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Modeling Interactions between Adrenal Suppression and T-Helper Lymphocyte Trafficking during Multiple Dosing of Methylprednisolone

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A physiologic pharmacodynamic model was developed to jointly characterize the effects of corticosteroid treatment on adrenal suppression and T-helper cell trafficking during single and multiple dosing in asthmatic patients. Methylprednisolone (MP), cortisol, and T-helper cell concentrations obtained from a previously published study during single day and 6 days of multiple dosing MP treatment were examined. The formation and disposition kinetics of MP were described with a compartmental model. The biorhythmic profile of basal cortisol secretion rate was analyzed using a recent Fourier approach based on circadian harmonics. A three-compartment loop model was proposed to represent three major T-helper cell pools: blood, extravascular site, and lymph nodes. T-helper cell synthesis and degradation rate constants were obtained from the literature. The suppressive effects of cortisol and MP on T-helper cell concentrations were described with a joint additive inhibition function altering the cell migration rate from lymph nodes to blood. The model adequately described both plasma cortisol profiles and T-helper cells in blood after single and multiple doses of MP. The potency of MP for suppression of cortisol secretion was estimated as IC_{50} = 0.8 ng/ml. The biorhythmic nature of the basal T-helper cells in blood was well described as under the influence of basal circadian cortisol concentrations with IC_{50} = 79 ng/ml. The model fitted potency of MP for suppression of T-helper cells was IC_{50} = 4.6 ng/ml. The observed rebound of T-helper cells in blood can also be described by the proposed model. The rhythm and suppression of plasma cortisol and T-helper cells before and during single and multiple dose MP treatment were adequately described by these extended indirect response models.

KEY WORDS: T-helper cells; trafficking; rebound; corticosteroids; circadian rhythm; methylprednisolone; drug interactions; pharmacokinetics; pharmacodynamics.

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INTRODUCTION

The trafficking of lymphocytes between blood and extravascular pools occurs throughout their life-span. Newly formed lymphocytes migrate from bone marow via the thymus to lymph nodes during which they undergo maturation. This migration process may take a period of weeks prior to their full differentiation into T lymphocytes. The trafficking of mature non-dividing lymphocytes involves migration from blood into lymphoid tissue and back to the blood. This trafficking process is relatively fast and can be measured in hours (1). The T lymphocytes in tissues move via the lymphatic system to blood. Therefore, the drainage of lymphocytes into blood from the thoracic duct lymph is the predominant process. The extent of lymphocyte trafficking through the blood is significant; in a 24-hr period the total mass of lymphocytes in blood can be replenished several times (2,3). The ability of lymphocytes to exchange between the blood and tissues is essential to enable the immune system to react to antigens virtually anywhere in the body. This allows lymphocytes to be concentrated at sites where they can most effectively respond to and eliminate foreign antigens (4).

Corticosteroids trigger multiple effects in the body. In addition to inhibition of cortisol secretion, one of the rapid effects of synthetic corticosteroids is producing lymphocytopenia (5). Lymphocytes in blood exhibit a circadian rhythm (6). This rhythm is partly caused and regulated by cortisol concentrations, which has a similar but opposite circadian profile (7). Among the lymphocytes, the T-helper cells are the most sensitive subset to corticosteroid treatment (8) and reside in the heart of the immune cross-talking network. Therefore, characterizing the T-helper lymphocyte temporal profile in response to corticosteroids is of importance for understanding the action of this important class of drugs.

The effort to model cortisol concentrations and lymphocyte trafficking under the influence of corticosteroids has been an evolutionary process. Dunn *et al.* (9) used a cosine function to quantitate the circadian rhythm of cortisol concentrations and the trafficking of T-helper cells from extravascular sites to blood. These two sets of pharmacodynamic (PD) data were modeled separately with the assumption that trafficking of T-helper cells to blood followed a zero-order process. Explicit equations were employed to describe the change in T-helper cells as affected by the corticosteroid. Fisher *et al.* (10) applied the concepts of indirect response modeling (11) on T-helper cell dynamics. Corticosteroids were assumed to inhibit the circadian input of cells into blood. The combined action of dexamethasone and hydrocortisone effects on lymphocyte distribution in blood was suggested by Braat *et al.* (12) based on a competitive interaction model of Ariens and Simonis (13). A multiple-dosing study of methylprednisolone (MP) was

