Risedronate Pharmacokinetics and Intra- and Inter-Subject Variability upon Single-Dose Intravenous and Oral Administration

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Purpose. To determine the pharmacokinetics and absolute bioavailability of risedronate after single-dose oral administration of 30 mg risedronate as a tablet and an aqueous solution, and 0.3 mg risedronate as an intravenous infusion.

Methods. This study was a randomized, three-treatment, four-period, partial replicate crossover study involving 33 healthy volunteers. Treatments were administered 7 weeks apart, and the third treatment was repeated during the fourth period. Serum and urine were collected over 72 hours and 672 hours, respectively.

Results. Following intravenous administration, renal clearance accounted for 87% of total clearance, with 65% of the dose excreted within 24 hours and 85% of the dose excreted within four weeks. The absolute bioavailability was approximately 0.62% after both oral formulations, and the relative bioavailability of the tablet compared with the oral solution was 104%. The rate and extent of absorption from the two formulations were bioequivalent based on the range proposed for highly variable drugs. Intrasubject variability following oral administration was 50–80%, and was primarily associated with absorption.

Conclusion. The majority of the total clearance after intravenous administration of risedronate was renal clearance, indicating that only a small percentage of a systemic dose is potentially incorporated, or "cleared," into bone. The absolute bioavailability of orally administered risedronate is ~0.6%, and is independent of formulation. Variability in the pharmacokinetics following oral administration is primarily associated with intrasubject variability in absorption.

KEY WORDS: bioavailability; intrasubject variability; pharmacokinetics; risedronate.

INTRODUCTION

Risedronate [1-hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt] is a pyridinyl bisphosphonate that induces remission in patients with Paget's disease (1) and increases bone mineral density and reduces vertebral and nonvertebral fractures in postmenopausal women with osteoporosis (2,3). It has a high affinity for bone hydroxyapatite (4) and is a potent inhibitor of osteoclast-mediated bone resorption (5).

Similar to other bisphosphonates, risedronate is not metabolized (data on file, Procter & Gamble Pharmaceuticals). Pharmacokinetic studies in healthy subjects indicated absorption of risedronate is relatively rapid (t_{max} ~ 1 hour) and is independent of the site of administration within the upper gastrointestinal tract (6). Risedronate absorption is independent of the oral dose from 2.5 to 30 mg (7). The bioavailability of risedronate is estimated to be low (less than 1%) based on cumulative urinary excretion (7,8) and regression analysis of CL_O and CL_R in subjects with impaired renal function (9). Once risedronate is absorbed, the serum concentration–time and urinary excretion rate–time profiles are multiphasic, with an initial half-life of 1.5 h and a terminal exponential half-life of 230 h in healthy volunteers (7,8). The long half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

Neither the pharmacokinetics following intravenous administration nor the absolute bioavailability of risedronate have been previously reported. Further, similar to other bisphosphonates, risedronate is a highly variable drug. However, the source of the variability, absorption or elimination, has not been elucidated. Therefore, the objectives of this study were to determine the pharmacokinetics after intravenous and oral administration, the oral bioavailability, and the intrasubject and intersubject variability of risedronate.

MATERIALS AND METHODS

Study Design

This was an open-label, randomized, crossover study, incorporating a partial replicate design. Healthy volunteers received 30 mg risedronate orally as a film-coated tablet or aqueous solution, or 0.3 mg risedronate intravenously, with doses separated by 7-week intervals; the third treatment was repeated during a fourth period to determine the intrasubject and intersubject variability in risedronate pharmacokinetics.

Subjects

Thirty-three healthy volunteers (30 male, 3 female), aged 19–45 years, participated in this study. All subjects were required to be within 10% of ideal weight for their height, and women were required to be surgically sterile. Subjects who previously received bisphosphonates, were taking concomitant medications, or were smokers were not eligible to participate in the study. The study followed the tenets of the Declaration of Helsinki and was approved by a local ethical review committee. Written informed consent was obtained from each subject prior to enrollment in the study.

Drug Administration and Study Procedures

Volunteers were orally administered 30 mg risedronate as a single film-coated tablet (phase III dosage form) and as an aqueous solution (risedronate dissolved in deionized water), and intravenous 0.3 mg risedronate (risedronate dissolved in sterile water) by a 1 hour intravenous infusion. The

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tablet and aqueous solution were administered with a total of 240 mL deionized water. All treatments were given 4 hours before a meal after an overnight fast.

