Corticosteroid Pharmacodynamic Modeling: Osteocalcin Suppression by Prednisolone

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INTRODUCTION

Loss of bone mass is frequently a limiting factor in using corticosteroids in patients with conditions such as rheumatoid arthritis and asthma. A sensitive marker for corticosteroid suppression of bone metabolism is osteocalcin, a protein secreted by osteoblast cells during osteogenesis (1). Much of the secreted osteocalcin is incorporated into the bone matrix, however, some is released into the blood (1). The normal baseline profile of osteocalcin is circadian, with an acrophase (peak) which is about 12 hr different from that of cortisol (2). The concentration of osteocalcin in serum is said to reflect the osteoid volume and is therefore directly related to the formation of new bone rather than resorption (3).

Suppression of osteocalcin has been evaluated after intravenous betamethasone (4), oral prednisone (2), and inhaled beclomethasone (5) and budesonide (6). Nevertheless, pharmacodynamic models have not yet been utilized to quantitate this corticosteroid action. Pharmacodynamic models have been used to characterize a variety of steroid-sensitive systems both at baseline and following corticosteroid administration (7). The general profile of osteocalcin suppression resembles other corticosteroid effects. This report shows that existing models can be adapted to characterize the baseline and suppression characteristics of osteocalcin as a function of corticosteroid concentration.

METHODS

Osteocalcin concentrations were interpolated from Fig. 3 of Nielsen *et al.* (2). In this study normal volunteers were given prednisone orally, 2.5 and 10 mg, at 2000 hr. Blood samples were collected for evaluation of serum osteocalcin every hour from 3 hr before the dose to 21 hr postdose. Additionally, a baseline phase in which no drug was administered was included to characterize the baseline circadian rhythm of osteocalcin.

Because prednisolone concentrations were not measured in this study, pharmacokinetic input was based on data previously generated in this laboratory. Rose *et al.* (8) characterized free prednisolone concentrations in normal male volunteers following an intravenous dose of 5 mg with a monoexponential function. Half-life was 1.74 hr and volume of distribution (V_{SS}) was 213 L. To estimate free prednisolone concentrations following the 2.5- and 10-mg oral doses of prednisone used in this study, the elimination constant ($k = 0.693/t_{1/2}$) and V values were used in a Bateman function. The apparent absorption/conversion rate constant (k_a) was assigned a value of 0.6 hr^{-1}. This value is based on observations that peak prednisolone concentrations are achieved at about 2 hr after an oral dose of prednisone (9).

The pharmacodynamic model equations are as follows:

$$R_{OC} = R_M + R_B \cdot \text{Cos}(T_c) \quad (1)$$

$$T_c = (t - T_Z) \cdot \frac{2\pi}{24} \quad (2)$$

$$\frac{dOC}{dt} = R_{OC} - k_{deg} \cdot OC \quad (3)$$

$$k_{deg} = R_M/\overline{OC} \quad (4)$$

$$\frac{dOC}{dt} = R_{OC} \cdot \left(1 - \frac{C_P}{(C_P + IC_{50})}\right) - k_{deg} \cdot OC \quad (5)$$

$$C_p = \frac{k_a \cdot \text{Dose}}{V \cdot (k_a - k_{el})} (e^{-k_{el} \cdot t} - e^{-k_a \cdot t}) \quad (6)$$

where R_{OC} is the circadian input rate of osteocalcin to the plasma compartment and R_B and R_M are the amplitude and mesor of the circadian cosine function. For computer fitting, units of time (t) are converted to radians by the ratio $2\pi/24$ (rad/hr). The acrophase, or peak, occurs at T_Z and the phase-adjusted time is T_C. In the absence of exogenous steroid, Eq. (3) characterizes the input of osteocalcin as R_{OC}, and its first-order elimination as k_{deg} times osteocalcin concentration (OC). The value of k_{deg} is found by dividing R_M by the average OC concentration ($\overline{OC}$). Following prednisolone administration, as in Eq. (5), R_{OC} is suppressed as a function of C_P, the free prednisolone concentration, and IC_{50}, the concentration of free prednisolone which diminishes R_{OC} by 50%. These equations were fitted simultaneously to the data of Nielsen *et al.* (2) using the PCNONLIN program (Statistical Consultants Inc., Lexington KY) and parameter estimates were obtained for R_M, R_B, T_Z, and IC_{50}. Weighting was performed using the function $1/Y^2$.

RESULTS AND DISCUSSION

The model successfully characterized the general pattern of osteocalcin concentrations during baseline and after the two prednisone doses as shown in Fig. 1. Prednisone doses were given at about 3 hr, at which time osteocalcin concentrations departed from their baseline pattern and remained suppressed for about 20 hr before returning to baseline concentrations. Pharmacodynamic parameters are presented in Table I with estimated standard errors along with the weighted sum of squared residuals (WSSR). The calculated value of OC was 3.35 nmol/L and $k_{deg} = 0.0642$ hr^{-1}. All parameters were estimated within a reasonable degree of precision considering the inherent variability in these average experimental data and the simultaneous fitting process.

