The Pharmacokinetics of Recombinant Human Relaxin in Nonpregnant Women After Intravenous, Intravaginal, and Intracervical Administration

Sharon A. Chen,[1,7] Andrew J. Perlman,[2] Noreen Spanski,[2] C. Matthew Peterson,[3] Steven W. Sanders,[4,8] Robert Jaffe,[5] Mary Martin,[5] Tamir Yalcinkaya,[5,9] Robert C. Cefalo,[6] Nancy C. Chescheir,[6] Mary K. Menard,[6] and Joyce Mordenti[1]

Received September 23, 1992; accepted January 5, 1993

The pharmacokinetics of recombinant human relaxin (rhRlx) after intravenous (iv) bolus administration and the absorption of rhRlx after intracervical or intravaginal administration were determined in nonpregnant women. The study was conducted in two parts. In part I, 25 women received 0.01 mg/kg rhRlx iv. After a minimum 7-day washout period, these women were dosed intracervically (n = 10) or intravaginally (n = 15) with 0.75 or 1.5 mg rhRlx, respectively, in 3% methylcellulose gel. Part II was a double-blind, randomized, three-way crossover study in 26 women. At 1-month intervals, each woman received one of three intravaginal treatments consisting of 0 (placebo), 1, or 6 mg rhRlx in 3% methylcellulose gel. The serum concentrations of relaxin following iv administration were described as the sum of three exponentials. The mean (±SD) initial, intermediate, and terminal half-lives were 0.09 ± 0.04, 0.72 ± 0.11, and 4.6 ± 1.2 hr, respectively. Most of the area under the curve was associated with the intermediate half-life. The weight-normalized clearance was 170 ± 50 mL/hr/kg. The observed peak concentration was 98 ± 29 ng/mL, and the weight-normalized initial volume of distribution was 78 ± 40 mL/kg, which is approximately equivalent to the serum volume. If central compartment elimination was assumed, the volume of distribution at steady state (V_{ss}/W) was 280 ± 100 mL/kg, which is approximately equivalent to extracellular fluid volume. V_{ss}/W could be as large as 1300 ± 400 mL/kg without this assumption. After intravaginal administration of the placebo gel, endogenous relaxin concentrations were evident (i.e., ≥20 pg/mL) in 9 of the 26 women (maximum concentrations, 23–234 pg/mL). A similar proportion of women (approximately 35–40%) exhibited measurable serum concentrations of relaxin following intravaginal rhRlx treatment; this proportion increased to 90% following intracervical rhRlx treatment. For both routes of administration, the maximum serum concentrations of relaxin were usually within the range of values observed for endogenous relaxin, suggesting that the absorption of rhRlx was minimal.

KEY WORDS: relaxin; pharmacokinetics; absorption; intravenous; intracervical; intravaginal.

INTRODUCTION

Relaxin is an endogenous hormone that is structurally related to insulin (1) and is produced in the corpus luteum (2,3) and placenta (4). Endogenous relaxin concentrations in the range of 30 to 150 pg/mL have been detected in plasma collected from nonpregnant women 7–10 days following the peak of the luteinizing hormone surge during the menstrual cycle (5). If the woman conceives during that cycle, relaxin increases dramatically at the time when human chorionic gonadotropin is first detectable in plasma. In normal pregnancies, endogenous relaxin reaches a peak of approximately 1100 pg/mL at 12 weeks after conception, then declines to approximately 500 pg/mL at the time of delivery (6).

The role of endogenous relaxin during pregnancy is unclear. In patients receiving ovum donations, serum relaxin is undetectable during pregnancy in the majority of patients because of the lack of a functioning corpus luteum (6). In a case report of one patient after an ovum donation, in whom no endogenous serum relaxin concentrations were expected, onset of labor was spontaneous, but delivery was prolonged (7). This suggested that systemic concentrations of endogenous relaxin were not necessary for labor but were necessary to facilitate delivery (7).

