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Gender-based effects on methylprednisolone pharmacokinetics and pharmacodynamics

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Abstract

The pharmacokinetics and selected pharmacodynamic responses to methylprednisolone were investigated in six men and six premenopausal women after a dose of 0.6 mg/kg ideal body weight. Women (luteal phase) exhibited a greater methylprednisolone clearance (0.45 versus 0.29 L/hr/kg) and shorter elimination half-life (1.7 versus 2.6 hours) than men. The volume of distribution of methylprednisolone was similar when normalized for ideal body weight. Pharmacodynamic models were used to examine the methylprednisolone suppressive effects on cortisol secretion and basophil and helper T lymphocyte trafficking. A significantly smaller 50% inhibitory concentration (IC₅₀) value (0.1 versus 1.7 ng/ml) was seen in the women for suppression of cortisol secretion, indicating increased sensitivity. However, the area under the concentration-time curve of effect was similar for both groups. The IC₅₀ values for effects of methylprednisolone on basophil trafficking related to estradiol concentrations in a log-linear fashion in women, with increased sensitivity found at higher estradiol concentrations. Men displayed a greater 24-hour net suppression in blood basophil numbers, but no difference was observed in net cortisol and helper T lymphocyte suppression between the sexes. These findings suggest that methylprednisolone dosages should be based on ideal body weight. Although women are more sensitive to methylprednisolone as measured by cortisol suppression, they eliminate the drug more quickly, generally producing a similar net response.

Male subjects typically have been used in most drug studies. However, the findings of these studies are applied clinically to both male and female patients, despite their physiologic differences. Of the studies that have enrolled both men and women, most fail to analyze their findings by gender and instead treat all the subjects as one homogeneous group.¹ This bias in clinical research has been of concern within the health professions.^{2–4} The literature currently lacks guidelines regarding dosing regimens based on gender.

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Gender-related differences in disposition have been observed for numerous drugs. The total and unbound clearance of diazepam, which undergoes oxidative metabolism, was found to be greater in women.⁵ Clearance of oxazepam (total and unbound)⁶ and acetaminophen,⁷ both of which undergo glucuronide conjugation, is significantly greater in men. The clearance of propranolol, which undergoes oxidative and conjugative metabolism, has been found to be greater in men, resulting in higher plasma levels of propranolol in women after oral dosing.⁸ Interestingly, subsequent findings suggest that this higher plasma propranolol level in women may not result in a greater β -blockade effect because it is the intrinsic clearance of the less active unbound *R*-isomer (1/100 potency of *S*-propranolol) that accounts for the difference.⁹ The intrinsic clearance of the *S*-isomer is similar between the sexes. Factors that may contribute to a gender-related difference in drug disposition in humans include differences in the ratio of muscle to adipose tissue, hormonal differences (including the menstrual cycle in women), and intrinsic enzyme activity.¹

Corticosteroids are widely used for their antiinflammatory and immunosuppressive effects and represent a class of drugs whose disposition may be influenced by gender. As early as 1958, a gender-related difference in hepatic metabolism of corticosteroids had been noted in rats by Yates et al.¹⁰ In humans, two studies have found a 23% and 21% greater clearance of free prednisolone in female compared with male adult subjects.^{11,12} Gender-related differences may also influence the pharmacodynamics of drugs, but this has not been studied extensively. An in vitro study evaluating whole blood platelet aggregation revealed that the antithrombotic effect of aspirin was significantly greater in men, most likely because of the difference in testosterone levels.¹³ In contrast, an estrogen-associated reduction in the number of pituitary receptors for corticosteroids has been observed in female rats.¹⁴

No study has yet examined the effect of gender on corticosteroid pharmacodynamics in humans. Recently pharmacodynamic models that describe the direct suppressive effects of corticosteroids have been used to characterize the response patterns of plasma cortisol concentrations, blood basophil counts (measured as whole blood histamine), and helper T lymphocyte counts after administration of methylprednisolone to young healthy male subjects.^{15–17} These models are applied in this study to jointly examine the pharmacokinetics and pharmacodynamics of methylprednisolone in relation to gender.

METHODS

Subjects

Twelve healthy, nonsmoking nonobese (within 20% of ideal body weight) subjects (age range, 31 to 49 years; mean age, 37 years) were enrolled in the study: six men and six premenopausal women (defined by the presence of monthly menstruation and absence of menopausal symptoms of the climacteric, including hot flushes, irritability, and night sweats). From the data of Reiss et al.,¹⁸ a minimum sample size of three study subjects in each group was required to provide an 80% power to detect a 25% difference in mean clearance of methylprednisolone with α set at the 0.05 level.¹⁹ The health status of each subject was assessed by a medical history, physical examination, and a blood chemistry and hematologic profile. The women also received a screening for serum human chorionic gonadotropin within 1 week of beginning the study and were not taking oral contraceptives.

