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Pharmacokinetics and pharmacodynamic modeling of direct suppression effects of methylprednisolone on serum cortisol and blood histamine in human subjects

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Abstract

Pharmacodynamic models for “directly suppressive” effects of methylprednisolone are based on the premise that receptor interactions of steroids are followed by immediate suppression of either the circadian secretion of cortisol or the constant rate recirculation of histamine-containing basophils that persists until inhibitory concentrations of methylprednisolone disappear. Methylprednisolone doses of 0, 10, 20, and 40 mg were given as the 21-succinate sodium salt in a balanced crossover study to six normal men. Plasma steroid concentrations and blood histamine were measured simultaneously. Both forms of methylnisolone exhibited linear kinetic parameters. One dynamic model quantitates the baseline circadian pattern and the decline and return of cortisol with similar parameter estimates for all three dose levels. A similar model describes the monoexponential decline and the log-linear return to steady-state baseline of blood histamine. Similar inhibitory concentration values for both effects approximated the equilibrium dissociation constant of in vitro steroid receptor binding. The new models are more physiologically appropriate for these steroid effects than three other models that are commonly employed in pharmacodynamics. Steroid effects generally appear to be receptor mediated with either nongene immediate responses or gene-mediated delayed effects. These models allow quantitation of the rapid effects of steroids with simple equations and common fitted parameters for all steroid dose levels.

The diverse immunosuppressive and the antiinflammatory effects of glucocorticoids in human beings complicate the development of realistic and comprehensive kinetic and dynamic models for this class of agents. This is partly because of the complex mode of action of corticosteroids, which involves receptor binding and the formation of second messengers and proteins (which is mediated by deoxyribonucleic acid [DNA]). Such responses are typically characterized by a slow and delayed induction period. This receptor-

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gene mode of action has been successfully modeled for prednisolone effects in rats.[1,2] In human beings, pharmacodynamic modeling of glucocorticoid responses has focused on Sheiner's model[3] of linkage of a hypothetical "effect compartment" to the plasma concentration. This approach has been used to characterize the fall and return of OKT3- and OKT4-positive lymphocytes in peripheral blood after single oral doses of prednisolone.[4] A threshold concentration was needed that represented the minimum concentration of prednisolone required to elicit a response. This modeling effort was seemingly successful in the generation of curve patterns relating lymphocytopenia to serum prednisolone concentrations. However, the model lacks a physiologic structure in that it does not consider circadian patterns of T cells trafficking in and out of blood. Also, the ability to extrapolate between doses and administration methods is not feasible because of the different model parameter values that were needed for each dose of prednisolone.

Many responses to glucocorticoids, including cortisol suppression, whole blood histamine suppression, and lymphocytopenia, exhibit rapid changes after intravenous bolus doses of glucocorticoids.[5–7] These immediate effects are probably too rapid to be associated with DNA-mediated events. Recent evidence suggests that glucocorticoids inhibit pro-opiomelanocortin (POMC) gene transcription in the anterior pituitary lobes of rats by 10 minutes and reach maximal effects within 20 minutes.[8] Similar inhibition of gene transcription has been reported for the interleukin β gene.[9] In addition, glucocorticoids produce relatively rapid reduction of corticotropin (adrenocorticotropic hormone, ACTH) release before demonstrable effects of corticotropin biosynthesis,[10,11] as well as rapid inhibition of basal or circadian release of corticotropin-releasing hormone (CRH) from hypothalamus and CRH-stimulated release of corticotropin from the pituitary.[8,12,13] This rapid inhibition is not affected by pretreatment with cycloheximide in a dose that inhibits protein synthesis.[14] This evidence relates well to our demonstrations in human subjects that, after intravenous administration of methylprednisolone, an initial rapid monoexponential decline of cortisol[5] and whole blood histamine occurs. These observations, together with other facts presented earlier, enable us to propose new "direct suppression pharmacodynamic models" to describe the rapid effects of glucocorticoids.

In this article we examine the pharmacokinetics of methylprednisolone succinate and methylprednisolone in human beings at three dose levels. However, our primary purpose is to propose simple direct suppression pharmacodynamic models to couple the serum concentrations of methylprednisolone with two pharmacodynamic events, namely serum cortisol and blood histamine patterns as a function of time. These models may apply to an array of other corticosteroid and drug effects.

THEORETICAL METHODS

The receptor-mediated mechanism of action of glucocorticoid hormones has been extensively reviewed.[1,2,15–17] Free steroid that diffuses from plasma and from within the cell binds reversibly to phospho-protein cytosolic receptor (typically termed glucocorticoid receptor), forming a steroid-receptor complex. Through a process termed activation, presumably dissociation and dephosphorylation of the receptor, this complex is rapidly transformed to an activated steroid-receptor form. Presumably, one form of this complex

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elicits the direct suppression effect on the release of corticotropin-releasing factor (CRF) from the hypothalamus and the release of corticotropin from the anterior pituitary lobe.[8,12,13] The distribution of steroid to these organs is assumed to be extremely rapid because of either high lipid solubility or the lack of blood-brain barrier to the hypothalamus and pituitary glands.[18] Blockage of the release of corticotropin, coupled with its extremely short half-life ($t_{½}$) of 8 minutes,[19] results in the loss of stimulatory secretion of cortisol from the adrenal glands and, consequently, the loss of the normal circadian rhythm. The subsequent monoexponential decline of serum cortisol is therefore dependent on its elimination clearance. The inhibition of the release CRF and corticotropin persists until inhibitory concentrations (IC_{50}) of methylprednisolone disappear.

Methylprednisolone concentrations (C_{MP}), the active moiety in plasma, can be adequately characterized by a monoexponential function without invoking more complicated issues such as metabolic interconversion.[20] Total serum concentrations are used because methylprednisolone exhibits linear protein binding at this dosage range.[21] After intravenous administration of the methylprednisolone 21-succinate salt (methylprednisolone sodium succinate), the active free alcohol is formed rapidly and then declines monoexponentially. This can be described by the equation:

$$C_{MP} = (Dose/V_{SS}) \cdot e^{-\lambda \cdot t} \quad (1)$$

in which V_{SS} is the steady-state volume of distribution, λ is the slope, and t is time.

Cortisol model

The circadian rhythm of baseline cortisol concentrations with the incorporation of its episodic nature has been kinetically modeled.[22] However, a simple cosine function can also be used to approximate the temporal profile of the circadian rhythm of cortisol.[23] The cosine (cos) function is given by the following equations:

$$R_{cort} = Rm + Rb \cdot \cos(t_c) \quad (2)$$

$$t_c = (T - t_z) \cdot (15/57.3) \quad (3)$$

in which R_{cort} is the circadian concentration of cortisol, Rm is the mean concentration, Rb is the concentration amplitude, T is the clock time within the 24-hour cycle, t_c is time in radians, and t_z is the acrophase or peak time of the circadian function. The numeric ratio in equation 3 converts the 24-hour period into degrees and subsequently into radians for the t_c time functions.