Purified porcine relaxin has been used as a single agent (8) and in combination with intravaginal estradiol or prostaglandin F_{2a} (9) to ripen the cervix in women and, in turn, to shorten the induction–delivery interval. Porcine relaxin has a similar molecular weight and approximately 40% sequence homology to that of human relaxin (10). Absorption of porcine relaxin following intracervical administration was observed in five of six near-term pregnant women who were treated with 2 mg porcine relaxin in a tylose gel prior to medical induction. Peak serum concentrations of relaxin in these women ranged from approximately 1000 to 3500 pg/mL and occurred 1.5–3 hr after dosing (11). Absorption of other proteins from the vagina has been described [i.e., insulin, peanut protein, thyroid-stimulating hormone, and a gonadotropin-releasing hormone analogue (TAP-144)] and is reviewed elsewhere (12).

Human relaxin is currently under development as a potential therapeutic agent to decrease the incidence of cesarean deliveries and to reduce maternal–fetal morbidity by changing the consistency of the cervix prior to induction of labor. The aim of our present study was to determine the pharmacokinetics of rhRlx after iv administration and the absorption of rhRlx after intracervical and intravaginal administration in a defined population of nonpregnant healthy women, prior to clinical studies in pregnant women.

[1] Department of Pharmacokinetics, Genentech, Inc., South San Francisco, California 94080-4990.
[2] Department of Clinical Research, Genentech, Inc., South San Francisco, California 94080-4990.
[3] Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Utah College of Medicine, Salt Lake City, Utah 84132.
[4] Drug Research Center, University of Utah Medical Center, Salt Lake City, Utah 84132.
[5] Reproductive Endocrinology Center, University of California San Francisco, San Francisco, California 94143.
[6] Clinical Research Unit, University of North Carolina Memorial Hospital, Chapel Hill, North Carolina 27514.
[7] To whom correspondence should be addressed.
[8] Present address: Theratech, Salt Lake City, Utah 84108.
[9] Present address: West Virginia University, Charleston, West Virginia 25302.

0724-8741/93/0600-0834$07.00/0

MATERIALS AND METHODS

Materials. Human relaxin consists of two polypeptide chains covalently bonded by two disulfide bridges: the A chain has 24 amino acids and an additional internal disulfide bridge, and the B chain has 29 amino acids. It has a theoretical molecular mass of 6.0 kDa, has a p*I* of 9.1, and is not glycosylated (13). Recombinant human relaxin (rhRlx) is produced in *Escherichia coli* and is identical in sequence to the predominant form of relaxin in human corpora lutea and pregnancy sera (14). The iv formulation was a solution of rhRlx in a sterile, isotonic buffer. For intracervical and intravaginal administration, rhRlx was formulated in 3% methylcellulose gel. *In vitro* testing demonstrated that rhRlx was immediately, and completely released from the gel into any suitable buffer upon mixing.

Experimental Design. The study was conducted in two parts. Part I was conducted in 25 nonpregnant women who had bilateral tubal ligations at least 9 months prior to the start of the study. All women received rhRlx as an iv bolus (0.01 mg/kg). After a minimum 7-day washout period, they received rhRlx in 3% methylcellulose gel. The doses were 1.5 mg intravaginally (n = 15) or 0.75 mg intracervically (n = 10). Part II was a double-blind, randomized, three-way crossover study in twenty-six nonpregnant women who had bilateral tubal ligations at least 1 year prior to the start of the study. At 1-month intervals, each subject received one of three intravaginal treatments consisting of 0 (placebo), 1, or 6 mg rhRlx in 3% methylcellulose gel.