None of the subjects had a documented allergy to corticosteroids and none was receiving any concurrent medications known to alter methylprednisolone metabolism. The study was approved by the Investigation Review Board of Buffalo General Hospital, and informed consent was obtained from each subject before enrollment into the study.

Procedures

Each subject completed both the baseline phase (24 hours; no drug) and the methylprednisolone phase (32 hours) of the study at the Buffalo General Hospital. Each study phase began at 8 AM and was separated by a 2-week period. Male subjects were randomized to initiate either the baseline or methylprednisolone phase. Female subjects underwent the methylprednisolone phase during the luteal phase (the 2-week period after ovulation during which estradiol and progesterone concentrations in the blood are relatively elevated and constant) and underwent the baseline phase during the follicular phase of their menstrual cycles. Estradiol and progesterone concentrations were measured for each woman during her methylprednisolone phase study day. Subjects were required to fast from 10 PM the evening before and for 2 hours after receiving the methylprednisolone dose. On each study day, an 18-gauge angiocatheter was inserted into an arm vein to facilitate blood sample collections. The device was kept patent with the frequent use of a dilute heparin (10 units/ml) solution.

During the baseline phase, plasma cortisol concentrations, whole blood histamine concentrations (reflecting basophil concentrations), and helper T lymphocyte counts were obtained in the absence of methylprednisolone. Approximately 5 ml blood samples were drawn into heparin-containing collection tubes every 2 hours for 24 hours. Whole blood (300 μ l) was removed from the heparin-containing collection tubes and stored at -20° C for later histamine analysis. The remaining blood was centrifuged and the plasma harvested and frozen at -20° C until assayed. In addition, 4 ml blood was drawn into EDTA tubes at 0, 2, 4, 8, 12, 16, 20, and 24 hours for the determination of helper T lymphocyte counts.

During the methylprednisolone phase, each subject received an intravenous bolus dose of methylprednisolone sodium succinate (Solu-Medrol; The Upjohn Company, Kalamazoo, Mich.) into the arm contralateral to the one used for blood sampling. A dose of 0.6 mg/kg ideal body weight (IBW) methylprednisolone was used to provide a similar initial blood concentration of methylprednisolone in each subject (as attained in a typical 70 kg man after a 40 mg dose) and to ensure a detectable suppressive response. Blood samples of approximately 5 ml were obtained at 0, $\frac{1}{4}$, $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 3, and 4 hours, then every 2 hours until 24 hours, and at 28 and 32 hours after administration to determine plasma methylprednisolone and cortisol concentrations and whole blood histamine concentrations. The blood samples were processed as described above. In addition to the above-mentioned blood draw times for helper T lymphocyte counts, two additional samples were obtained at 1 and 32 hours.

Assays

Plasma methylprednisolone and cortisol concentrations were determined simultaneously by the HPLC method of Ebling et al.²⁰ The procedure was slightly modified by replacing a

sodium hydroxide wash with water and extracting at 4° C to prevent in vitro hydrolysis of methylprednisolone succinate. The lower and upper limits of quantitation are 10 and 1000 ng/ml. Cortisol concentrations below the limit of quantitation were arbitrarily assigned a value of 5 ng/ml in assessing the cortisol pharmacodynamics. Intraday coefficients of variation (CV) for cortisol and methylprednisolone were 2.2% and 4.8% at 40 ng/ml and 4.5% and 4.4% at 600 ng/ml. Interday CV values were 5.0% and 8.1% at 40 ng/ml and 6.4% and 8.7% at 600 ng/ml. Plasma protein binding of methylprednisolone was determined by ultrafiltration at 37° C by use of the Centrifree Micropartition System (Amicon Inc., Beverly, Mass.).

Whole blood histamine was analyzed by a commercial radioimmunoassay (RIA) procedure (Immunotech International, Westbrook, Maine). The lower limit of quantitation was 0.05 ng/ml. Intraday CV values for the low- and high-quality control samples were 3.0% and 5.8%. Interday CV values for the low- and high-quality control samples were 6.7% and 11.9%.

Total leukocyte counts were performed by an automated hemocytometer (Coulter Counter S-Plus IV; Coulter Electronics Inc., Hialeah, Fla.) on the whole blood samples collected for helper T lymphocyte analysis. The proportion of lymphocytes and monocytes was determined microscopically, and the total number of total circulating lymphocytes per cubic millimeter was determined. The whole blood samples were then lysed, reacted with monoclonal antibody (CD4⁺; Becton Dickinson and Co., Cockeysville, Md.), and analyzed on an automated flow cytometer (FACS 440; Becton Dickinson and Co.). The total number of circulating helper T cells was determined by multiplying the proportion of fluorescent cells by the number of circulating lymphocytes.

Estradiol and progesterone concentrations were measured by a commercial RIA kit (Coat-A-Estradiol and Coat-A-Progesterone; Diagnostic Products Corporation, Los Angeles, Calif.). Low- and high-quality control values were within the company's specified range.