The pharmacodynamic model describing the time course of plasma cortisol (C) after a bolus dose of methylprednisolone is shown in Fig. 1, and is given by the equation:

$$C = CO \cdot e^{-k_c \cdot t} + R_{cort}\left(1 - \frac{C_{MP}}{C_{MP} + IC_{50}}\right) \quad (4)$$

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where CO is the initial plasma cortisol concentration, k_c is the first-order decline constant of cortisol, and IC_{50} is the concentration of methylprednisolone producing 50% inhibition of maximum effect (E_{max}).

The fraction of maximum effect is as follows:

$$E/E_{max}=C_{MP}/(C_{MP}+IC_{50}) \quad (5)$$

This is the well-known Hill equation with the Hill coefficient equal to unity.[3,24] Structurally, equation 5 is identical to the drug-receptor binding relationship:

$$B_{sp}/B_{max}=D_F/(D_F+K_D) \quad (6)$$

in which B_{sP} reflects specific binding, B_{max} is maximum binding, D_F is free drug concentration, and K_D is the equilibrium dissociation constant of the steroid-receptor complex. Thus if binding of steroid to its receptor followed by rapid activation elicits its direct inhibitory effect then, conceptually, the fraction of maximum effect (E/E_{max}) should be proportional to the fraction of occupied receptors (B_{sP}/B_{max}), and IC_{50} should be a function of the equilibrium dissociation constant (K_D). The two equations should be interconvertible by use of pharmacokinetic methods for interrelating D_F in the cytosol to C_{MP} in plasma. This concept is essentially Clark's "occupancy theory" of drug-receptor interaction.[25,26] Related time-dependent phenomena accounted for by drug distribution, receptor transformation, and DNA interaction are deemed unnecessary for rapid corticosteroid effects.

Blood histamine model

Glucocorticoids cause a rapid shift of circulating leukocytes, including monocytes, basophils, and eosinophils, to extravascular compartments such as the bone marrow and the lymphoid tissues.[6,27] The exact mechanism of such redistribution is not known; however, cytoplasmic glucocorticoid receptors are implicated in the affected cells.[28] More than 97% of blood histamine is contained in basophils,[29,30] and steroids inhibit basophil IgE-dependent activated release of histamine through a specific glucocorticoid receptor.[31] Therefore, through receptor binding and subsequent rapid redistribution of basophils to extravascular sites and with prevention of their return to the vascular compartment, it is proposed that steroids exert a direct suppression effect on the steady-state blood histamine levels. Sufficiently large doses of steroids produce a monoexponential decline of blood histamine that persists until inhibitory concentrations (IC_{50}) of methylprednisolone disappear followed by an increase in the typical log-linear fashion until the baseline plateau is regained.

Methylprednisolone concentrations in plasma or serum are described by equation 1. The model (Fig. 1) that describes the time course of blood histamine concentrations (H) after a dose of methylprednisolone is analogous in appearance to that of cortisol (equation 4), except that the steady-state or baseline blood histamine (HO) serves in place of the circadian function:

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$$H = HO \cdot e^{-k_H \cdot t} + HO\left(1 - \frac{C_{MP}}{C_{MP} + IC_{50}}\right) \quad (7)$$

in which k_H is the first-order rate constant for the decline of blood histamine. This provides an adequate approximation of the two-compartment blood-extravascular model shown in Fig. 1; an exact model would require differential or more complex equations.

EXPERIMENTAL METHODS

Subjects

Six healthy nonsmoking men between the ages of 19 and 38 years who weighed between 68 and 89 kg volunteered to participate in this study. All were within 20% of their ideal body weights. Health status was assessed by a medical history, a physical examination, and a blood chemistry profile. None of the subjects had a history of allergy to glucocorticoids. One subject reported occasional marijuana use (one to two times a year), and four subjects reported occasional alcohol use. Subjects abstained from drug use for at least 1 month before the start of the study.

Subjects received either no drug or 10, 20, and 40 mg of methylprednisolone (Solu-Medrol, Upjohn Co., Kalamazoo, Mich.) as a rapid intravenous injection. The dose equivalents of methylprednisolone sodium succinate given were 12.7, 25.4, and 50.8 mg. The administration of each dose was separated by 1 week, and the crossover sequencing of dosage administration was randomized.

At the start of each study day (approximately 8 AM), a 20-gauge angiocatheter was inserted into an arm vein opposite the methylprednisolone injection site and was kept patent by the instillation of small volumes of a 10 IU/ml heparinized saline solution. Blood samples were obtained in heparinized collection tubes at the following times: 0, ¼, ½, ¾, 1, 1½, 2, 3, and 4 hours after steroid administration and every 2 hours until 24 hours and at 28 and 32 hours after steroid administration. Whole blood (300 μl) was stored at −20° C for determination of blood histamine levels. The remaining blood was separated immediately to harvest plasma. Plasma (500 μl) was stored at −20° C until assay of cortisol by radioimmunoassay (RIA). The remaining plasma was mixed with 100 μl of 3 mol/L sulfuric acid per ml of plasma to stabilize the succinate pro-drug and stored at −70° C until assayed. Urine was collected during the following intervals: 0 to 1, 1 to 2, and 2 to 12 hours after steroid administration.

Assays

Plasma and urine methylprednisolone succinate and methylprednisolone concentrations were measured by use of the HPLC assay of Kong et al.[32] When methylprednisolone succinate concentrations were negligible, methylprednisolone concentrations were determined by use of the HPLC procedure of Ebling et al.[33] (an easier assay). The sensitivity of both assay methods was 10 ng/ml for these steroids. Interday and intraday variability for both assay procedures for both compounds was below 7.0%. Excellent agreement existed between the two assay procedures for the measurement of

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methylprednisolone for the plasma concentration range of 30 to 200 ng/ml (slope = 0.9926, intercept = 13.7, r^2 = 0.94, n = 22).

Plasma protein binding of methylprednisolone was determined by ultrafiltration at 37° C by use of the Centrifree system (Amicon, Cherry Hill, N.J.) after first checking the system against equilibrium dialysis.[21] Methylprednisolone concentrations of 200 and 500 ng/ml were employed.

Cortisol concentrations that were below the HPLC detection limit (i.e., <20 ng/ml), were assayed by a modified solid-phase RIA (Coat-A-Count:Cortisol, Diagnostic Products Corp., Los Angeles, Calif.). The lowest calibrator (10 ng/ml) supplied by the manufacturer was serially diluted to 5, 2.5, and 1.25 ng/ml with the zero calibrator (0 ng/ml) to provide lower values for the standard curves. The sample size was increased from 25 to 100 μl. The standard curve ranged from 1.25 to 200 ng/ml. All assays were performed in duplicate and were counted with an LKB gamma counter (LKB Diagnostics, Inc., Gaithersburg, Md.). The standard curve was regressed with a Spline program. The lowest concentration of the standard curve, 1.25 ng/ml, averaged 90.5% ± 2.8% binding, of which above 95% binding is considered the detection limit. Quality control samples yielded intraday and interday coefficients of variation of 2.9% and 5.9% at 40 ng/ml and 2.6% and 3.9% at 120 ng/ml.