Part I. Twenty-five women (mean ± SD age, 38 ± 5 years; range, 23–46 years; weight, 62.4 ± 12.1 kg; range, 41.3–84.6 kg; and height, 163.4 ± 8.0 cm; range, 141.0–177.8 cm) participated in the study. The women arrived at the study center on the mornings of dosing after at least a 10-hr fast. A standardized lunch, dinner, and breakfast the next morning were provided 4, 10, and 24 hr after dosing, respectively. For iv administration, a catheter was placed in a vein in each arm; one catheter was used exclusively for dosing and one catheter for blood collection. After obtaining a predose blood sample, the women received 0.01 mg/kg rhRlx as a rapid bolus into the dosing catheter. Twenty-six blood samples (3.0 mL each) were removed from the sampling catheter over the next 24 hr. After a minimum 7-day washout period, the women returned to the study center, where they were assigned to intravaginal (n = 15) or intracervical (n = 10) treatment groups. For intravaginal administration, 4 mL of methylcellulose gel containing 1.5 mg rhRlx was inserted into the posterior cul-de-sac of the vagina, and a Koromex diaphragm (Youngs Drug Products Corp., Piscataway, NJ) was used for 8 hr postadministration to keep the relaxin in place. For intracervical administration, 2 mL of methylcellulose gel containing 0.75 mg rhRlx was inserted into the cervical canal using a glass syringe with a Makler cannula (SEFI Medical Instruments, Haifa, Israel). A diaphragm was not used after intracervical administration. After either topical dose, 19 blood samples (3.0 mL each) were removed from a sampling catheter in an arm vein over the next 48 hr. The women were asked to keep a calendar of the start and stop of each menses for the month prior to their first treatment, throughout the two treatment periods, and for 6 weeks following their second treatment. The women were not dosed during menses.

Part II. Twenty-six women (mean ± SD age, 34 ± 6 years; range, 23–46 years; weight, 65.8 ± 9.1 kg; range, 52.3–85.5 kg; and height, 165.4 ± 4.1 cm; range, 158.8–175.3 cm) participated in the study. The women arrived at the study center on the mornings of dosing after at least a 10-hr fast. A standardized breakfast, lunch, dinner, and breakfast the next morning were provided 1, 4, 8, and 24 hr after dosing, respectively. After obtaining a predose blood sample from a catheter in an arm vein, the women were dosed intravaginally with 4 mL methylcellulose gel containing either 0, 1, or 6 mg rhRlx at concentrations of 0, 0.25, and 1.5 mg/mL, respectively. The women were recumbent for at least 1 hr after dosing. A diaphragm was not used in part II. After dosing, 10 blood samples (3.0 mL each) were removed from a sampling catheter in an arm vein over the next 24 hr. The women were asked to keep a calendar of the start and stop of each menses for the month prior to their first treatment, throughout the three treatment periods, and for 8 weeks following their third treatment. The women were not dosed during menses.

Sample Processing and Assay. The blood samples were allowed to clot at room temperature for approximately 30 min after collection and centrifuged within 1 hr. After centrifugation, the serum was separated and stored frozen (at approximately −20°C) until analysis. The stability of rhRlx in blood during clotting and in frozen serum was verified (data on file at Genentech, Inc.). The relaxin-immunoreactive protein concentrations were determined in serum using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) specific for human relaxin (15). An affinity-purified goat anti-human relaxin polyclonal antibody was used for coating, and a horseradish peroxidase-conjugated affinity-purified rabbit anti-human relaxin antibody was used for detection. The assay range was 20 to 1250 pg/mL. The standard curve and controls consisted of rhRlx added to normal male serum. Goat IgG (in quantities proportional to the concentration of the goat anti-human relaxin capture antibody) was added to each standard, control, and sample to prevent the nonspecific interactions that are common for assays of this type (16). The recovery of 200 to 800 pg/mL rhRlx that had been spiked into male serum was 84 to 102%. The interassay precision (%CV) was less than 15% for control preparations at 500, 150, and 45 pg/mL; the within-run precision (%CV) ranged from 5 to 12% for these high, mid, and low controls.