Pharmacokinetics

Methylprednisolone plasma concentration (C_{MP}) versus time (t) curves were fitted to the following equation:

$$C_{MP} = \frac{k_f \cdot \text{Dose}}{CL - V \cdot k_f} \cdot (e^{-k_f \cdot t} - e^{-(CL/V) \cdot t}) \quad (1)$$

by use of the nonlinear least-squares regression computer program PCNONLIN (SCI Software Inc., Lexington, Ky.). In equation 1, k_f is the first-order rate constant for the formation of methylprednisolone from the methylprednisolone succinate ester, CL represents the clearance of methylprednisolone, and V is the volume of distribution for methylprednisolone. This equation assumes negligible reversible metabolism between methylprednisolone and methylprednisolone. The elimination rate constant for methylprednisolone (k) was then calculated as follows:

$$k = CL/V \quad (2)$$

Pharmacodynamics

The direct suppressive effects of methylprednisolone on cortisol and blood basophils (measured by whole blood histamine) concentrations and on helper T lymphocyte counts were characterized by use of previously developed pharmacodynamic models.^{15–17} These models relate the changing methylprednisolone plasma concentrations with the suppressive and return to baseline measures of the pharmacodynamic parameters.

Baseline cortisol concentrations exhibit a circadian rhythm that can be approximated by a cosine function for its circadian input rate (R_{cort}):

$$R_{\text{cort}} = R_m + R_b \cdot \cos \left([T - t_z] \cdot \frac{2\pi}{24} \right) \quad (3)$$

In equation 3, R_m is the mean input rate, R_b is the amplitude of the input rate, T is the clock time within the 24-hour cycle, t_z is the acrophase or peak time of the circadian rhythm, and the ratio $2\pi/24$ converts the 24-hour period into radians. The equation assumes negligible episodic bursts of cortisol secretion.

The pharmacodynamic model characterizing the circadian changes in cortisol concentrations (C) in the blood is described by the following equation:

$$\frac{dC}{dt} = R_{\text{cort}} - k_c \cdot C \quad (4)$$

in which $C = C_0$ at $t = 0$ (initial cortisol concentration). Equation 4 is based on the assumption that the rate of change in the cortisol concentrations at any given time (dC/dt) is a function of both the circadian secretion of cortisol (R_{cort}) and the first-order elimination of cortisol (k_c). After methylprednisolone administration, the inhibitory effect on cortisol secretion yields the following equation:

$$\frac{dC}{dt} = R_{\text{cort}} \cdot \left(1 - \frac{C_{\text{MP}}}{C_{\text{MP}} + \text{IC}_{50}} \right) - k_c \cdot C \quad (5)$$

The value for 50% inhibitory concentration (IC_{50}) represents the concentration of methylprednisolone producing 50% suppression of cortisol circadian secretion. The PCNONLIN program was used to generate the R_m , R_b , t_z , IC_{50} , k_c , and C_0 parameters.

Basophils circulate between the central blood compartment and extravascular compartments. Whole blood histamine (H) is mainly in basophils (98%); thus measures of whole blood histamine directly reflect basophil count.¹⁶ An assumption is made that the whole blood histamine to basophil count ratio remains constant. Corticosteroids act to inhibit the zero-order rate of return of basophils (k_r^0) from the extravascular compartment back into the central blood compartment without affecting movement out of the central blood compartment (k_h). The following equation describes basophil trafficking:

$$\frac{dH}{dt} = k_r^o - k_h \cdot H \quad (6)$$

in which $H = H_0$ at $t = 0$. In the presence of methylprednisolone, this equation is modified to the following:

$$\frac{dH}{dt} = k_r^o \cdot \left(1 - \frac{C_{MP}}{C_{MP} + IC_{50}}\right) - k_h \cdot H \quad (7)$$

in which C_{MP} is described by equation 1. The IC_{50} value is the concentration of methylprednisolone concentration causing 50% inhibition of the basophil return rate into the blood compartment (k_r^o). The PCNONLIN program was used to fit the k_r^o , IC_{50} , k_h , and H_0 values.

Helper T lymphocytes in the blood stream (TH) have been shown to exhibit a circadian rhythm.²¹ The cells circulate between the central blood compartment and extravascular sites and the overall trafficking process can be described by the following equation:

$$\frac{dTH}{dt} = R_m + R_b \cdot \cos\left([T - t_z] \cdot \frac{2\pi}{24}\right) - k_t \cdot TH \quad (8)$$

After administration of methylprednisolone, the relationship is as follows:

$$\frac{dTH}{dt} = R_m + R_b \cdot \cos\left([T - t_z] \cdot \frac{2\pi}{24}\right) \cdot \left(1 - \frac{C_{MP}}{C_{MP} + IC_{50}}\right) - k_t \cdot TH \quad (9)$$

in which $TH = TH_0$ at time $t = 0$. R_m represents the mean number of helper T cells returning back into the blood per unit time, R_b is the amplitude of the entry rate, T is the clock time, t_z is the acrophase or peak time of the function, C_{MP} is the methylprednisolone concentration described by equation 1, IC_{50} is the concentration of methylprednisolone needed to cause 50% inhibition of helper T cell return to the blood compartment, and k_t is the first-order rate constant describing helper T cell movement out of the blood compartment. The PCNONLIN program was used to determine the best-fitted parameters (R_m , R_b , t_z , IC_{50} , k_t , and TH_0) by simultaneous fitting of the baseline (equation 8) and methylprednisolone (equation 9) phases.