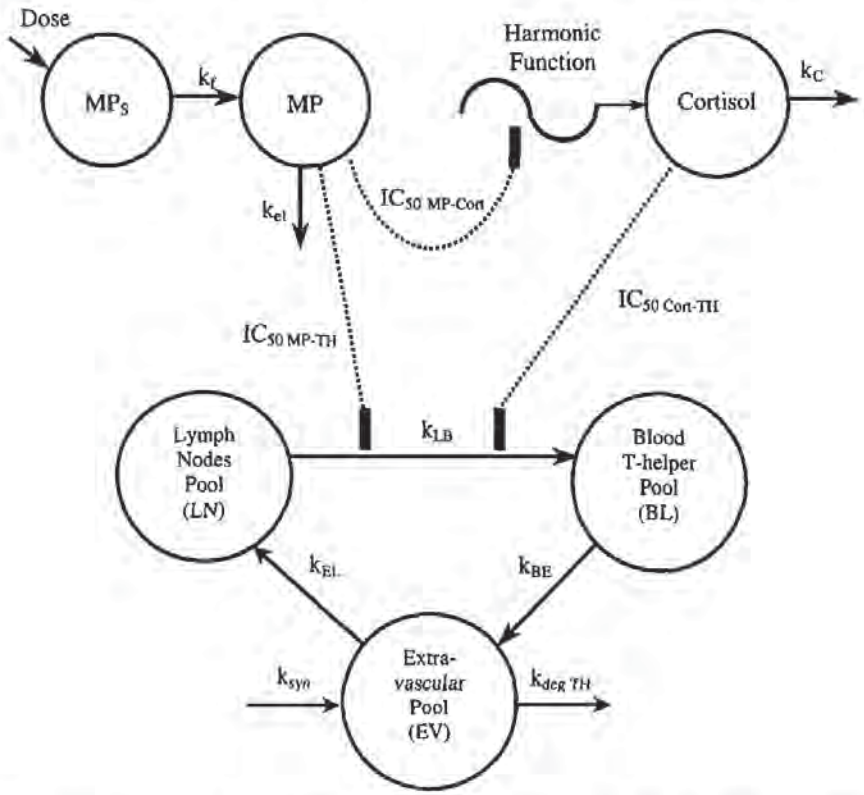

Fig. 1. Schematic diagram of the joint cortisol and T-helper cell trafficking models.

published by Milad *et al.* (14) in which the T-helper lymphocyte time profile was described with a model similar to Fisher *et al.* (10) and included the joint competitive effects of exogenous and endogenous corticosteroids. However, some important features of these data had not been explored. First, a higher degree of T-cell suppression occurred after multiple dosing. After seven doses of MP, the predose T-helper cell concentration showed a higher value than baseline with a pronounced rebound after the last dose. Moreover, differences in estimated IC_{50} values were found when separately fitting the single and multiple-dose data. In this paper, data from Milad *et al.* (14) were reexamined to develop a physiological explanation and model for characterizing the effects of MP on cortisol suppression and their dual role in T-helper cell dynamics.

THEORETICAL

The proposed model is shown in Fig. 1. Blood (TH_{BL}), extravascular (TH_{EV}), and lymph node (TH_{LN}) pools as well as natural production (k_{syn}) and loss (k_{deg}) of T-cells along with the joint effects of exogenous and

endogenous corticosteroids are utilized to explain the natural baseline circadian rhythms, acute suppression, and rebound phenomena of the time profiles of blood T-helper cells during multiple dosing with methylprednisolone.

Pharmacokinetics

The kinetics of MP after doses of its prodrug have been well characterized (14,15). The soluble prodrug, methylprednisolone sodium succinate (MPs) was rapidly metabolized with a first-order rate (k_f) to its active form. The elimination of methylprednisolone was best described by a monoexponential decline. The equations used were

$$\frac{dMPs}{dt} = -k_f \cdot MPs \tag{1}$$

$$\frac{dMP}{dt} = k_f \cdot MPs - \frac{CL}{V} \cdot MP \tag{2}$$

where CL and V are the systemic clearance and volume of distribution of MP. Model-estimated parameters were k_f, CL, and V.