The IC_{50} is a direct measure of steroid sensitivity in this system; the value of 4.5 ng/ml closely corresponds to IC_{50}

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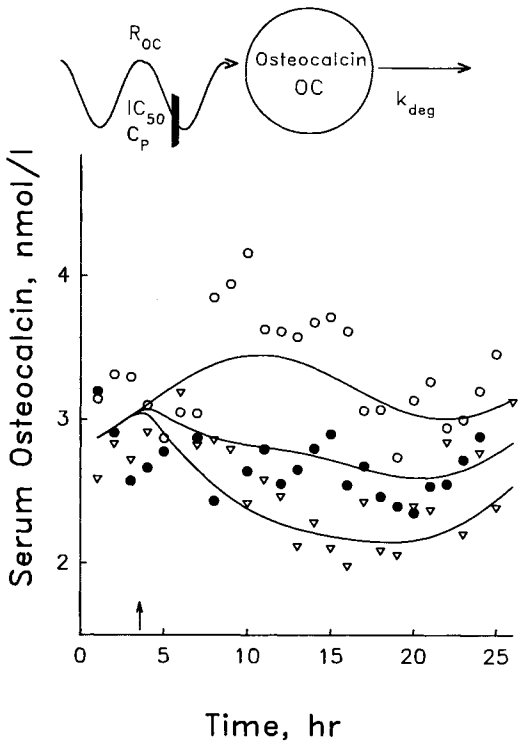

Fig. 1. Composite graph showing the pharmacodynamic model and serum osteocalcin suppression patterns after administration of 0 (○), 2.5 (●), and 10 (▽) mg of prednisone and lines generated by fitting the model [Eqs. (1)–(6)] to the three data sets simultaneously. The vertical arrow designates the time at which prednisone was administered.

values based on free prednisolone for endogenous cortisol and basophil histamine suppression (1.0 and 5.7 ng/ml) in man (10). Furthermore, these values closely correspond to the receptor binding affinity for prednisolone *in vitro* in rat liver (22 ng/ml) (11). Because T_Z is the time when R_B reaches its maximal value, it does not clearly correspond to the *OC* peak. In alternate versions of the model, Eq. (4) was omitted and k_{deg} was estimated with the other parameters. However, the extra parameter produced no improvement in model fitting. The appearance of the fitted curves was moderately improved when initial conditions for the three differential equations were fitted as separate parameters. The addition of these two parameters failed to improve the overall quality of the fit as the Akaike's information criterion was larger for the more complicated model (120) than the primary model (118).

Prednisolone concentrations were not available in this study and kinetic and dynamic estimates are thus approximations and population average values. We have assumed complete bioavailability of prednisolone from the prednisone formulation. Rose *et al.* found that a 5-mg oral prednisone dose was 99% bioavailable when compared to intravenous prednisolone at the same dose (8). The assumption of linear pharmacokinetics of free prednisolone (in contrast to total drug concentrations) is supported by Rose *et al.* as well. Moreover, free prednisolone pharmacokinetics were extrapolated over a very small range. Unrecognized nonlinearities or circadian differences in the kinetics or dynamics of prednisone/prednisolone might produce biased results, particularly in the IC_{50} value. Nevertheless, this model allows for a reasonable characterization of the observed data.

Differing subject characteristics might also modestly complicate this analysis. Both male and female subjects were used in the Nielsen *et al.* study (2), as opposed to only males in the pharmacokinetic study (8). There are no gender differences in the baseline patterns of *OC* (12). However, the clearance of total and free prednisolone is about 20% greater in females (13). Also, the clearance of free prednisolone following a morning dose is about 14% lower compared to a dose administered at 1800 hr (13). Optimally, pharmacodynamic modeling should be performed using jointly measured pharmacokinetic data.

This system, typified by readily responsive serum osteocalcin concentrations and a low IC_{50} value, shows a high sensitivity to prednisolone. Indeed, prednisolone concentrations are usually well in excess of the IC_{50} value of 4.5 ng/ml. Similar to other "direct effects," osteocalcin seems to respond immediately to steroid, more quickly than can be accounted for by gene-mediated processes, which incur a lag phase of 0.5 hr to 2 hr (11). In further studies this aspect might be more fully explored by giving the steroid dose at the acrophase. This will provide a larger dynamic range in which to evaluate whether the initial response is an exponential decline of osteocalcin concentrations. Factors such as cortisol, basophils measured by whole-blood histamine, and T-helper cells are useful and important markers of corticosteroid pharmacodynamics in humans (7). Similarly, osteocalcin suppression is both clinically relevant to corticosteroid adverse effects and readily evaluable with immunoassay and pharmacodynamic modeling. Further study of corticosteroid suppression of osteocalcin is warranted.

Table I. Pharmacodynamic Parameters for Osteocalcin Suppression with Approximate Standard Errors

	Parameter	SE
R_m (nmol/L · hr)	0.215	0.043
R_b (nmol/L · hr)	0.0704	0.0129
T_Z (hr)	5.05	0.82
IC_{50} (ng/ml)	4.54	0.90
WSSR	2.03	

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