In all three pharmacodynamic models (cortisol, basophil (histamine), and helper T lymphocytes), a separate initial concentration (C_0 , H_0 , and TH_0) for the baseline and methylprednisolone phases was fitted because the zero time (initial) values varied between the 2 study days. This provided a more accurate estimate of the elimination/egression constant for that model parameter (k_c , k_h , and k_t).

Twenty-four-hour area under the curve values were calculated with use of LaGrange polynomial interpolation for cortisol, basophil (histamine), and helper T lymphocyte concentrations for both the baseline ($AUC_{BL(0-24)}$) and methylprednisolone phase

(AUC_{MP(0-24)}).²² The area between the baseline and effect curves (ABEC) was calculated as a measure of the 24-hour suppressive effects of methylprednisolone:

$$ABEC = AUC_{BL(0-24)} - AUC_{MP(0-24)} \quad (10)$$

A larger ABEC indicates greater suppression. The time for plasma methylprednisolone concentrations to fall to the IC₅₀ value (T_{IC50}) after its administration was compared as a measure of the duration of suppressive effects.

Statistical analysis

Pharmacokinetic and pharmacodynamic parameters were compared (male versus female subjects) by the nonparametric Wilcoxon rank sum test with statistical significance indicated at the $p = 0.05$ level.

RESULTS

Subject characteristics

Six healthy men and six healthy women completed the study. Table I lists their characteristics. Because the men weighed more than the women, all subjects received 0.6 mg/kg doses based on IBW. The estradiol and progesterone concentrations of the female subjects on the day of the methylprednisolone phase are listed on Table II. The values are within the usual range exhibited during the luteal phase except for estradiol in female No. 1, which is more suggestive of a midcycle (ovulation) value, and the estradiol and progesterone concentrations in female No. 5, which are typically seen during the follicular phase.

Pharmacokinetics

The disposition of methylprednisolone for a selected male subject and female subject is illustrated in Fig. 1. The elimination of methylprednisolone occurs faster in female subjects as indicated by the steeper terminal slope and lower plasma concentrations.

Table III lists the pharmacokinetic parameters for methylprednisolone in the two groups. The AUC was significantly larger in the male group (2133 ± 348 versus 1443 ± 426 ng · hr/ml) because of the greater clearance normalized to IBW observed in the women. The clearance normalized to IBW was 55% higher in women ($p = 0.02$). Female subjects exhibited a 51% higher elimination rate constant ($p < 0.02$), which is reflective of a shorter elimination half-life. The absolute volume of distribution was 43% greater in male subjects but was similar when normalized for IBW or total body weight. No differences in protein binding was seen between the two groups, with men exhibiting a free fraction of $23.1\% \pm 2.6\%$ versus $24.7\% \pm 2.9\%$ in the women; these data are consistent with previous binding results in humans.^{15,23}

Pharmacodynamics

Fig. 2 shows the normal circadian variation in plasma cortisol concentration in a representative male and female subject during baseline conditions. A first-order decline in cortisol concentration is observed after administration of methylprednisolone because of

suppression of endogenous cortisol secretion. Suppressive nadirs tended to occur between 13 to 17 hours before a return to the baseline occurred. The initial cortisol values ($t = 0$) were higher for the methylprednisolone phase. Thus it is necessary to assess return to baseline by comparison with data from the baseline phase. Return to baseline occurred by 32 hours.

The pharmacodynamic parameter estimates for the cortisol model are listed in Table IV. Cortisol data from two women and one man were excluded from the cortisol analysis for various reasons. One woman showed no cortisol suppressive response after the 0.6 mg/kg IBW methylprednisolone dose. The second woman had peak baseline cortisol levels in midafternoon, which is consistent with a reversed sleep-wake cycle and was unlike the typical peak cortisol levels achieved in the morning by the remaining subjects. One male subject's cortisol data were excluded because his baseline cortisol values showed a suppression that yielded lower concentrations than those after methylprednisolone administration.

The IC_{50} value, a measure of intrinsic sensitivity to the suppressive effects of methylprednisolone, was significantly lower in women (0.11 ± 0.09 versus 1.69 ± 1.64 ng/ml; $p < 0.02$). All the individual IC_{50} values for women were smaller than the lowest IC_{50} value for men. There was also greater cortisol suppression observed in the women as indicated by the higher ABEC value (933 ± 348 versus 698 ± 297 ng · hr/ml), although this difference was not statistically different. The remaining parameters were similar between male and female subjects.