Pharmacokinetic Analyses. Triexponential equations were fitted to weighted [weight = 1/predicted concentration)^2] immunoreactive serum protein concentration–time data from individual women after iv dosing using nonlinear least-squares regression analysis (NONLIN84, version 1987, SCI, Lexington, KY). The coefficients and exponents of the triexponential equations were used to calculate the area under the serum concentration versus time curve (AUC), clearance (CL), half-lives ($t_{1/2}$), and initial volume of distribution (V_1) (17), as well as the volume of distribution at steady state (V_{ss}), permanence time in the serum (T_1), mean exit time from the serum (Ω_1), and mean exit time from the body (Ω_{body}) (18), assuming that the system was linear and state determined. The V_{ss} and Ω_{body} were calculated as minimum (min) and maximum (max) values, because only serum concentration versus time data were available and because no

assumptions were made regarding site (compartment) of elimination (18). The ratio $\Omega_{body,max}/\Omega_{body,min}$ is exactly equal to the ratio $V_{ss,max}/V_{ss,min}$; in addition, $\Omega_{body,min}$ is equal to Ω_1, when assuming elimination only from the central compartment.

The serum concentrations of relaxin following intravaginal and intracervical administration of rhRlx gel were tabulated and compared to the concentrations of endogenous relaxin after placebo treatment.

RESULTS

The relaxin serum concentration versus time data for the 25 women after iv administration of 0.01 mg/kg were described by triexponential equations (part I). The individual coefficients and exponents of the triexponential equations were averaged, and the resulting mean curve was superimposed on the mean data in Fig. 1. The mean calculated pharmacokinetic parameters are summarized in Table I. The observed peak concentration of relaxin after an iv bolus dose of 0.01 mg/kg was 98 ± 29 ng/mL. The predose serum samples from seven women had measurable concentrations of relaxin (21 to 86 pg/mL). These endogenous relaxin serum concentrations generally occurred when the women were in the last half of their menstrual cycle and were similar to the endogenous plasma concentrations of relaxin reported by Stewart *et al.* (5). Endogenous concentrations of relaxin minimally influenced the data after iv administration, because the relaxin concentrations that comprised 95% of the serum concentration–time curve (0 to 7 hr after dosing) were 10- to 1000-fold higher.

Following intracervical administration of 0.75 mg rhRlx, one woman had undetectable human relaxin concentrations (i.e., <20 pg/mL) throughout the 48-hr sampling interval. The remaining nine women exhibited maximum serum concentrations (C_{max}) ranging from 34 to 165 pg/mL. Following intravaginal administration of 1.5 mg rhRlx, nine women had undetectable human relaxin concentrations, and one subject had one serum sample containing measurable human relaxin (40 pg/mL). The C_{max} in the remaining five women was 67 to 248 pg/mL.

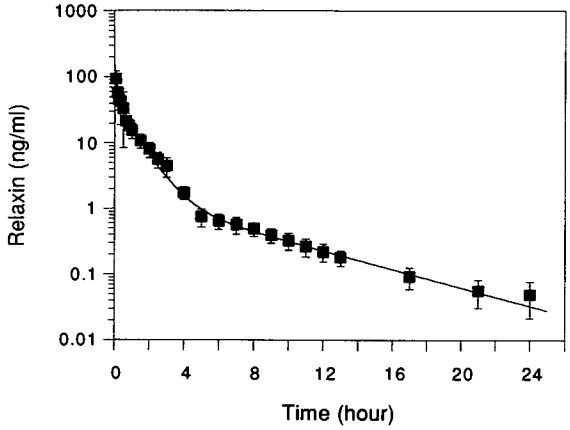

Fig. 1. Mean serum concentration versus time data for relaxin in nonpregnant women after iv bolus administration of 0.01 mg/kg. Filled squares are the mean ± SD (n = 25). The mean fitted equation is superimposed on the data [$C(t) = 123e^{-9.13t} + 40.5e^{-0.99t} + 1.55e^{-0.16t}$, where C is ng/mL and t is hr].