Whole blood histamine was analyzed by use of RIA (NMS Pharmaceuticals, Inc., Newport Beach, Calif.). For this assay, 100 μl whole blood were added to three times the volume of supplied buffer in 3 ml polycarbonate tubes and placed in a boiling water bath for 10 minutes. After centrifugation at 8000g for 15 minutes at 40° C, 50 μl of the supernatant was used for assay. The standard curve ranged from 1.562 to 200 ng/ml and was regressed with a logit program. The maximum likelihood estimates of the parameters were obtained with iteratively reweighted least-squares analysis by use of PCNONLIN (Statistical Consultants, Lexington, Ky.). The lowest concentration of the standard curve, 1.562 ng/ml, averaged 86.6% ± 4.3% binding. The intraday coefficients of variation were 5.3% and 6.0%, and the interday coefficients of variation were 9.6% and 10.8% at 10 and 60 ng/ml.

Data analysis

Noncompartmental analysis was used to obtain the pharmacokinetic parameters.[34] The area under the plasma concentration-versus-time curve (AUC) was determined by Lagrange[34] polynomial interpolation and integration with use of the least-squares terminal slope (λ) to extrapolate to infinity. The area under the first moment curve (AUMC) was determined by multiplication of each plasma concentration by its time. Clearance (CL) was determined from Dose/AUC, mean residence time (MRT) from AUMC/AUC, and V_{SS} from CL · MRT. The renal clearance (CL_R) of methylprednisolone succinate was determined from A_u/AUC, where A_u is the total amount of compound recovered in urine. Nonrenal clearance (CL_{NR}) was determined by subtraction of CL_R from CL.

The serum concentration-versus-time curves of methylprednisolone for each individual subject at each dose level were also fitted to a monoexponential function (equation 1) by use of the nonlinear least-squares regression computer program PCNONLIN. The resulting pharmacokinetic parameters for each individual were then used in fitting their individual

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effect data (cortisol and blood histamine) to the pharmacodynamic models by use of PCNONLIN. In addition, a combined fit of effects for all the dose levels (and baseline for the cortisol model) simultaneously was undertaken to examine the goodness of fit and the applicability of the dynamic parameters across all doses.

An analysis of variance (ANOVA) technique developed for repeated measure design[35] was performed to detect significant variances in pharmacodynamic parameters for the three doses administered when examining the fit of individual doses. Differences between the various means were tested for significance by use of the Tukey multiple comparison test. All statistical procedures were assessed for differences at the $p < 0.05$ level.

For comparison purposes, the blood histamine data (employed as fractional change from baseline) were fitted to three alternative effect models: the E_{max} model, the sigmoid E_{max} model, and the "threshold" E_{max} model as used by other investigators.[3,4] These models may include an exit rate constant (k_{co}) for the effect compartment, the Hill coefficient, and sometimes a threshold drug concentration and the IC_{50} value. Visual inspection of the fittings, sum of square deviations, correlation coefficients (r), and plots of residuals were used to compare results from the different models.

RESULTS

Pharmacokinetics

Fig. 2 shows the serum concentration-versus-time profiles of methylprednisolone succinate and methylprednisolone after three doses of the steroid pro-drug in a representative subject. Methylprednisolone succinate disappeared in a slightly biexponential fashion, with a $t_{½}$ of about 0.3 hour. The mean data for all dose levels are presented in Table I. With the exception of CL values for two subjects at the high dose (496 and 528 ml/hr/kg), CL averaged about 1200 ml/hr/kg. The unchanged ester in the urine (A_u) averaged 9% to 10% for all doses and the CL_R remained unchanged. The V_{SS} averaged 0.35 L/kg and was constant for three doses. There was no statistically significant effect of administered dose on the calculated parameters.

All three disposition curves of methylprednisolone decayed in a monoexponential fashion with a terminal $t_{½}$ of approximately 2.3 hours. The mean pharmacokinetic parameters at each dosage level are presented in Table II. No statistical differences in CL, V_{SS}, $t_{½}$, or λ were found. However, when AUC values were plotted (Fig. 3), two subjects exhibited a disproportional relationship at the high dose. This may be indicative of occasional nonlinearity in the conversion of methylprednisolone succinate to methylprednisolone. The general constancy of parameters is indicative of linear kinetics of methylprednisolone, which is consistent with previous findings.[20] This linearity obviates the need for invoking a more complicated pharmacokinetic model to suitably input methylprednisolone kinetics into the dynamic models.

The normal volunteers exhibited constant plasma protein binding of methylprednisolone that averaged 78.0% ± 2.5% binding. This is identical to binding data obtained previously in humans.[21]

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Cortisol dynamics

The circadian rhythm of plasma concentrations of cortisol in a representative subject is shown in Fig. 4. The episodic nature of cortisol secretion is clearly noticeable. Our aim here was not to model this complication, which has been accomplished previously with more intensive blood sampling,[22] but to provide a temporal profile of the circadian rhythm of cortisol with a general function (equation 2), which would allow for a suitable rate of return of cortisol to baseline. As shown in Fig. 4, there was reasonable agreement between the observed and the predicted profiles.

Fig. 4 also shows the suppression of plasma concentrations of cortisol after the three intravenous doses of methylprednisolone succinate. Cortisol concentrations rapidly decline in a monoexponential fashion, attain a nadir at about 15 hours after administration, and then rise at about 20 hours (4 AM) to peak around 24 hours (i.e., 8 am the next day). The best fitting of these data simultaneously to our model provides a reasonable quantitation of the baseline, the decline, and the return of cortisol for all three dose levels, except for several data points at 18 to 21 hours.

Table III contains the pharmacodynamic parameter estimates for the cortisol model. Although the IC_{50} of the 10 mg dose appears to be smaller than that of the 20 and 40 mg doses, no statistically significant difference could be detected at the level of $p < 0.05$. This is true for all other parameters for the three dose levels from the individual fittings and for the combined analysis. This constancy and agreement of individual and combined fittings indicates the adequacy of the dynamic model to generally describe effects for the entire dosage range with one set of parameters. This is one of the basic requirements for the predictive value of any model.

Blood histamine dynamics

The suppression of whole blood histamine after methylprednisolone is shown in Fig. 5. Modest fluctuations in concentrations are seen during the baseline day. Suppression occurs after the 10 mg dose; however, it is less than that after the 20 and 40 mg doses of methylprednisolone. The nadir of blood histamine occurs at about 6 to 10 hours after dosing. This is consistent with results for basophils[6,29] and is similar to lymphocyte[28] data. The model describes very well the monoexponential decline and the typical log-linear return to baseline of blood histamine as observed from the least-square fittings in Fig. 5.

Table IV contains the pharmacodynamic parameter estimates of the blood histamine model for five subjects (one subject was excluded because of problems encountered analytically in the RIA). No statistical differences in the parameter estimates between the three dose levels could be detected by ANOVA except for the initial decline, k_H, for the 10 mg dose. Individual and combined fittings yielded similar parameter estimates. The relatively small sum of squared deviations and good correlation coefficients between the observed and the predicted values also reinforces the general suitability of our model.

Table V contains pharmacodynamic parameter estimates of the blood histamine data fitted to the E_{max}, sigmoidal E_{max}, and threshold models.[3,4] Fig. 6 displays the fittings of blood histamine to the best three models selected for a representative subject. The threshold E_{max}

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model characterized the data least well. The sigmoid E_{max} model fitted almost as well as our model, as assessed by visual inspection and from correlation coefficients (Table V). However, the sigmoid model typically underpredicted the early time points because of the inherent nature of the time delay, k_{co}, incorporated into this model type. Statistically significant differences ($p < 0.05$) are seen for the parameter estimates, such as the IC_{50} between the 20 and 40 mg dose and for *r* between the 10 and 40 mg dose (Table V). Visual inspection of the fittings, plots of residuals, and statistics, such as smaller sum of squared deviations values, also favored the direct suppression model for these data.