Blood basophils were measured as whole blood histamine and profiles for a representative male and female subject are depicted in Fig. 3. Blood histamine concentrations were relatively constant during the baseline phase. During the methylprednisolone phase, a decrease in blood histamine concentration occurred after steroid administration, with the nadir occurring at about 7 to 11 hours. Return to baseline occurred by 24 to 32 hours.

The pharmacodynamic parameters for whole blood histamine are shown in Table V. A slower zero-order rate of entry of basophils into the central blood compartment (k_p^0) was observed in the group of women (7.98 ± 3.66 versus 14.57 ± 7.32 ng/ml/hr; $p = 0.05$). The k_h value, indicative of the egress constant for basophils, was similar between both groups. A lower IC_{50} value was observed for the female subjects (14.33 ± 10.88 versus 6.64 ± 5.30 ng/ml), although this did not reach statistical significance. The group of female subjects exhibited a significantly smaller ABEC value (401 ± 199 versus 660 ± 273 ng · hr/L; $p = 0.02$).

Helper T lymphocytes in both male and female subjects exhibited a circadian rhythm in the blood during baseline conditions (Fig. 4). However, this rhythm was not as apparent as that observed with the cortisol data because of its lesser amplitude and the fewer data points (8 to 10) obtained. After administration of methylprednisolone, there was a rapid decline of helper T lymphocyte counts, with the nadir occurring between 5 and 8 hours and a return to baseline by 24 hours.

The pharmacodynamic parameters obtained from modeling of the helper T lymphocyte data are presented in Table VI. There were no significant differences in these parameters between male and female subjects. The mean IC₅₀ value was 35% greater in the men; however, this difference was not statistically different (20.12 ± 17.20 versus 14.87 ± 20.36 ng/ml) because of the large intersubject variability.

DISCUSSION

Pharmacokinetics

Gender-specific forms of cytochrome P450 have been isolated in the rat and are important in determining sex-dependent steroid metabolism.²⁴ Gender-based differences in the metabolic activity of specific hepatic cytochrome P450 enzyme families have also been identified in humans. Relling et al.²⁵ found that the P450 isoform CYP1A2 had lower activity in women, as measured by urinary metabolic ratios, after administration of caffeine. Hunt et al.²⁶ found that the activity of the P450 isoform CYP3A was higher in women, as quantified by measuring erythromycin *N*-demethylation in an in vitro experiment with human liver. Methylprednisolone undergoes a variety of biotransformation processes that involve the mixed-function oxidase system of the liver and possibly other organs, including CYP3A-catalyzed 6 β -hydroxylation.^{27,28} Thus the findings of Hunt et al.²⁶ concur with our observation of faster clearance of methylprednisolone in women. This produces a shorter elimination half-life in women and is an important feature because the latter determines how long plasma methylprednisolone concentrations exceed the IC₅₀ value and thus how long suppressive responses will be maintained. The greater clearance of methylprednisolone in women is consistent with two studies that show a greater clearance of free prednisolone in women.^{11,12} However, neither study indicated the women's menstrual cycle phase at the time of the study.^{11,12}

Two female subjects in our study had clearance/IBW values that were similar to those of the male subjects, whereas the remaining four women had markedly larger clearance/IBW values. This diversity of methylprednisolone clearances in women is consistent with the findings of Pfaffenberger and Horning,²⁹ who examined 24-hour urinary excretion of endogenous steroid metabolites in 52 healthy men and premenopausal women (all younger than 36 years of age). About two thirds of the women were found to have a distinctly different urinary metabolic profile from that observed in men, whereas the urinary excretion pattern in the remaining third of the women was similar to men. No information was given regarding the menstrual cycle phase.

In our study, all female subjects received methylprednisolone during the luteal phase of their menstrual cycle (Table II). However, in female subject No. 5, the low estradiol and progesterone levels were more consistent with those found during the follicular phase. In fact, this subject's menses started about 24 hours into the methylprednisolone phase. Thus large variation was observed in the estradiol levels of the six female subjects. No clear relationship could be observed between the female hormone levels and methylprednisolone clearance. Female subject No. 2, with the second highest hormone levels, and female subject No. 5, with the lowest hormone levels, displayed the greatest methylprednisolone clearances.

We chose to study the methylprednisolone phase during the luteal phase of the menstrual cycle based on the premise that any pharmacokinetic or pharmacodynamic perturbation caused by hormonal differences would be most apparent when the female hormones were relatively high. Recently, Bruguerolle et al.³⁰ examined the effect of menstrual phase on theophylline metabolism in nine women with asthma (mean age, 23.9 years) and observed the opposite finding. Single 240 mg parenteral theophylline doses were given on days 0, 10, and 20 (day 0 = first day of menstrual cycle). The clearance of theophylline was significantly lower on day 20 (luteal phase). Clearance was 28% and 59% faster on days 10 and 0. No measurements of estradiol or progesterone were made.

