An Interactive Algorithm for the Assessment of Cumulative Cortisol Suppression During Inhaled Corticosteroid Therapy

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ABSTRACT The objective of the study was to develop an algorithm based on a pharmacokinetic-pharmacodynamic (PK/PD) modeling approach to quantify and predict cumulative cortisol suppression (CCS) as a surrogate marker for the systemic activity of inhaled corticosteroid therapy. Two Excel spreadsheets, one for single dose and another for steady-state multiple doses of inhaled steroids, were developed for predicting CCS. Four of the commonly used inhaled steroids were chosen for the purposes of simulation: fluticasone propionate (FP), budesonide (BUD), flunisolide (FLU), and triamcinolone acetonide (TAA). Drug-specific PK and PD parameters were obtained from previous single- and multiple-dose studies. In cases in which multiple-dose data were not available, the single-dose data were extrapolated. The algorithm was designed to calculate CCS based on 5 input parameters: name of drug, dose, dosing interval, time(s) of dosing, and type of inhaler device. In addition, a generalized algorithm was set up to calculate CCS based on clearance, volume of distribution, absorption rate, protein binding, pulmonary deposition, oral bioavailability, and unbound EC_{50} of the corticosteroid of interest. The spreadsheet allowed predictions of CCS for single doses as well as steady-state conditions. A simple method has been developed that facilitates comparisons between various drugs and dosing regimens and has the potential to significantly reduce the number of comparative clinical trials to be performed for

evaluating the short-term systemic activity of inhaled corticosteroids).

INTRODUCTION

The safety of corticosteroid therapy has been a topic of many investigations over a number of years. The delivery of modern corticosteroids topically has revolutionized the treatment and management of asthma and has reduced the incidence of systemic side-effects to a great extent. However, at high doses, inhaled corticosteroid therapy is not devoid of systemic effects, such as growth suppression, reduction in bone density, and cataracts (1). Hence, it becomes important to monitor for these effects, which is a difficult task considering the years it would require to establish and isolate the effects specifically related to the therapy.

Endogenous cortisol suppression, although not of direct clinical concern, has been shown in a number of studies to be a reliable surrogate marker for estimating the systemic activity of inhaled steroids. Testing methodologies such as the integrated cortisol levels (cortisol area under the curve [AUC]) by multiple blood sampling at frequent intervals and the corticotropin stimulation test are now well-established as sensitive and early indicators of adrenal suppression by inhaled steroids (2,3). In clinical settings, the degree of cumulative cortisol suppression (CCS) is usually reported as the difference in the AUCs (calculated using the trapezoidal rule) between the placebo and the drug-treated groups over a 24-hour period either after a single or during multiple doses of the inhaled steroid. This approach is a descriptive method only, and its ability to provide predictive clinical outcomes is fairly limited by the complexities of the number of factors involved. In other words, a large number of clinical studies would have to be conducted in order

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to account for differences in dose, inhaler device, patient population, duration, frequency, timing, route of administration, and relative potency of the administered corticosteroid. To address this issue, several pharmacokinetic/pharmacodynamic (PK/PD) modeling approaches have been developed that describe the circadian rhythm in the plasma concentration-time course of endogenous cortisol and its suppression after administration of exogenous corticosteroids (4-10).

A clinically valuable, integrated, $E_{\max}$ -based PK/PD model has also been developed and reported in several clinical trials that has been shown to predict cumulative cortisol suppression with good accuracy (11). The objective of this research was to extend the PK/PD approach by designing a computer algorithm to facilitate predictions and comparisons of CCS involving various clinically relevant situations in inhaled corticosteroid therapy.

MATERIALS AND METHODS

Microsoft Excel software (Microsoft, Redmond, WA) was used to develop the algorithm. Four of the commonly used inhaled steroids were chosen for the purposes of simulation: fluticasone propionate (FP), budesonide (BUD), flunisolide (FLU), and triamcinolone acetonide (TAA). The average drug-specific PK and PD parameters were obtained from previously published single- and multiple-dose studies. For cases where multiple-dose data were not available, the single-dose data were extrapolated under the assumption of linear pharmacokinetics. Data on the systemic bioavailability of commercially available formulations of the 4 steroids (eg, dry powder inhalers, metered dose inhalers) were also obtained from the literature.