Table I. Pharmacokinetic Parameters for Relaxin in Nonpregnant Female Women After Intravenous Bolus Administration of 0.01 mg/kg (Mean ± SD)

Parameter	(n = 25)
CL/W (mL/hr/kg)	170 ± 50[a]
V_1/W (mL/kg)	78 ± 40
$V_{ss,min}/W$ (mL/kg)	280 ± 100
$V_{ss,max}/W$ (mL/kg)	1300 ± 400
$t_{1/2\lambda 1}$ (hr)	0.090 ± 0.036
	(20 ± 7% AUC)
$t_{1/2\lambda 2}$ (hr)	0.72 ± 0.12
	(65 ± 8% AUC)
$t_{1/2\lambda 3}$ (hr)	4.6 ± 1.2
	(15 ± 5% AUC)
T_1 (hr)	0.45 ± 0.16
Ω_1 (hr)[b]	1.6 ± 0.3
$\Omega_{body,max}$ (hr)	7.8 ± 1.8

[a] Equivalent to 170 ± 50 mL/min.

[b] $\Omega_{body,min}$ is equal to Ω_1, when assuming elimination only from the central compartment.

In part II, 17 women had undetectable human relaxin concentrations following intravaginal administration of the placebo gel. Four women had one serum sample containing measurable human relaxin (ranging from 23 to 59 pg/mL), and four women exhibited occasional serum concentrations of relaxin (C_{max}, 26 to 234 pg/mL). Only one subject had persistent relaxin serum concentrations that fluctuated between 46 and 77 pg/mL throughout the 24-hr sampling interval.

Following intravaginal administration of 1 mg rhRlx, 17 women had undetectable relaxin concentrations, and 3 women had one serum sample containing measurable relaxin (ranging from 41 to 52 pg/mL). The C_{max} in the remaining six women was 25 to 104 pg/mL.

Following intravaginal administration of 6 mg rhRlx, 16 women had undetectable relaxin concentrations, and 2 women had one sample serum containing measurable relaxin (28 and 359 pg/mL). The C_{max} in the remaining nine women ranged from 55 to 363 pg/mL, except in one subject where concentrations as high as 1704 pg/mL were achieved.

Endogenous relaxin concentrations confounded the assessment of absorption after intravaginal and intracervical administration; therefore, the systemic availability of rhRlx after topical administration is not reported.

DISCUSSION

Relaxin was cleared from serum rapidly after iv administration. Both the kidneys and the liver have been proposed as eliminating organs, although the mechanism of relaxin clearance is unknown (19). Relaxin does not appear to bind to serum proteins and there is no evidence that relaxin associates with human red blood cells (S. Chen, unpublished data), so blood clearance was calculated from the serum clearance after adjustment by an average hematocrit value (i.e., 45%). This blood clearance (310 mL/min) is signifi-

cantly lower than average renal or hepatic blood flow (1200 and 1500 mL/min, respectively) (20).

V_1/W was approximately equivalent to the weight-normalized plasma volume (~60 mL/kg) (21), and $V_{ss,min}/W$ was approximately equivalent to the weight-normalized extracellular volume (~200 mL/kg) (21). The ratio $(V_{ss,max}/W)/(V_{ss,min}/W)$ is an indicator of the uncertainty of the amount of drug in the body following chronic administration when only the serum is sampled and when no assumptions are made about the site (compartment) of elimination (18). This uncertainty factor is 4.8 for rhRlx. Current analytical methodologies for proteins do not allow further resolution of this uncertainty; however, it is expected to be clinically inconsequential given the acute nature of the therapy and the minimal absorption following intravaginal application of rhRlx. The permanence time in the serum (T_1) is 0.45 hr. The difference between the mean exit time from the body (Ω_{body}) and T_1 is the time relaxin spends in the tissues before being eliminated; this value ranges between 1.2 and 7.4 hr.