Pharmacodynamics

The cortisol pharmacodynamic model used in this study differed from our previous studies.^{15,18,23,31} This model examines the rate of change in cortisol concentration as a function of both the circadian cortisol secretion and the suppressive effect of methylprednisolone concentrations with time. This model is similar to the helper T lymphocyte model redefined by Fisher et al.¹⁷ As such, the pharmacodynamic parameters of R_m and R_b have rate rather than concentration units and the values from the previous studies have to be converted for direct comparison.¹⁷ Such converted R_m and R_b values are similar to those obtained in the present study.^{15,23,31}

The cortisol IC_{50} value was more than 15-fold lower in the female group compared with the male group. The large variance seen in the latter group was caused by one man who had an IC_{50} value of 4.54 ng/ml. Exclusion of this value would still yield a nine-fold greater mean IC_{50} of 0.98 ± 0.45 ng/ml for the male group. This indicates a greater sensitivity in women to the suppressive effects of methylprednisolone on cortisol secretion. In contrast, Turner¹⁴ found a 20% lower number of glucocorticoid receptors in the pituitary gland of female rats because of the presence of estrogen. Turner¹⁴ suggested that decreased glucocorticoid receptor density in the female pituitary gland should contribute to a reduction in the negative feedback (suppressive) effects of glucocorticoids at the pituitary level. However, the study did not examine receptor binding affinities.

Horrocks et al.³² studied plasma corticotropin and cortisol concentrations in five men and five premenopausal women (during the follicular phase of their menstrual cycle) over a 24-hour period.³² The mean corticotropin concentration and the 24-hour corticotropin AUC was significantly larger in the male group without any difference in the 24-hour cortisol AUC or in the mean cortisol concentration, suggesting that the female adrenal cortex may be more sensitive to corticotropin. Thus any equivalent reduction in corticotropin secretion should yield a larger cortisol suppressive effect in the female group. Our study also did not find a difference in the mean cortisol concentration (calculated as R_m/k_c) or 24-hour cortisol AUC between genders.

The cortisol IC_{50} values for the men were similar to those obtained previously.^{15,23,31} Although the women had a lower IC_{50} value, their duration of cortisol suppression, as reflected by their $T_{IC_{50}}$ values and nadir times, were similar to the men and is explained by their increased elimination rate of methylprednisolone. The net suppressive response of

cortisol to methylprednisolone in both groups were similar, as indicated by the ABEC values (Table IV).

It is unclear whether estrogen or progesterone is responsible for the increased sensitivity observed in the women. Estrogen (0.1 mg estradiol twice daily) treatment in nine subjects with mild diabetes was found to potentiate the glucosuric effect of exogenously administered cortisol.³³ The same effect could not be seen with prednisone or prednisolone. Also, addition of estrogens to corticosteroid therapy resulted in a threefold to twentyfold reduction in the corticosteroid requirement for control of inflammatory skin diseases.³⁴ Neither of these two human studies separated possible metabolic versus pharmacodynamic interactions. In our study, no clear relationship was observed between the female hormone levels and the methylprednisolone IC₅₀ values for cortisol suppression. Carandente et al.³⁵ demonstrated that the circadian rhythm of serum cortisol in women is consistent and unaffected by the hormonal changes throughout the menstrual cycle.

The k_c values did not differ between genders (Table IV). This parameter represents the elimination rate constant of cortisol for a fully suppressive dose of methylprednisolone and suggests that cortisol disposition is unaffected by gender. This is of interest in light of the increased elimination observed for methylprednisolone and the previously indicated gender difference in elimination of prednisolone.^{11,12} Our cortisol k_c values were similar to those reported previously.^{15,18,23,31}

For the basophil trafficking model, the IC₅₀ values were more than twofold lower in the women (Table V). A linear correlation ($r = -0.988$; $p = 0.0002$) was found (Fig. 5) between these IC₅₀ values and the natural logarithm of the estradiol concentration (the estradiol concentration below the detection limit of 20 pg/ml was assigned a value of 10 pg/ml). This suggests that the sensitivity to methylprednisolone effect on basophil trafficking is inversely affected by estradiol in women.

Subjects in the male group exhibited a greater degree of basophil (histamine) suppression as shown by the significantly larger ABEC value. This is attributable to the gender differences in several ABEC determinants. The components of ABEC were previously defined¹⁶ and can be simplified to the following equation:

$$ABEC \approx H_o \cdot t + \frac{k_r^o}{k \cdot k_h} \cdot [\ln k - \ln IC_{50} - k \cdot t + \ln AUC] \quad (11)$$

in which all the variables are as previously defined in the pharmacokinetic (k and AUC) and basophil (histamine) models (H_o , k_r^o , k_h , and IC_{50}) with $t = 24$ hours. The AUC and k_r^o values are greater in the men, while k is larger in the women. All three of these factors favor a larger ABEC in the male group. These factors are of sufficient magnitude to overcome the gender difference in IC_{50} , which favors a larger ABEC value in the women. The larger k_r^o value in the men is reflective of the larger baseline (basophil) histamine concentration (H_o). Thus, for a fully suppressive methylprednisolone dose, a greater net suppression can occur in men.