DISCUSSION

Pharmacokinetics

Methylprednisolone succinate clearance was linear in all subjects for the dose range of 12.7 to 25.4 mg and in four of six subjects when the dose was increased to 50.8 mg. Mean CL values in the range of 76 to 108 L/hr were higher than previously reported by Derendorf,[36] who reported mean CL values that averaged about 48 L/hr after a 63.1 mg intravenous dose.

The CL_{NR} values for methylprednisolone succinate averaged 1300 to 1600 ml/min, which is quite similar to hepatic blood flow reported in healthy young men.[37] This, plus findings of markedly reduced clearances in patients with cirrhosis (Ludwig EA, Kong AN, Camara DS, Jusko WJ. July 1989. Unpublished observations) and the small degree of blood hydrolysis,[32] would indicate that the liver is the primary site of hydrolysis of the succinate ester and that CL by this process is dependent on hepatic blood flow. Animal studies indicate that esterases responsible for the hydrolysis of succinate esters are primarily present in the liver.[38]

The amount of methylprednisolone succinate in urine was consistent with that previously reported for higher doses,[36] averaging 9% to 10% of the administered dose. The CL_R was also independent of dose, averaging about 110 to 120 ml/hr/kg. This value appears to exceed normal glomerular filtration rate by approximately 50%, suggesting that renal elimination may involve both glomerular filtration and active secretion. Active secretion is commonly expected for many weak acids. The CL_R of the succinate ester, however, represents only about 10% of the systemic clearance; this pathway is therefore of relatively minor importance to its overall elimination.

The metabolically formed dose of methylprednisolone, calculated by the difference between the administered dose and A_u, was consistent between each subject at each dose, with maximal differences being less than 10%. Thus variance in the renal elimination of methylprednisolone succinate had little influence on the formation of methylprednisolone. The AUC of these compounds were linearly related both within and between subjects up to a methylprednisolone succinate AUC of 1000 ng · hr/ml (Fig. 3). Above this value, it appears that this relationship becomes nonlinear. This suggests that the metabolism of the succinate ester to methylprednisolone is predominantly a linear process for the dosage range studied. The slope value obtained for the linear portion of this graph represents the ratio of the formation CL to disposition CL of methylprednisolone,[39] therefore covariance in these two

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distinctly different metabolic processes (hydrolysis versus oxidative metabolism) appears to exist.

The AUC of methylprednisolone increased proportional to received dose, whereas its CL, $t_{½}$, and V_{SS} remained unchanged. These pharmacokinetic parameters must be considered apparent values because of the incomplete hydrolysis of methylprednisolone succinate and because of the small degree of interconversion that takes place between this compound and the metabolite, methylprednisone.[20,40] Methylprednisone was not measured in this study. The values obtained and the dose-independent pharmacokinetic behavior of this steroid are consistent with previous observations in which only methylprednisolone was measured.[20] Also, a recent study by Al-Habet and Rogers,[41] in which 20 to 80 mg doses of methylprednisolone succinate were used, yielded linear parameters for methylprednisolone that were very similar to ours.

Pharmacodynamics

It is possible to accurately characterize the relationship between methylprednisolone plasma concentrations and its effects on cortisol (Fig. 4) and whole blood histamine (Fig. 5) with our proposed direct suppression models (Fig. 1). Excellent individual fittings to each dose level and good combined fittings of all three doses for each subject for both effects were obtained with our models. The functioning of the two models is essentially identical and is based on the assumption that the interaction of steroid with receptor elicits a direct suppressive response upon the influx rate processes. This is supported by the similar IC_{50} values (Tables III and IV). The pharmacodynamic parameter estimates obtained are plausible when compared with in vitro glucocorticoid receptor binding data. The IC_{50} of 3 ng/ml total plasma methylprednisolone is equivalent to 2 nmol/L of free methylprednisolone, assuming 78% binding to plasma proteins.[21] This is similar to the K_D of 43 nmol/L for methylprednisolone binding to cytosol receptors in human lung at 20° C[42] and to the K_D of 9.6 nmol/L in human skin fibroblasts at 22° C,[43] considering the temperature differences and uncertain degree of steroid partitioning into receptor sites.

The monoexponential decline of cortisol, k_C, is similar for all three dose levels, indicating dose-independent elimination after complete suppression of the hypothalamic-pituitary-adrenal axis after administration of methylprednisolone. These values are similar to literature reports for cortisol elimination.[5,22] The parameter estimates for the circadian rhythm of cortisol are of similar magnitude as reported in the literature.[22,44] For the monoexponential decay of whole blood histamine, k_H, there is a difference between the 10 mg and higher doses. This observation was also made by other investigators,[30] but the exact mechanism is unclear. This could be because of incomplete suppression of basophil return to blood or because of two different populations of steroid sensitive basophils. Leonard[30] has found that each subpopulation of basophils reacts differently in vivo after administration of prednisone.

The data we have presented (Figs. 4 and 5) demonstrate that there is excellent characterization of certain pharmacodynamic data (cortisol and blood histamine) for methylprednisolone when the kinetics of drug effect are directly modeled by incorporation of C_{MP} into the direct suppression equation. Indeed, when drug effect was separately

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modeled to account for a temporal displacement between C_{MP}. and effect, as has been done previously,[4] the quality of fitting was significantly poorer for blood histamine when fitted to the E_{max} and the threshold models (Table V). For the sigmoid E_{max} model, inconsistancy in parameter estimates such as the IC_{50} between doses (Table V), the Hill coefficient value greater than one, which contradicts current steroid-receptor binding data,[1,15–17] and the lack of physiologic meaning for "k_{co}" and the "effect compartment" for this rapid glucocorticoid response, severely limits its usefulness. In addition, for the cortisol data, no effect model has attempted to date to incorporate its physiologic circadian rhythm under baseline and poststeroid elimination conditions.

Reasons for the inadequacy of the "effect compartment model" may be partly that these glucocorticoid effects are direct and very rapid and that they do not occur through the typical DNA mediation. In vitro evidence for direct action of corticosteroids includes rapid inhibition of both POMC gene[8] and interleukin 1β gene transcription,[9] and rapid inhibition of corticotropin release from pituitary gland and CRF release from hypothalamus.[8,12–14] In human subjects, after an intravenous bolus dose of steroids, rapid lymphocytopenia[28] and an immediate decline of serum cortisol[5] are observed. The effect site for blood histamine (basophils) probably occurs directly in the cells, whereas that for cortisol is in highly perfused organs, the hypothalamus and pituitary.[18] In addition, the high lipophilic nature of steroids, with an octanol and water partition coefficient of 70 for methylprednisolone,[21] and its relatively small size and nonionic nature enables rapid penetration into cells.[45] In quantitating hepatic uptake and cytosolic binding of prednisolone in rats, the occupation of receptors occurs at an extremely rapid rate.[1,2] It therefore appears unnecessary, kinetically and physiologically, to include a separate effect compartment for these direct suppression effects. However, for gene-mediated responses, the effect compartment could be considered the cell nucleus and receptor-mediated changes in ribonucleic acid (RNA) or messenger RNA (mRNA) synthesis, but the controlling processes for induction and dissipation of effects would be biologic factors rather than drug distribution factors.[2]