After intravaginal administration of the placebo gel, endogenous relaxin concentrations were evident (i.e., ≥20 pg/mL) in 9 of the 26 women (maximum concentrations, 23–234 pg/mL). These endogenous relaxin serum concentrations were similar to the endogenous plasma concentrations of relaxin reported by Stewart *et al.* (5). A similar proportion of women (approximately 35–40%) exhibited measurable serum concentrations of relaxin following intravaginal rhRlx treatment; this proportion increased to 90% following intracervical rhRlx treatment. For both routes of administration, the maximum serum concentrations of relaxin were usually within the range of values observed for endogenous relaxin, suggesting the absorption of rhRlx was minimal. Furthermore, topical dosing occurred at every phase of the menstrual cycle, and the vaginal changes (e.g., morphologic and pattern changes of the microridges on the vaginal epithelium cells, volume of fluid that coats the epithelium, and pH) that occur throughout a menstrual cycle (22) did not appear to increase the absorption of rhRlx after intravaginal administration.

In conclusion, relaxin was cleared rapidly after iv administration, and the volume of distribution was estimated to be small (assuming central compartment elimination). These data were predicted by preclinical pharmacokinetic studies in mice, rats, rabbits, and rhesus monkeys (23). Serum concentrations of relaxin were low and variable following intracervical administration and undetectable in many of the women following intravaginal administration; only a small amount of the rhRlx dose, if any, was absorbed. The presence of endogenous relaxin confounded the estimation of absolute bioavailability and may have contributed to the apparent variable absorption profiles. The limited absorption of rhRlx gel following intravaginal administration was predicted by studies in nonpregnant rabbits and rhesus monkeys (24) and was similar to the results obtained in postdate women with uncomplicated pregnancies who received 1.5 mg rhRlx gel intravaginally (A. Perlman, personal communication).

ACKNOWLEDGMENTS

The authors gratefully acknowledge the expert contributions of Christina Swenson and the Clinical Assay Services Group to the sample analyses, Kerrie Nemo and Carol Deasy to the data listings, and Drs. James Green and Aldo Rescigno for scientific discussions.