The integrated PK/PD modeling approach is described in detail elsewhere. Briefly, the circadian rhythm in endogenous cortisol plasma concentrations, which is generated by a complex pulsatile release pattern, is described by a linear release rate model. The change in cortisol plasma concentrations (C_{Cort}) at baseline situation is then described by Equation 1, where R_c is the release rate

(concentration/time) and k_e^{Cort} is the first-order elimination rate constant for cortisol.

$$\frac{dC_{Cort}}{dt} = R_c - k_e^{Cort} \cdot C_{Cort} \quad (Eq. 1)$$

Based on Equation 1, an indirect response model is then deducted to characterize the suppression of endogenous cortisol concentrations during exogenous corticosteroid therapy, thereby relating the corticosteroid concentrations to the effect on cortisol release according to Equation 2.

$$\frac{dC_{Cort}}{dt} = R_c \cdot \left(1 - \frac{E_{\max} \cdot C}{EC_{50} + C} \right) - k_e^{Cort} \cdot C_{Cort} \quad (Eq. 2)$$

$E_{\max}$ 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 whose pharmacokinetic profile is described using either a 1- or a 2-compartment body model with first-order absorption. Because the maximum possible effect is complete, suppression of cortisol release, $E_{\max}$ is fixed at 1.

RESULTS AND DISCUSSION

Two spreadsheets (2 separate Excel files) were designed to quantify CCS; one for single dose and another for steady-state multiple doses (see Appendix I for the algorithm). Five input parameters were used for quantifying percentage of CCS: name of the drug, dose, dosing interval (for multiple dosing), time(s) of dosing, and type of inhaler device. Figure 1 shows the format of the Excel spreadsheet.

Instructions on using the spreadsheet are given in Appendix II. Two cases (A and B) with identical algorithms were set up adjacent to each other on the spreadsheet to facilitate comparisons between different combinations of the input parameters. The outcome variables were percentage of CCS (ie, the percentage difference in the areas under the plasma cortisol concentration-time curves calculated over 24 hours between the placebo and the drug-treated groups), the terminal half-life of the drug, and the overall systemic availability.

Figure 1. Screen capture of the Excel spreadsheet to calculate the cumulative cortisol suppression of inhaled steroids. For detailed explanation, see Appendix II.

For single-dose situations, cortisol AUC was calculated from the time of the dose until 24 hours later. For multiple-dosing situations, the cortisol AUC was calculated during a 24-hour period when 1 or more steady-state doses of the drug were administered. The spreadsheet-based predictions were found to be consistent with those obtained using a different software, thereby confirming the validity of the (Table 1 and Figure 2).

Table 1. Validation of the Excel algorithm by comparing the spreadsheet-based predictions with those from a commercial software program (Scientist; Micromath, Salt Lake City, Utah) employed in reference 11.

Regimen	Predicted CCS (%)	
	Excel	Scientist
Single dose		
FP 250 µg at 8 am	18.5	18.6
FP 250 µg at 8 pm	12.9	12.9
FP 1000 µg at 8 am	40.3	40.3
FP 1000 µg at 8 pm	34.9	35.1
Multiple steady state		
FP 250 µg at 8 am and 8 pm	33.2	33.1
FP 1000 µg at 8 am and 8 pm	64.8	64.5
FP 250 µg at 10 am and 10 pm	33.1	32.9
FP 1000 µg at 10 am and 10 pm	64.9	64.6

Figure 2. Validation of the Excel algorithm for predicting the cortisol concentration time profiles under various dosing situations. The lines (short dash, long dash, and solid) indicate the profile generated using the commercial software and the points (square, diamond, and circle) indicate the spreadsheet-based predictions for baseline and fluticasone propionate (FP) 250- and 1,000-µg treatments, respectively, during (A) a single dose at 8 am, (B) a single dose at 8 p.m., (C) steady-state doses at 8 a.m. and 8 p.m., and (D) steady-state doses at 10 a.m. and 10 p.m.

The applicability of the spreadsheet is illustrated using the following example, in which the influence of administration time of the steroid on CCS was assessed. Using simulations, it has been previously shown for FP and FLU that dose timing, especially of single doses, is a pivotal influential factor that determines the extent of cortisol suppression (12). Using the spreadsheet, the approach was also extended for TAA and BUD for both single-dose as well as steady-state situations in order to evaluate the diurnal variation in CCS.