There is notable generality in the nature of the two effects that differ primarily in the incorporation of the circadian rhythm into the cortisol model. This direct suppression model is conceptually analogous to that used by Powers et al.[46] to describe anticoagulant effects of warfarin in human subjects. This type of behavioral response after drug administration was first observed by Nagashima et al.[47] for warfarin inhibitory effects on prothrombin complex activity. Indeed, the zero-order return of steroid effects to baseline (see Figs. 5 and 6) is essentially the slope defined by Levy[48] for describing some pharmacologic effects. The present models, in principle, are representative of an array of effects in being able to characterize the movement of other blood cells, such as T cells, in and out of the circulation,[4,6,7,27] although our model would have to be augmented by the consideration of circadian rhythms of some of these cells. For adrenal suppression, this approach should replace earlier methods,[49] which do not adequately separate kinetic from dynamic factors that determine steroid responses. At present, these models pertain to a limited dose range of corticosteroids and to the effects of alternative dosing schedules (pm instead of am), larger doses, and long-term treatment may require adjustments.

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In summary, we have presented a direct suppression model for glucocorticoid responses, with the utilization of serum methylprednisolone concentrations in the pharmacodynamic model. The model is consistent with both in vitro and in vivo observations of this rapid mode of glucocorticoid action. The parsimony of the model will be advantageous for other direct suppression effects after drug administration that require a first-order decline process and subsequent return to baseline after drug concentrations fall below the IC_{50}. This report presents the first model that allows quantitation of the immediate effects of steroids with *one equation* and common fitted parameters for *all* tested steroid dose levels. It avoids the use of an unphysiologic "black box effect compartment." It instead directly incorporates steroid concentrations into the effect model with realistic physiologic consideration of the properties of corticosteroids; it characterizes the complete concentration-response curve accurately, including the extremes of response (0% to 100%). These efforts also add to considerations of the diverse array of glucocorticoid responses in regard to nongene immediate responses versus gene-mediated delayed effects.[2]

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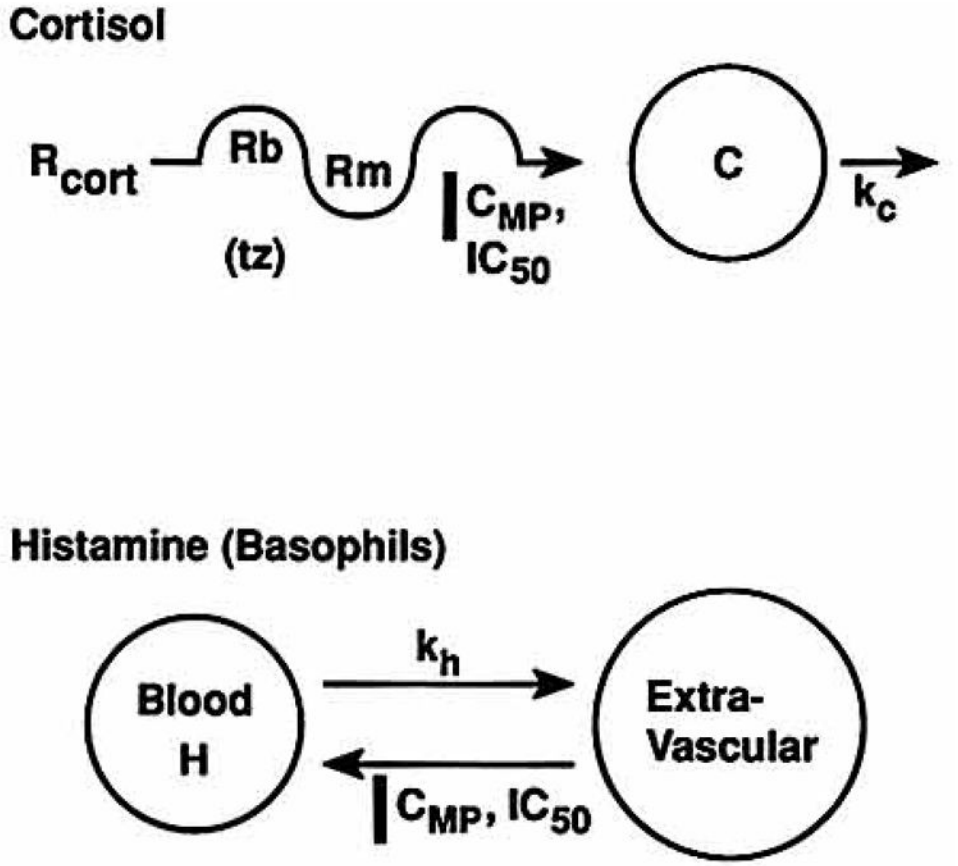

Fig. 1.

Diagrammatic representation of the direct suppression models. **Top figure** depicts the circadian secretion and suppression model of cortisol. **Bottom figure** depicts the two-compartment basophil distribution and suppression model of whole blood histamine. R_{cort}, Circadian concentration of cortisol; Rb, concentration amplitude; Rm, mean concentration, C_{MP}, methylprednisolone concentration; IC_{50}, concentration of methylprednisolone that produces 50% inhibition of maximum effect; C, cortisol; k_c, monoexponential decline of cortisol; t_z, peak time of the circadian function; H, blood histamine concentrations; k_h, first-order rate constant for decline of blood histamine.