REFERENCES

1. O. D. Sherwood. Relaxin. In E. Knobil and J. Neill (eds.), *The Physiology of Reproduction*, Raven Press, New York, 1988, pp. 585–673.
2. F. S. Khan-Dawood, L. T. Goldsmith, G. Weiss, and M. Y. Dawood. Human corpus luteum secretion of relaxin, oxytocin, and progesterone. *J. Clin. Endocrinol. Metab.* **68**:627–631 (1989).
3. P. Hudson, M. John, R. Crawford, J. Haralambidis, D. Scanlon, J. Gorman, G. Tregear, J. Shine, and H. Niall. Relaxin gene expression in human ovaries and the predicted structure of a human preprorelaxin by analysis of cDNA clones. *EMBO J.* **4**:2333–2339 (1984).
4. V. Sakbun, S. M. Ali, F. C. Greenwood, and G. D. Bryant-Greenwood. Human relaxin in the amnion, chorion, decidua parietalis, basal plate, and placental trophoblast by immunohistochemistry and northern analysis. *J. Clin. Endocrinol. Metab.* **70**:508–514 (1990).
5. D. R. Stewart, A. C. Celniker, C. A. Taylor, J. R. Cragnun, J. W. Overstreet, and B. L. Lasley. Relaxin in the periimplantation period. *J. Clin. Endocrinol. Metab.* **70**:1771–1773 (1990).
6. M. R. Johnson, M. E. Wren, H. Abdalla, A. Kirkland, A. C. J. Allman, and S. L. Lightman. Relaxin levels in ovum donation pregnancies. *Fertil. Steril.* **56**:59–61 (1991).
7. L. W. Eddie, I. T. Cameron, J. F. Leeton, D. L. Healy, and P. Renou. Ovarian relaxin is not essential for dilation of cervix. *Lancet* **336**:243 (1990).
8. A. H. MacLennan, R. C. Green, G. D. Bryant-Greenwood, F. C. Greenwood, and R. F. Seamark. Ripening of the human cervix and induction of labour with purified porcine relaxin. *Lancet* **1**:220–223 (1980).
9. A. H. MacLennan, R. C. Green, G. D. Bryant-Greenwood, F. C. Greenwood, and R. F. Seamark. Cervical ripening with combinations of vaginal prostaglandin F_{2a}, estradiol, and relaxin. *Obstet. Gynecol.* **58**:601–604 (1981).
10. S. J. Shire, L. A. Holladay, and E. Rinderknecht. Self-association of human and porcine relaxin as assessed by analytical ultracentrifugation and circular dichroism. *Biochemistry* **30**:7703–7711 (1991).
11. A. H. MacLennan, R. C. Green, P. Grant, and R. Nicolson. Ripening of the human cervix and induction of labor with intracervical purified porcine relaxin. *Obstet. Gynecol.* **68**:598–601 (1986).
12. D. P. Benziger and J. Edelson. Absorption from the vagina. *Drug Metab. Rev.* **14**:137–168 (1983).
13. E. Canova-Davis, T. J. Kessler, P.-J. Lee, D. T. W. Fei, P. Griffin, J. T. Stults, J. D. Wade, and E. Rinderknecht. Use of recombinant DNA derived human relaxin to probe the structure of the native protein. *Biochemistry* **30**:6006–6013 (1991).
14. J. W. Winslow, A. Shih, J. H. Bourell, G. Weiss, B. Reed, J. T. Stults, and L. T. Goldsmith. Human seminal relaxin is a product of the same gene as human luteal relaxin. *Endocrinology* **130**:2660–2668 (1992).
15. B. L. Ferraiolo, J. Winslow, G. Laramee, A. Celniker, and P. Johnston. The pharmacokinetics and metabolism of human relaxins in rhesus monkeys. *Pharm. Res.* **8**:1032–1038 (1991).
16. M. Rånby, N. Bergsdorf, T. Nilsson, G. Mellbring, B. Winblad, and G. Bucht. Age dependence of tissue plasminogen activator concentrations in plasma, as studied by an improved enzyme-linked immunosorbent assay. *Clin. Chem.* **32**:2160–2165 (1986).
17. J. G. Wagner. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J. Pharmacokin. Biopharm.* **4**:443–467 (1976).
18. J. Mordenti and A. Rescigno. Estimation of permanence time,

exit time, dilution factor, and steady-state volume of distribution. *Pharm. Res.* 9:17–25 (1992).
19. P. A. Cossum, K. A. Dwyer, M. Roth, S. A. Chen, B. Moffat, R. Vandlen, and B. L. Ferraiolo. The disposition of a human relaxin (hRlx-2) in pregnant and nonpregnant rats. *Pharm. Res.* 9:419–424 (1992).
20. M. Rowland and T. N. Tozer. In *Clinical Pharmacokinetics: Concepts and Applications,* Lea and Febiger, Philadelphia, 1980, pp. 48–78.
21. J. W. Prothero. Scaling of blood parameters in mammals. *Comp. Biochem. Physiol.* 67A:649–657 (1980).
22. H. Ludwig and H. Metzger. *The Human Female Reproduction Tract,* Springer-Verlag, Berlin, 1976, pp. 8–15.
23. J. Mordenti, S. A. Chen, J. A. Moore, B. L. Ferraiolo, and J. D. Green. Interspecies scaling of clearance and volume of distribution data for five therapeutic proteins. *Pharm. Res.* 8:1351–1359 (1991).
24. S. A. Chen, B. Reed, T. Nguyen, N. Gaylord, G. B. Fuller, and J. Mordenti. The pharmacokinetics and absorption of recombinant human relaxin in nonpregnant rabbits and rhesus monkeys after intravenous and intravaginal administration. *Pharm. Res.* 10:223–227 (1993).