Figure 3 shows the simulated relationship between administration time and CCS after inhalation of single doses of 500 and 1,000 µg of TAA, BUD, and FLU and 250 and 500 µg of FP.

A circadian pattern in CCS was observed, with maximum CCS occurring when the drugs were administered in the early morning around 3 to 4

a.m. and minimum CCS when administered in the afternoon between 4 and 7 p.m.

Figure 3. Relationship between daily administration time and cumulative cortisol suppression (CCS %) compared with baseline within 24 hours after inhalation of single doses of 500 µg (blue) and 1,000 µg (red) of triamcinolone acetonide (TAA), flunisolide (FLU), budesonide (BUD), and 250 µg (blue) and 500 µg (red) of fluticasone propionate (FP).

This pattern is a result of the temporal arrangement of the systemic drug activity in relation to endogenous cortisol release. On one hand, CCS reaches its maximum if the time of maximum cortisol release in the early morning falls within the period of high systemic activity. Conversely, CCS is minimized if the period of high systemic activity is located around the time of minimum cortisol release in the late evening, several hours before the release maximum. Because the period of systemic activity is modulated by the corticosteroid's terminal half-life, it is shorter for corticosteroids with shorter terminal half-lives,

such as FLU (1.6 hours), BUD (3.0 hours), and TAA (3.6 hours) and longer for drugs with long terminal half-lives such as FP (11.7 hours). Hence, in order to minimize systemic activity during the period of increased endogenous cortisol release (early morning), the optimum administration time was slightly shifted from late afternoon around 7 p.m. for FLU to early afternoon at 4 p.m. for FP. Despite the fact that FP exhibited diurnal rhythms similar to the other drugs, its degree of fluctuation of CCS was much less pronounced than theirs.

Figure 4. Relationship between administration time and cumulative cortisol suppression (CCS %) after inhalation of single doses of FLU (850 µg, triangle), BUD (1,150 µg, diamond), TAA (1,350 µg, square), and FP (400 µg, x). The doses were calculated to produce an identical 25% CCS when administered at 8 a.m. via commercially available metered-dose inhalers. See Figure 3 caption for explanation of abbreviations.

This pattern is readily observed in Figure 4 which relates the administration time with CCS after administration of equipotent doses of FP, FLU, TAA, and BUD, determined by calculating the dose delivered via a metered dose inhaler (MDI), using literature values of overall systemic bioavailability, that caused 25% CCS when administered at 8 a.m. CCS caused by a single dose of BUD or FLU is minimized 2-fold or more if administered at 8 p.m. instead of 8 a.m., whereas the change in CCS after a FP dose at 8 p.m. is relatively insignificant (approximately 10%) compared to the 8 a.m. dose.

Hence, without considering the administration time, one might conclude that the HPA suppression between FP and BUD or FP and FLU is either equivalent or has a 2:1 ratio (Figure 5).

Figure 5. Fluctuation in percentage of cumulative cortisol suppression when single doses of FP (blue), BUD (red), and FLU (yellow) that produced 25% CCS when administered at 8 a.m. were administered at 8 p.m. See Figure 3 caption for explanation of abbreviations.

These observations have a potentially profound effect on the comparability of clinical studies regarding the systemic activity of these steroids. Because multiple and not single dosing regimens are used for inhaled steroids, results derived at steady-state conditions are more clinically relevant than those obtained from single-dose studies. An approach similar to that employed for single dosing was used to assess the time dependency of CCS during multiple-bid dosing at steady state, with the dosing regimen following a circadian periodicity, ie, doses and dosing times identical for each day (eg, 500 μ g given at 8 a.m. and at 8 p.m.). Simulations were performed for 500- and 1,000- μ g steady-state twice daily (BID) doses of BUD, TAA, and FLU and 250- and 500- μ g doses for FP inhaled at various combinations of times (eg, 8 a.m. and 8 p.m.; 9 a.m. and 9 p.m.). The results indicate that the systemic activity of inhaled steroids during multiple BID dosing is most likely not influenced by the times of administration (Figure 6).