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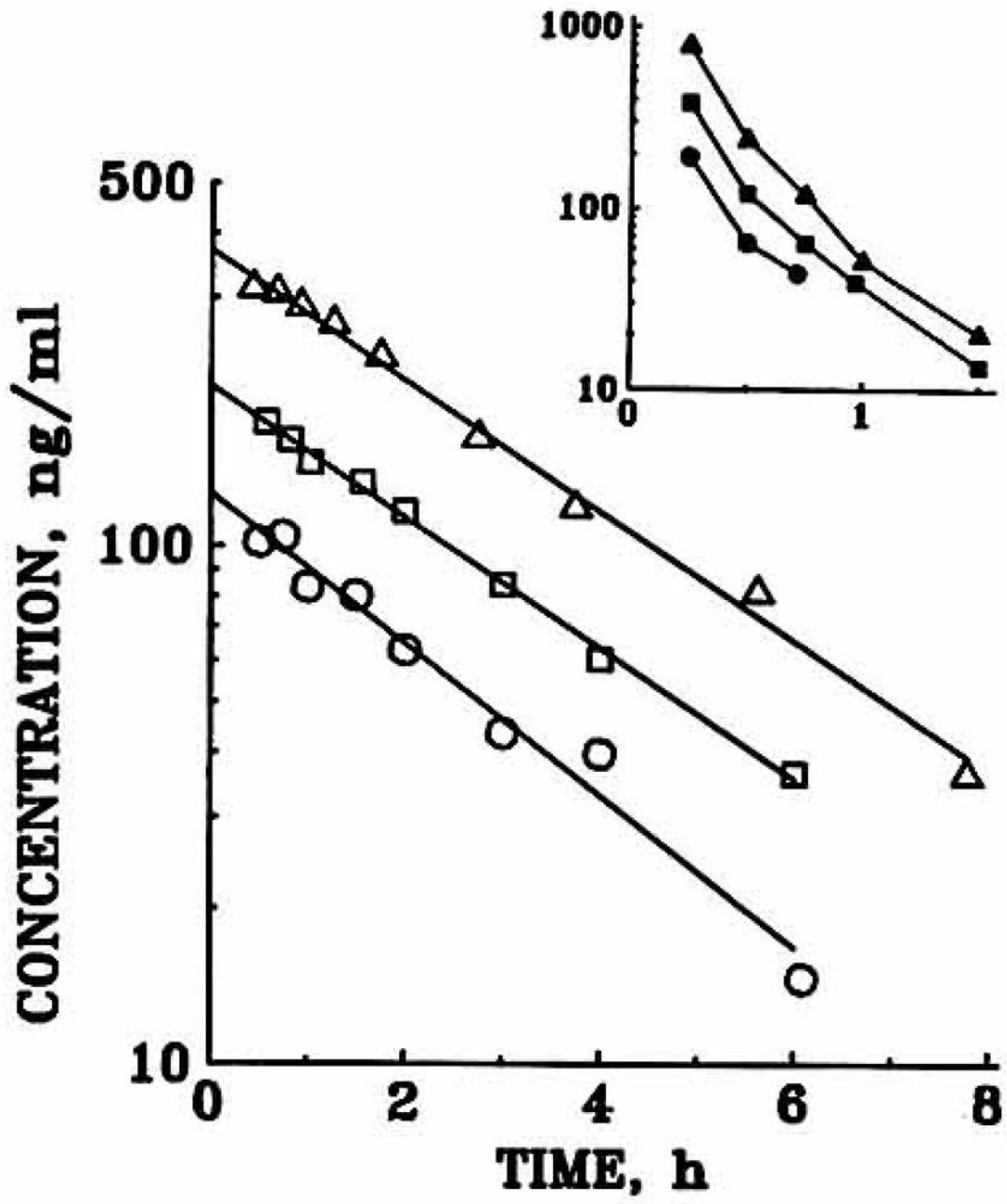

Fig. 2.

Disposition of methylprednisolone and methylprednisolone succinate (*inset*) in a representative subject after administration of 10 (*circles*), 20 (*squares*), and 40 mg (*triangles*) of methylprednisolone as its succinate ester. *Solid lines* for methylprednisolone represent the least-squares curve fittings by equation 1.

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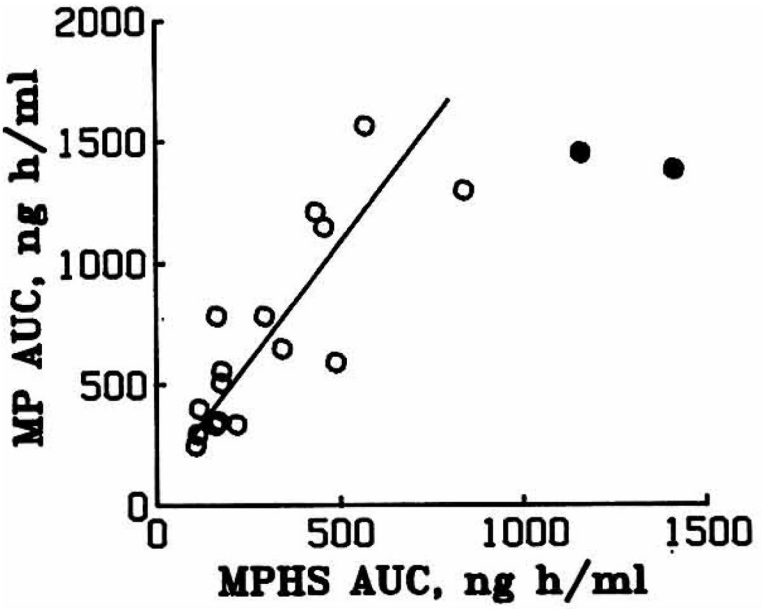

Fig. 3.

Linear relationship between AUC of methylprednisolone (MP) and methylprednisolone succinate (MPHS). The regression line (assuming error in both variables) is: MP AUC = 1.97 MPHS AUC + 95.3; $r = 0.827$. *Solid circles* are two subjects who showed a slower MPHS clearance after the 50.8 mg dose and who are not included in the regression analysis.

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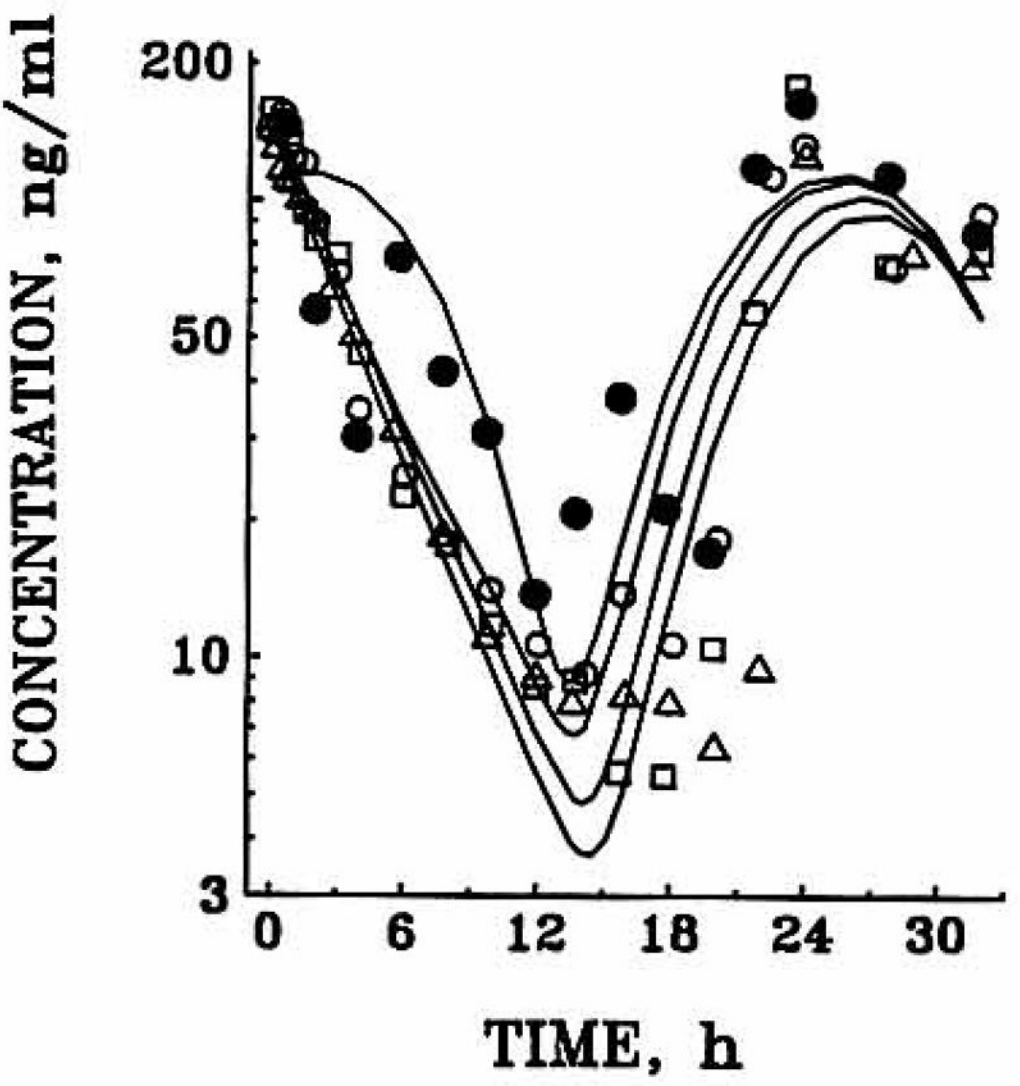

Fig. 4.