In our helper T lymphocyte model, no statistically significant differences in parameters were found; however, the mean helper T lymphocyte IC_{50} value was 37% larger in the male group. However, estrogen receptors are found on lymphoid cells and estrogen may modulate helper T lymphocyte function and differentiation.^{36,37} Helper T lymphocyte maturation is facilitated by estrogen.³⁶ A gender-based difference in lymphocyte subsets have also been shown. Tollerud et al.³⁸ examined 266 nonsmoking adults and found that women had a significantly higher proportion of $CD4^+$ (helper T lymphocytes) cells and a lower proportion of $CD8^+$ (suppressor T lymphocytes) than men. A similar tendency was observed in our 12 subjects. T lymphocyte counts also vary throughout the menstrual cycle, displaying an inverse relationship to the estradiol concentrations, with counts lowest at ovulation when estradiol concentrations are at its highest.³⁹

The differences in IC_{50} values for cortisol secretion and basophil and helper T lymphocyte trafficking indicate their relative sensitivities to methylprednisolone suppressive effects. Thus for a constant methylprednisolone dose, the ability to detect a gender-related difference in the IC_{50} value (intrinsic sensitivity) would be greatest with cortisol relative to basophil, followed by helper T lymphocyte suppression. This is consistent with our finding that mean male to female IC_{50} ratios ranged from 1.4 to 15.4 and were greatest with cortisol and lowest with helper T lymphocyte suppression.

The findings of this study indicate that pharmacokinetic and pharmacodynamic differences exist between men and women for methylprednisolone. Women have a larger clearance of methylprednisolone when normalized to IBW. Women were more sensitive to the effects of methylprednisolone on cortisol suppression and may be more sensitive with respect to basophils and helper T lymphocytes as well, although the latter two findings were not statistically significant. Methylprednisolone suppressive effects on basophil trafficking showed greater sensitivity at higher estradiol concentrations in women. In general, our findings suggest that men and women should receive the same methylprednisolone dose normalized to IBW (e.g., 0.6 mg/kg), because even though women eliminate the drug faster, they also have a greater response (as measured by sensitivity to cortisol suppression) to a lower concentration of the drug. The similar time for plasma methylprednisolone concentrations to fall to the IC_{50} value (T_{IC50}) after its administration and the similar net response (ABEC) between the two groups support the recommendation of identical doses based on IBW.

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Fig. 1. Plasma methylprednisolone versus time profiles for a selected male subject (*solid circles*) and female subject (*open circles*). Symbols are experimental data and lines indicate the least-squares regression fittings. Time 0 is the time of the administration of the dose.

Fig. 2. Plasma cortisol concentration versus time profiles for a selected male subject (**top panel**) and female subject (**bottom panel**). Symbols show experimental data and lines represent the fittings to the pharmacodynamic model shown above. The baseline phase is displayed by the open symbols and broken lines. The methylprednisolone phase is displayed by the solid symbols and solid lines.

Fig. 3. Whole blood histamine concentration versus time profiles for a selected male subject and female subject. The panels, symbols, and lines are defined in the *legend* of Fig. 2.

Fig. 4.

Helper T lymphocyte concentration versus time profiles for a selected male subject and female subject. The panels, symbols, and lines are defined in the *legend* of Fig. 2.

Fig. 5.

Correlation between the methylprednisolone 50% inhibitory concentration (IC₅₀) value for basophil (histamine) suppression and the logarithm of the estradiol concentration (in women). The *solid line* ($IC_{50} \text{ (ng/ml)} = -4.32 \cdot \ln [\text{estradiol (pg/ml)}] + 25.1$) represents the regression ($r = -0.988$; $p = 0.0002$).

Table I

Subject characteristics

Comparison	Men	Women
Age (yr)	37.3 ± 6.6	37.0 ± 6.0
TBW (kg)	80.6 ± 11.3	56.2 ± 5.3
IBW (kg)	75.5 ± 5.7	53.0 ± 4.1
Dose/IBW (mg/kg)	0.60 ± 0.00	0.60 ± 0.01
Dose/TBW (mg/kg)	0.57 ± 0.05	0.57 ± 0.04

Data are mean values ± SD ($n = 6$).

TBW, Total body weight; IBW, ideal body weight.