Figure 6. Relationship between daily administration times of a BID regimen and cumulative cortisol suppression compared with baseline during inhalation of steady-state doses of 500 μ g (blue) and 1,000 μ g (black) of TAA, FLU, and BUD and 250 μ g (blue) and 500 μ g (black) of FP. See Figure 3 caption for explanation of abbreviations.

However, during once-daily dosing, this may not be the case because the drugs are rapidly eliminated, resulting in negligible carryover effect from one dose to another to mask the influence of administration time. A few clinical studies have also used the 24-hour cortisol AUC after the last dose of a multiple-bid dosing regimen (13-16). In such cases, depending on the study design, there may be considerable differences in cortisol suppression depending on the administration time of the last dose. The spreadsheet is very useful in identifying such complexities.

In addition to simulating CCS for the 4 inhaled steroids, a generalized algorithm was also designed to predict CCS based on PK/PD parameters such as clearance, volume of distribution, absorption rate, protein binding, pulmonary deposition, oral bioavailability, and unbound EC_{50} (see Appendix II for instructions). Additionally, CCS could also be evaluated for orally administered steroids, provided the necessary PK/PD parameters are available.

In summary, a simple-to-handle, interactive, Excel-based algorithm has been developed to assess the cumulative cortisol suppression during inhaled corticosteroid therapy. Although the model may not be able to provide individualized predictions of CCS in all cases, it gives a good estimate of the respective population averages that may aid in designing meaningful comparative studies or allow for comparative predictions of different treatment schedules. Because 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. The algorithm could also serve as an educational tool in understanding the complexity involved in predicting the systemic exposure of inhaled corticosteroids. Future research efforts should involve the correlation of long-term safety profiles of these compounds with the 24-hour serum cortisol concentrations to validate their use as surrogate markers. By fully understanding the underlying mechanisms, it will be possible to optimize the safety profile of corticosteroids.

APPENDIX I.

Algorithm for the determination of cumulative cortisol suppression (% CCS) of inhaled steroids using Microsoft Excel.

- Scale is a parameter used for equally dividing the time interval over 1,000 time points. It is calculated in the following manner: Let cell number 1 be given the value 1. Cell number 2 (next row, same column) is calculated by simply adding 1 to the previous cell (ie, cell number 1). Similarly, cell number 3 gets the

value 1 + value in cell number 2, and so forth, until 1,000 points are generated.

- Absolute time, (generation of 1,000 time points)

$$T_{\text{abs}} = \text{Scale}/1,000 * \text{Number of hours of simulation}$$

- Let M be the number of 24-hour intervals in the simulation.
- If $T_{\text{abs}} \leq T_{\text{max}}$ (time of maximum release of cortisol), then $M = 0$; otherwise $M = \text{Truncate}[(T_{\text{abs}} - T_{\text{max}})/24 + 1]$, where "Truncate" truncates a number to an integer by removing the fractional part of the number.

$$\text{Time, } t = T_{\text{abs}} - (M * 24)$$

The model describes the daily cortisol release (R_c in concentration/time) at baseline situation with 2 straight lines (R_{c1} and R_{c2}). 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} (R_{c1})

$$R_{c1} = \frac{R_{\text{max}}}{V_d^{\text{Cort}} \cdot (t_{\text{max}} - t_{\text{min}} - 24)} \cdot t - \frac{R_{\text{max}} \cdot t_{\text{min}}}{V_d^{\text{Cort}} \cdot (t_{\text{max}} - t_{\text{min}} - 24)} \quad (\text{Eq. 3})$$

where V_d^{Cort} is the volume of distribution of cortisol (33.7 L) and t is the time after cortisol monitoring was initiated ($t_0 = 8$ am). For the time between t_{min} and t_{max} , R_c increases according to Equation 4 (R_{c2}).

$$R_{c2} = \frac{R_{\text{max}}}{V_d^{\text{Cort}} \cdot (t_{\text{max}} - t_{\text{min}})} \cdot t - \frac{R_{\text{max}} \cdot t_{\text{min}}}{V_d^{\text{Cort}} \cdot (t_{\text{max}} - t_{\text{min}})} \quad (\text{Eq. 4})$$

IF $T_{\text{min}} \geq t$, THEN let $F1 = 1$; otherwise $F1 = 0$.