Plasma concentrations of cortisol in the same subject during baseline *(solid circles)* and after 10 *(open circles)*, 20 *(squares)*, and 40 *(triangles)* mg doses of methylprednisolone. *Symbols* are experimental data and *lines* are least-squares regression lines fitted by equations 2, 3, and 4.

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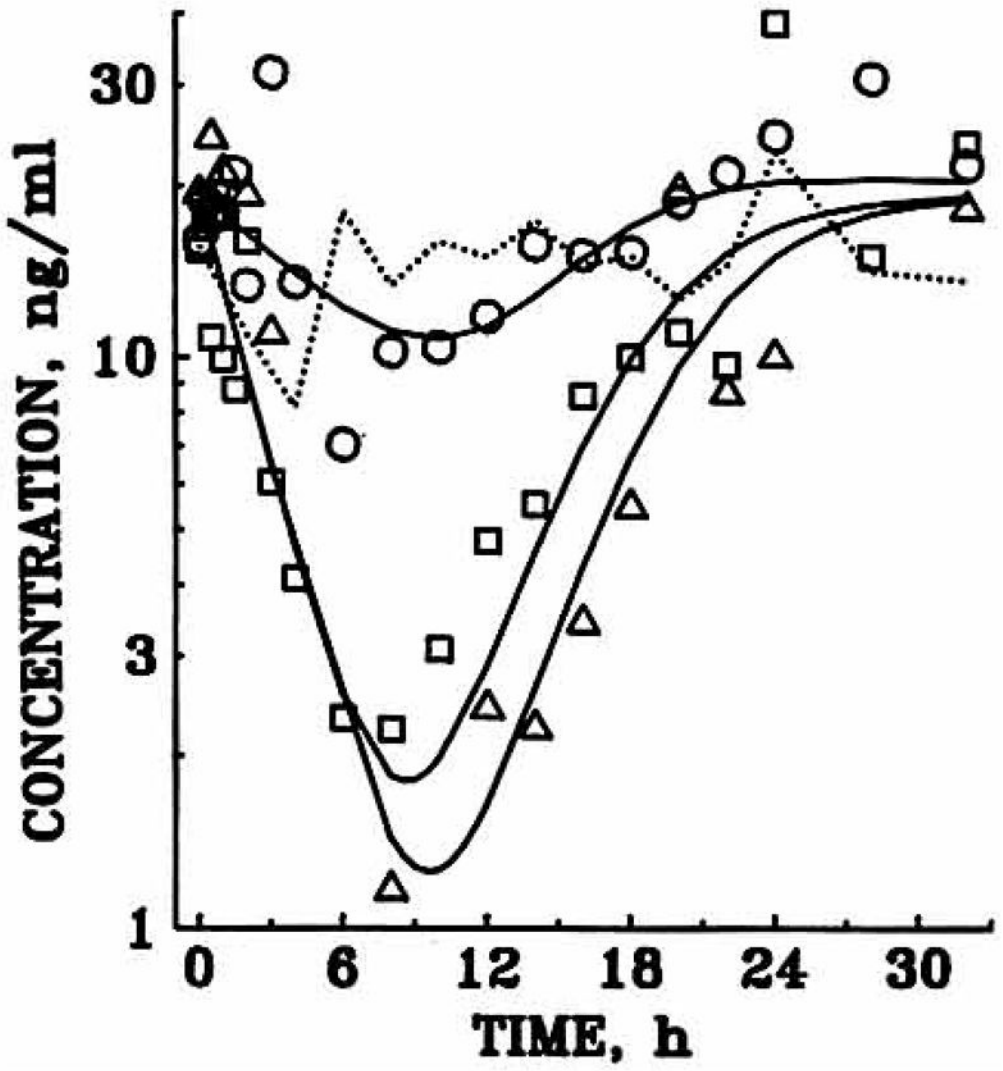

Fig. 5.

Whole blood histamine concentration-versus-time profile in one subject at baseline *(dotted line)* and after 10 *(circles)*, 20 *(squares)*, and 40 *(triangles)* mg doses of methylprednisolone. *Symbols* are experimental data and *solid lines* are least-squares regression lines fitted to equation 7.

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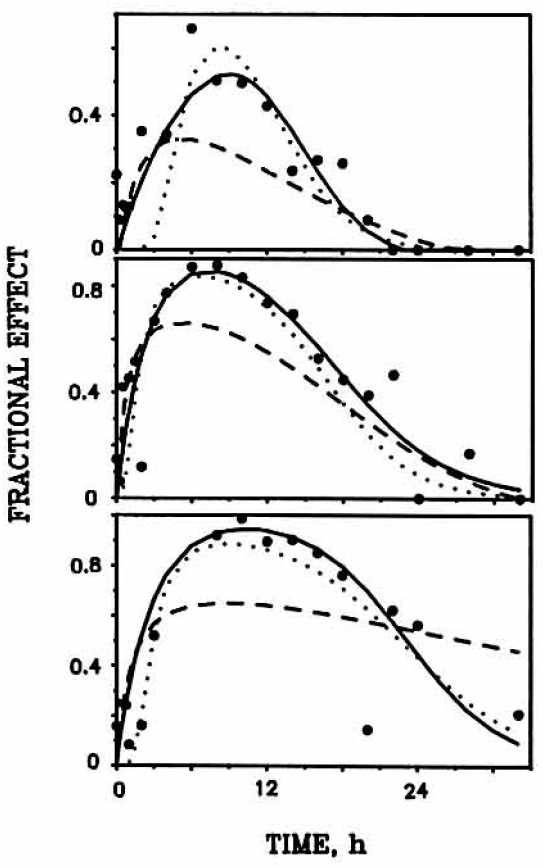

Fig. 6.

Fractional effcct-versus-time profiles of whole blood histamine after 10 (**top panel**), 20 (**middle panel**), and 40 mg (**bottom panel**) doses of methylprednisolone in one subject. *Lines* depict fittings to direct suppression *(solid lines)*, sigmoid E_{max}, *(dotted lines)*, and threshold *(broken lines)* models.