Table II

Hormone levels of female subjects during methylprednisolone phase

Female subject	Day since start of menstruation	Estrogen (estradiol) (pg/ml)	Progesterone (ng/ml)
1	22	343	15.4
2	24	128	12.1
3	20	35	2.5
4	17	91	4.8
5	23	<20	0.7
6	18	103	12.4
Normal range	—	15–260	2.5–28

Table III

Pharmacokinetic parameters for methylprednisolone

Parameter	Men	Women	p Value
AUC (ng · hr/ml)	2133 ± 348	1443 ± 426	0.02
CL (L/hr)	21.6 ± 2.7	23.3 ± 5.8	NS
CL/IBW (L/hr/kg)	0.288 ± 0.047	0.447 ± 0.124	0.02
V (L)	80.1 ± 14.3	56.1 ± 7.7	<0.02
V/IBW (L/kg)	1.06 ± 0.18	1.07 ± 0.18	NS
k _{MP} (hr ⁻¹)	0.274 ± 0.048	0.413 ± 0.070	<0.02
t _{1/2} (hr)	2.58 ± 0.40	1.72 ± 0.29	<0.02
k _f (hr ⁻¹)	9.54 ± 9.37	3.14 ± 2.02	<0.05
Unbound fraction (%)	23.1 ± 2.6	24.7 ± 2.9	NS

Data are mean values ± SD (*n* = 6).

AUC, Area under the methylprednisolone concentration versus time curve from time zero to infinity; CL, clearance; NS, not significant; IBW, ideal body weight; V, apparent volume of distribution; k_{MP}, methylprednisolone elimination rate constant; t_{1/2}, methylprednisolone elimination half-life; k_f, methylprednisolone formation rate constant from the succinate ester.

Table IV

Pharmacodynamic parameters for cortisol suppression

Parameter	Men	Women	p Value
R_m (ng/ml/hr)	18.0 ± 5.9	18.0 ± 3.7	NS
R_b (ng/ml/hr)	14.8 ± 5.9	13.3 ± 2.6	NS
t_z (24 hr clock)	7.53 ± 2.02	7.02 ± 1.65	NS
k_c (hr ⁻¹)	0.294 ± 0.078	0.276 ± 0.045	NS
IC ₅₀ (ng/ml)	1.69 ± 1.64	0.11 ± 0.09	<0.02
ABEC (ng · hr/ml)	698 ± 297	933 ± 348	NS
T _{IC50} (hr)	22.0 ± 3.0	22.7 ± 2.5	NS

Data are mean values $\pm$ SD (men: $n = 5$; women: $n = 4$).

R_m , Mean cortisol circadian secretory rate; R_b , cortisol circadian secretory rate amplitude; t_z , peak time of the circadian function; k_c , cortisol elimination rate constant; IC₅₀, 50% inhibitory concentration; ABEC, area between the baseline and effect curves; T_{IC50}, time for methylprednisolone concentration to decline to IC₅₀ value.

Table V

Pharmacodynamic parameters for basophil (histamine) trafficking

Parameter	Men	Women	p Value
k_r^O (ng/ml/hr)	14.57 ± 7.32	7.98 ± 3.66	0.05
k_h (hr ⁻¹)	0.297 ± 0.078	0.227 ± 0.055	NS
IC ₅₀ (ng/ml)	14.33 ± 10.88	6.64 ± 5.30	NS
ABEC (ng · hr/ml)	660 ± 273	401 ± 199	0.02
T _{IC50} (hr)	14.9 ± 3.4	12.7 ± 2.4	NS

Data are mean values $\pm$ SD ($n = 6$).

k_r^O , Zero-order rate of return of basophils from the extravascular compartment; k_h , first-order rate constant for egress of basophils from blood to the extravascular compartment; IC₅₀, 50% inhibitory concentration; ABEC, area between the baseline and effect curves; T_{IC50}, time for methylprednisolone concentration to decline to IC₅₀ value.

Table VI

Pharmacodynamic parameters for helper T cell trafficking

Parameter	Men	Women	p Value
R_m (cells/mm ³ /hr)	535 ± 195	525 ± 117	NS
R_b (cells/mm ³ /hr)	120 ± 87	156 ± 79	NS
t_z (24 hr clock)	20.2 ± 4.6	21.6 ± 2.0	NS
k_1 (hr ⁻¹)	0.520 ± 0.105	0.613 ± 0.102	NS
IC ₅₀ (ng/ml)	20.12 ± 14.63	14.87 ± 20.36	NS
ABEC (cells · hr/mm ³)	12987 ± 4455	9261 ± 4513	NS
T _{IC50} (hr)	13.4 ± 2.0	11.2 ± 2.6	NS

Data are mean values ± SD ($n = 6$).

R_m , Mean circadian number of helper T cells entering into blood from the extravascular compartment per unit time; R_b , amplitude of the circadian entry rate; t_z , peak time of the circadian function; k_1 , first-order rate constant describing helper T cell movement out of the blood compartment; IC₅₀, 50% inhibitory concentration; ABEC, area between the baseline and effect curves; T_{IC50}, time for methylprednisolone concentration to decline to IC₅₀ value.