Similarly, IF $T_{\text{min}} \leq t$, THEN let $F2 = 1$; otherwise $F2 = 0$.

- Release rate before drug administration:

$$RR = F1 * R_{c1} + F2 * R_{c2}.$$

- Release rate after drug administration:

$$RR_{\text{drug}} = RR * \Delta t * [1 - E_{\text{max}} * C / (EC_{50} + C)],$$

where Δt is the time interval between 2 adjacent times.

- Amount of cortisol eliminated over time, calculated using the trapezoidal rule:

$$E_t = CL^{\text{Cort}} * [C_j + C_{j+1}] / 2 * \Delta t; (C_0 = 120 \text{ ng/mL}),$$

where C_j and C_{j+1} are concentrations at times j and $j + 1$.

- Plasma cortisol concentrations before drug administration:

$$C_{\text{baseline}} = [C_j * V_d + (RR * \Delta t) - E_t] / V_d; (\text{units} - \text{ng/mL})$$

- Plasma cortisol concentrations after drug administration:

$$C_{\text{drug}} = [C_j * V_d + (RR_{\text{drug}} * \Delta t) - E_t] / V_d; (\text{units} - \text{ng/mL})$$

- Calculation of the number of doses.

Until the time of administration of the dose, the concentration of the drug $C = 0$.

IF $\{T_{\text{adm}} + (\text{Dosing interval } (\tau) * \text{Total number of doses})\} \leq T$

THEN $N = \text{Total number of doses}$ ELSE

$$N = \text{INTEGER} \{(T - T_{\text{adm}}) / \tau + 1\}$$

Time (R_{time}) to be used for calculating drug concentration,

IF $T < T_{\text{adm}}$ then $R_{\text{time}} = 0$, ELSE $R_{\text{time}} = \{T - T_{\text{adm}} - (N - 1) * \tau\}$

Simulating plasma drug concentrations after single doses:

IF $T_{\text{adm}} \geq T$, Then 0 ELSE

IF number of compartments in the model (excluding depot compartment) = 1

THEN use One-Compartment Body Model

$$C = C_1 * (e^{-\lambda_1 * t} - e^{-\lambda_2 * t})$$

ELSE use Two-Compartment Body Model

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

where C_1 and C_2 are unbound intercepts (ng/mL) and λ_1 , λ_2 , and λ_3 are hybrid constants (h^{-1}).

Simulating plasma drug concentrations after multiple steady-state doses:

IF $T_{\text{adm}} \geq T$, THEN 0 ELSE

IF Number of compartments in the model (excluding depot compartment) = 1

THEN use One-Compartment Body Model

$$C = C_1 * \left(e^{-\lambda_1 * t} * \frac{1 - e^{-n * \lambda_1 * \tau}}{1 - e^{-\lambda_1 * \tau}} - e^{-\lambda_2 * t} * \frac{1 - e^{-n * \lambda_2 * \tau}}{1 - e^{-\lambda_2 * \tau}} \right)$$

ELSE use Two-Compartment Body Model

$$C = C_1 * e^{-\lambda_1 * t} * \frac{1 - e^{-n * \lambda_1 * \tau}}{1 - e^{-\lambda_1 * \tau}} + C_2 * e^{-\lambda_2 * t} * \frac{1 - e^{-n * \lambda_2 * \tau}}{1 - e^{-\lambda_2 * \tau}} - (C_1 + C_2) * e^{-\lambda_3 * t} * \frac{1 - e^{-n * \lambda_3 * \tau}}{1 - e^{-\lambda_3 * \tau}}$$

where C_1 and C_2 are unbound intercepts (ng/mL) and λ_1 , λ_2 , and λ_3 are hybrid constants (h^{-1}) and n is the number of doses. For steady state, $n \rightarrow \infty$.