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Table I

Pharmacokinetic parameters for methylprednisolone succinate

	Dose (mg)				
Parameter	**12.7**	**25.4**	**50.8**	**Mean**	**p Value**
AUC (ng · hr/ml)*	148 ± 48	275 ± 140	814 ± 400	NA	0.01
A_u (mcg)*	1140 ± 229	2400 ± 849	4890 ± 1884	NA	0.01
CL (ml/hr/kg)	1180 ± 305	1389 ± 572	980 ± 565	1183 ± 419	NS
CL_R (ml/hr/kg)	108 ± 42	122 ± 41	93 ± 58	108 ± 42	NS
CL_{NR} (ml/hr/kg)	1073 ± 269	1267 ± 553	887 ±418	1075 ± 390	NS
V_{SS} (L/kg)	0.33 ± 0.07	0.41 ± 0.17	0.32 ± 0.10	0.35 ± 0.11	NS
$t_{½}$(hr)	0.29 ± 0.13	0.32 ± 0.11	0.50 ± 0.25	0.37 ± 0.15	NS

AUC, Area under the plasma concentration-versus-time curve; NA, not applicable; A_u, total amount of drug recovered in urine; CL, total clearance; NS, not significant; CL_R, renal clearance; CL_{NR}, nonrenal clearance; V_{SS}, steady-state volume of distribution; $t_{½}$, half-life.

*Mean value after the 50.8 mg dose was different from the lower doses.

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Table II

Pharmacokinetic parameters for methylprednisolone

Parameter	Dose (mg)			Combined fitting	P Value
	10	20	40		
AUC (ng · hr/ml)*	327 ± 48	645 ± 106	1341 ± 142	NA	0.01
CL (ml · hr/kg)	368 ± 52	375 ± 71	356 ± 44	353 ± 53	NS
V_{SS} (L/kg)	1.33 ± 0.23	1.41 ± 0.37	1.24 ± 0.14	1.23 ± 0.24	NS
$t_{½}$ (hr)	2.48 ± 0.44	2.50 ± 0.36	2.36 ±0.13	2.37 ± 0.23	NS
λ (hr^{-1})	0.29 ± 0.05	0.29 ± 0.05	0.30 ± 0.02	0.29 ± 0.03	NS

AUC, Area under the plasma concentration-versus-time curve; NA, not applicable; CL, total clearance; NS, not significant; V_{SS}, steady-state volume of distribution; $t_{½}$, half-life; λ, terminal slope.

*Mean value from the higher doses was different from the next lower doses.

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Table III

Pharmacodynamic parameters for cortisol based on the direct suppression model

Parameter	Baseline	Dose (mg)*			Combined mean*
		10	20	40	
k_c (hr^{-1})	NA	0.34 ± 0.04	0.38 ± 0.07	0.30 ± 0.06	0.31 ± 0.03
IC_{50} (ng/ml)	NA	0.96 ± 0.81	3.61 ± 3.82	3.34 ± 3.58	0.53 ± 0.45
Rm (ng/ml)	55 ± 14	53 ± 9	44 ± 11	43 ± 12	57 ± 13
Rb (ng/ml)	35 ± 11	50 ± 10	41 ± 10	39 ± 11	39 ± 10
t_z (hr)	2.21 ± 1.65	3.78 ± 1.45	4.03 ± 1.51	5.03 ± 1.62	2.32 ± 1.69
SSD	7.58 ± 2.85	2.10 ± 0.53	1.94 ± 0.95	1.89 ± 1.05	20.6 ± 11.2
r	0.67 ± 0.15	0.86 ± 0.05	0.85 ± 0.09	0.83 ± 0.10	0.78 ± 0.12

Data are mean values ± SD.

k_C, Monoexponential decline of cortisol; NA, not applicable; IC_{50}, concentration of methylprednisolone that produces 50% inhibition of maximum effect; Rm, mean concentration; Rb, concentration amplitude; t_Z, peak time of the circadian function; SSD, sum of squarc deviations; *r*, correlation coefficient.

*$n = 6$.

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Table IV

Pharmacodynamic parameters for whole blood histamine based on the direct suppression model

Parameter	Dose (mg)*			Combined mean*
	10	20	40	
k_H (hr^{-1})	0.18 ± 0.06†	0.34 ± 0.06	0.36 ± 0.09	0.16 ± 0.08‡ 0.34 ± 0.06§
IC_{50} (ng/ml)	3.51 ± 2.64	3.10 ± 1.63	2.73 ± 2.34	2.07 ± 1.69
HO (ng/ml)	19 ± 7	18 ± 7	20 ± 10	18 ± 8
SSD × 10^{-2}	1.85 ± 1.40	1.99 ± 1.51	0.82 ± 0.58	5.95 ± 5.19
r	0.70 ±0.13	0.71 ± 0.13	0.88 ± 0.05	0.75 ± 0.14‖

Data are mean values ± SD.

k_H, First-order rate constant for decline of blood histamine: IC_{50} concentration of methylprednisolone that produces 50% inhibition of maximum effect: HO, baseline blood histamine level; SSD, sum of square deviations; *r*, correlation coefficient.

*$n = 5$.

†Tukey comparison between doses: $\bar{x}_{10} = \bar{x}_{20} = \bar{x}_{40}$, $p < 0.05$.

‡10 mg dose.

§20 and 40 mg dose.

‖10, 20, and 40 mg doses combined.

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Table V

Pharmacodynamic parameters for whole blood histamine based on three alternative models

Method and dose	Parameter					
	$k_{co}(hr^{-1})$	IC_{50} (ng/ml)	Hill coefficient	Threshold concentration (ng/ml)	SSD	*r*
E_{max} (Hill coefficient value = 1)						
10 mg	0.161 ± 0.191	44.9 ± 38.8	NA	NA	5.64 ± 7.20	0.428 ± 0.229†
20 mg	0,144 ± 0.019	53.7 ± 30.0	NA	NA	3.23 ± 3.31	0.572 ± 0.236
40 mg	0.085 ± 0.050	40.0 ± 15.6	NA	NA	0.94 ± 0.19	0.770 ± 0.044
Sigmoidal E_{max}						
10 mg	0.094 ± 0.102	27.6 ± 22.3	4.58 ± 4.93	NA	5.32 ± 7.26	0.487 ± 0.262†
20 mg	0.079 ± 0.019	23.6 ± 6.9*	7.15 ± 4.80	NA	2.46 ± 2.78	0.716 ± 0.160
40 mg	0.053 ± 0.024	34.2 ± 7.3	5.22 ± 1.18	NA	0.41 ± 0.03	0.907 ± 0.009
Threshold E_{max}						
10 mg	0.127 ± 0.137	23.9 ± 14.1	NA	4.36 ± 4.02	4.95 ± 6.08	0.432 ± 0.232†
20 mg	0.125 ± 0.024	44.2 ± 21.6	NA	4.85 ± 1.89	3.16 ± 3.34	0.567 ± 0.233
40 mg	0.080 ± 0.045	38.5 ± 14.0	NA	3.79 ± 2.58	0.91 ±0.18	0.759 ± 0.044

Data are mean values ± SD.

k_{CO}, Exit rale constant; IC_{50}, concentration of methylprednisolone that produces 50% of maximum effect; SSD, sum of square deviations; *r*, correlation coefficient; E_{max}, maximum effect; NA, not applicable.

*Tukey comparison between doses: $\bar{x}_{20} \neq \bar{x}_{40}$, $p < 0.05$.

†Tukey comparison between doses: $\bar{x}_{10} \neq \bar{x}_{40}$, $p < 0.05$.