Circadian Rhythmic Secretion Rate of Cortisol

Over the past 5 years, various extensions of indirect response models have been proposed to describe the circadian nature of cortisol time profiles (15–19). Each of these models has its unique features, advantages, and disadvantages in regard to characterizing the nature of cortisol secretion. A review and comparison of these models was done by Chakraborty *et al.* (20). Among these models, the multicomponent harmonic function with a 24-hr rhythm was the most accurate model for the cortisol secretion rate. A new Fourier analysis method with a circadian (i.e., 24 hr) constraint was used to describe the secretion rate of cortisol (19). Briefly, the baseline cortisol concentrations ($C_{Cort}(t)$) are represented as the Fourier series

$$C_{Cort}(t) = a_0 + \sum_{n=1}^{\infty} [a_n \cos(2\pi nt/24) + b_n \sin(2\pi nt/24)] \tag{3}$$

where a_0, a_i, and b_i are Fourier coefficients which can be obtained by fitting Eq. (3) to baseline or placebo data. The value of n represents the frequency of the harmonic function. For example, when $n = 0$, the harmonic function describes a steady baseline value of a_0, when $n = 1$, the harmonic function has a period of 24 hr; when $n = 2$, the period is 12 hr; and so on. The L^2-norm approximation method was used to derive the secretion rate function, $R_{Cort}(t)$. The selection of the numbers of harmonics which are best to

describe the baseline cortisol concentrations was determined by the percentage contribution of each harmonic to the overall data fitting. To generate the cortisol secretion rate, the following equation was applied:

$$R_{\text{Cort}}(t) = \frac{dC_{\text{Cort}}}{dt} + k_{\text{C}} \cdot C_{\text{Cort}} \tag{4}$$

where k_{C} is the cortisol disposition rate constant. Endogenous cortisol synthesis and loss is then described by

$$\frac{dC_{\text{Cort}}}{dt} = R_{\text{Cort}}(t) \cdot I(t) - k_{C} \cdot C_{\text{Cort}} \tag{5}$$

where the inhibition function ($I(t)$) is added when MP is present. The pharmacodynamics is related to MP and cortisol via

$$I(t)_{\text{MP-Cort}} = -\frac{C_{\text{MP}}}{IC_{\text{MP-Cort}} + C_{\text{Mp}}} \tag{6}$$

Equation (6) depicts the effect of MP on the suppression of cortisol secretion rate. The circadian secretion rate of cortisol is inhibited decreasing hyperbolic function ($I(t)_{\text{MP-Cort}}$) with methylprednisolone concentration from Eq. (2) as the driving force.

Circadian Rhythmic Trafficking of T-Helper Cells

Movement of *TH* cells between the three pools is given by

$$\frac{dTH_{\text{EV}}}{dt} = k_{\text{syn}} - k_{\text{deg TH}} \cdot TH_{\text{EV}} - k_{\text{EL}} \cdot TH_{\text{EV}} + k_{\text{BE}} \cdot TH_{\text{BL}} \tag{7}$$

$$\frac{dTH_{\text{LN}}}{dt} = k_{\text{EL}} \cdot TH_{\text{EV}} - k_{\text{LB}} \cdot I(t)_{\text{Cort-TH}} \cdot TH_{\text{LN}} \tag{8}$$

$$\frac{dTH_{\text{BL}}}{dt} = k_{\text{LB}} \cdot I(t)_{\text{Cort-TH}} \cdot TH_{\text{LN}} - k_{\text{BE}} \cdot TH_{\text{BL}} \tag{9}$$

The inhibition function related to cortisol concentrations is

$$I(t)_{\text{Cort-TH}} = 1 - \frac{C_{\text{Cort}}}{IC_{50\,\text{Cort-TH}} + C_{\text{Cort}}} \tag{10}$$

where $IC_{50\,\text{Cort-TH}}$ reflects the cortisol concentration producing a 50% change in the rate constant, k_{LB}.

The synthesis rate of T-helper cells follows a zero-order rate constant (k_{syn}) while the elimination of these cells from blood is by a first-order rate

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