated for the respective devices and doses under the assumption of linear pharmacokinetics [23]. Mean baseline parameters for the cortisol linear release model were obtained from a previous publication that monitored cortisol plasma concentrations prior to exogenous corticosteroid therapy [7]. R_{max} was reported to be 2966 µg/h, t_{max} 20.7 h, t_{min} 16.2 h, and k_e^{Cort} 0.64 h^{-1}. Vd^{Cort} has been described as 33.7 l [24].

Fig. 2 shows the correlation between model predicted CCS and measured CCS values for the four drugs after inhalation. The predictions correlate fairly well with the measured data for all four drugs irrespective of the inhaler device or dose. The overall model prediction bias was found to be approximately −8%.

After single doses, CCS increased with increasing dose for all four corticosteroids. Equal administered amounts of the four drugs, however, produced different degrees of CCS according to their pharmacokinetic and pharmacodynamic properties in the order TA < FLU < BUD < FP.

The described model was able to adequately quantify the differences in cumulative suppressive effects when inhaled via different inhalers. For example, the model predicted values of 40% and 25% CCS after a single dose of 1 mg FP inhaled via MDI and Diskhaler®, respectively were consistent with the reported values [7, 25–29]. Similar differences between Turbohaler® and MDI were also accounted for by the model, however in this case the suppression was slightly higher for Turbohaler after a single dose of BUD [25, 28, 30, 31]. The model also accounted for the diurnal variation in cortisol suppression, which is pronounced for short half life drugs like BUD, FLU and TA [32].

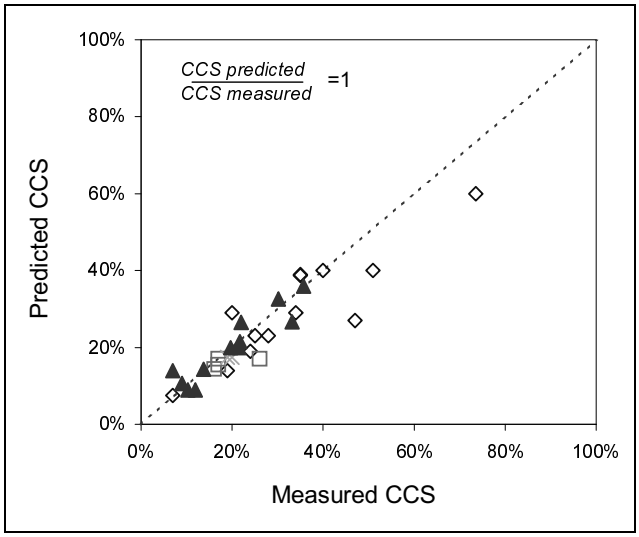

Fig. 2: Correlation between cumulative cortisol suppression (CCS) measured in clinical studies and predicted by simulation of the respective situation for FP (◇), BUD (□), FLU (▲) and TA (×) with the PK/PD-approach ($r^2 = 0.84$). The dotted line describes the ideal situation, where measured and predicted CCS would be identical

Since inhaled corticosteroids are administered on a regular rather than intermittent basis, results derived at steady-state conditions are more clinically relevant than those obtained from single dose studies. However an understanding of single dose effects is essential for forecasting the systemic bioactivity during long-term therapy. Further studies are needed to assess the predictive power of the PK/PD approach under steady state conditions.

These predictive capabilities may be used to optimize dosing regimens as well as to compare different corticosteroids with regard to cumulative systemic activity without or with a reduced number of clinical trials to be performed. Since the therapeutic safety of inhaled corticosteroids is predominantly governed by the magnitude of their systemic activity, the method also allows assessing the benefit-to-risk ratio of inhaled corticosteroids if additional data on efficacy are considered.

2.4. Conclusion

In conclusion, the predictive power of the described PK/PD-approach was evaluated and was found to adequately

Table 2: Pharmacokinetic and pharmacodynamic parameters used for the simulation of cumulative cortisol suppression during single dosing

Drug	Device	Dose (mg)	C_1 (ng/ml)	C_2 (ng/ml)	λ_1 (h^{-1})	λ_2 (h^{-1})	λ_3 (h^{-1})	$EC_{50,tot}$ (ng/ml)	f_u (%)	F_{inh} (%)	Ref.
Flunisolide	MDI	1	3.20	1.80	14.0	1.10	0.40	0.33	20	39[c]	[26]
Triamcinolone acetonide	MDI	1	1.80	–	1.2	0.25	–	0.72	29	22[d]	[33]
Budesonide	TBH	1	0.50	1.28	17.8	2.03	0.30	0.44[a]	12	38	[20]
Fluticasone propionate	DH	0.5	0.13	0.02	4.2	0.30	0.05	0.13[b]	10	12[e]	[35]

[a] – [34], [b] – [26], [c] – [22], [d] – [21], [e] – [19]

MDI – Metered dose inhaler, TBH – Turbohaler, DH – Diskhaler, C_1, C_2, λ_1, λ_2 and λ_3 are hybrid constants, $EC_{50,tot}$ – Concentration of drug that produces 50% of maximum suppression, f_u – unbound fraction of the drug in plasma, F_{inh} – Systemic bioavailability after inhalation, Ref-reference.

reflect the observed systemic effects of ICS in actual clinical trials. Future work is needed to evaluate the benefits of this method with regard to multiple doses and its applicability to asthmatics in clinical settings. By fully understanding the underlying mechanisms it will be possible to further improve their therapeutic index.

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