Determination of PK model parameters for the generalized algorithm from clearance, volumes of distribution (V_c , V_{dss} , and V_{darea}), absorption rate constant (first order), protein binding, oral bioavailability, pulmonary distribution.

$$K_{10} = \frac{CL}{V_C}$$

$$K_{21} = \frac{V_c \cdot (K_{10} - \beta)}{(V_{darea} - V_{dss})}$$

$$\alpha = \frac{K_{21} \cdot K_{10}}{\beta}$$

$$\beta = \frac{CL}{V_{darea}}$$

$$K_{12} = \alpha + \beta - K_{21} - K_{10}$$

IF = Pulmonary deposition + (1-pulmonary deposition) * Oral bioavailability

$$C_1 = \frac{D \cdot F \cdot f_u \cdot K_a \cdot (K_{21} - \alpha)}{V_c \cdot (\alpha - \beta) \cdot (\alpha - K_a)}$$

$$C_2 = \frac{D \cdot F \cdot f_u \cdot K_a \cdot (K_{21} - \beta)}{V_c \cdot (\alpha - \beta) \cdot (K_a - \beta)}$$

where K_a - absorption rate constant (or λ_3), K_{12} , K_{21} , K_{10} are transfer-rate constants, α (or λ_1) and β (or λ_2) are hybrid constants, CL is clearance after iv administration, V_c is volume of central compartment, V_{dss} - volume of distribution at steady state, V_{darea} - terminal volume of distribution, F is overall systemic availability, f_u is unbound fraction, and D is dose.

(Note: If pulmonary deposition is given a value of 0, then the system can be used for orally administered steroids if the PK/PD parameters are available.)

Determination of % CCS

$$\%CCS = \frac{AUDC - AUBC}{AUDC} \cdot 100$$

where, AUBC and AUDC are the areas under the curve of the baseline and the drug-treated groups either over a 24-hour period immediately following a single dose or during short term multiple-dose treatment. They are calculated using the trapezoidal rule.

$$AUDC = \int_{t_{adm}}^{t_{adm}+24} C_{drug} \cdot dt \text{ and}$$

$$AUBC = \int_{t_{adm}}^{t_{adm}+24} C_{baseline} \cdot dt$$

APPENDIX II.

Instructions on using the Excel spreadsheet to assess the CCS of inhaled steroids

Two Excel files were developed: one for single doses (CCS-Single Dose) and another for steady-state multiple doses (CCS-Multiple Dose). Dosing interval is not included in the single-dose file. Use Figure 1 to follow the instructions.

Interactive Algorithms

CCS-Single Dose

CCS-Multiple Dose

1. Input section

The input section of the spreadsheet is indicated in Figure 1. Two situations (A in blue and B in red) having identical functions are provided to enable comparisons.

Drug name. The abbreviations FP for fluticasone propionate, BUD for budesonide, TAA for triamcinolone acetonide, and FLU for flunisolide can be entered in the corresponding spaces for situations A and B. They are not case sensitive.

Dose. Dose needs to be entered in micrograms (eg, 1,000).

Time of administration. Time of administration is entered as clock time (8 for 8 am, 20 for 8 p.m., 24 for midnight, etc.).

Dosing interval. Applicable only for steady-state multiple doses. They range from 1-24 hours (eg, 12 for drug administered every 12 hours beginning with

the time of first dose indicated in the time of administration cell).

Device. FP is commercially available in metered dose (MDI), Diskhaler (DH) (GlaxoWellcome, Greenford, UK) and Diskus (DSKS) (GlaxoWellcome) inhalers. Hence for FP, the numbers 1 or 2 or 3 corresponding to MDI, DH, and DSKS can be entered. The software returns a 0% CCS if the number 4 is entered because FP is not available in the Turbohaler lung device (AstraZeneca, Lund, Sweden). Similarly, only numbers 1 and 4 are applicable for BUD, because it is not available in the DH or DSKS devices. TAA and FLU are available in the MDI only. Hence, numbers 2 to 4 will return a % CCS of 0 for TAA and FLU.

2. Parameters section

Parameters corresponding to the respective drugs entered in the "Input" section are displayed. This section is for display only and cannot be changed.

3. Graphics section

The graphics are directly linked to the situations and therefore refresh automatically whenever the parameters are changed.

4. Output section

Displays the output for both situations. The output parameters are % CCS, the terminal half-life, and overall bioavailability. The third column in this section (titled NEW) is based on parameters in the "NEW" section.

5. NEW section

This is the generalized algorithm designed to calculate CCS based on PK/PD parameters. Parameters such as the dose and clearance can be altered and the output can be observed in the third column of the "output" section. In this section, CCS can be calculated for an orally administered steroid as well if the PK/PD parameters are known. (Note: The pulmonary deposition is set to zero in this case.)

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