Blood samples for the measurement of serum risedronate concentrations were obtained before dosing, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 40, 48, 60, and 72 hours after dosing. Blood samples were collected in 10 mL siliconized glass Vacutainers (Becton Dickinson, Franklin Lakes, NJ, USA) and allowed to clot for 30 minutes. Samples were centrifuged and serum was stored at –20°C until analyzed. Urine samples were collected over 12 hours prior to dosing, at 0–1, 1–4, 4–8, 8–12, 12–16, 16–24, 24–32, 32–40, and 40–48 hours after dosing, and at 12-hour intervals to 672 hours (28 days) after dosing. Urine samples from the first period were combined to estimate the 24-hour creatinine clearance.

Bioanalytical Methods and Pharmacokinetic Analysis

Serum (10) and urine risedronate concentrations were determined using a solid phase extraction procedure coupled with an enzyme-linked immunosorbent assay (ELISA). In this method 1 mL of serum or urine is acidified, processed through a cation exchange column, and the column eluate subjected to ELISA. The ELISA is based on competitive inhibition between a solid-phase antigenic risedronate equivalent and risedronate for the binding sites on a constant amount of primary antibody. Using a secondary antibody, the primary antibody is quantified using absorbance detection of color development. The quantitative range of the four-parameter standard curve was 0.19–6.0 and 0.28–4.7 ng/mL for serum and urine, respectively. Duplicate serum and urine quality control samples with risedronate concentrations of 0.470, 1.88, and 4.70 ng/mL were analyzed with each analytical batch of study samples. The interassay coefficients of variation for quality control samples ranged from 11–15% for serum and 12–19% for urine.

Serum concentration-time data and urinary excretion rate-time data were analyzed simultaneously using PCNONLIN (version 4.2) (11), and the following equations:

oral administration:

$$C = \left(\sum_{i=1}^{n} C_i e^{-\lambda_i t} \right) + C_o e^{-\lambda_Z (t - t_o)} \quad (1)$$

$$\frac{dA_e}{dt} = \left(CL_R \sum_{i=1}^{n} C_i e^{-\lambda_i t_{mid}} \right) + \left(\frac{dA_e}{dt} \right)_o e^{-\lambda_Z (t_{mid} - t_o)} \quad (2)$$

with:

$$C_n = -1 \cdot \left(\sum_{i=1}^{n-1} C_i \right) \quad (3)$$

intravenous administration:

$$C = \left(\sum_{i=1}^{n} \frac{(c_i (1 - e^{(-\lambda_i t_B)}) \cdot e^{(-\lambda_i t_A)})}{(\lambda_i \cdot TI)} \right) + C_o e^{-\lambda_Z (t - t_o)} \quad (4)$$

$$\frac{dA_e}{dt} = \left(CL_R \sum_{i=1}^{n} \frac{(c_i (1 - e^{(-\lambda_i t_B)}) \cdot e^{(-\lambda_i t_A)})}{(\lambda_i \cdot TI)} \right) + \left(\frac{dA_e}{dt} \right)_o e^{-\lambda_Z (t_{mid} - t_o)} \quad (5)$$

where C is the serum concentration at time t, dA_e/dt is the urinary excretion rate occurring at the midpoint of the collection interval, t_{mid} is the midpoint time of the collection interval, TI is the duration of the infusion, t_A is the time after the end of the infusion, t_B is the t_{mid} during the infusion or TI after the end of the infusion, t_0 is the midpoint time of the predose urine collection, n is the number of exponents necessary to characterize serum concentration-time and urinary excretion rate-time profiles, C_i is the ith coefficient, C_0 is the predicted concentration at t_0 that is calculated as dA_e/dt from the predose urine collection ($(dA_e/dt)_0$) divided by the renal clearance (CL_R) of risedronate from the preceding period, λ_i is the ith exponent, and λ_Z is the terminal exponential rate constant from the preceding period. Initial pharmacokinetic parameters estimates were obtained from a previous study (12). Predicted serum concentrations and urinary excretion rates were weighted (1/p or $1/p^2$) for use in data analysis, where p is the predicted value for that function. Decisions on appropriate weighting and number of exponents required to characterize the serum concentration-time and urinary excretion rate-time profiles were based on randomness of scatter of observed data about the fitted line and sum of weighted squared residuals (13). Estimated maximum serum concentration (C_{max}) and time C_{max} occurs (t_{max}) after oral administration were derived from the model using the equations listed above (excluding C_0); estimated C_{max} after intravenous infusion was derived from the model using the equations listed above (excluding C_0) with the t_{max} set to the time at the end of the infusion. Area under the serum concentration-time curve (AUC), area under the moment curve (AUMC), terminal exponential half-life ($t_{½,Z}$), total clearance (CL), volume of distribution of the central compartment (V_c), volume of distribution at steady state (V_{ss}), and terminal volume of distribution (V_Z) were calculated from coefficients and exponents using standard equations (14,15). Cumulative urinary excretion (A_e) of risedronate was calculated as the product of AUC and CL_R. The percent of dose excreted in urine (A'_e) was calculated as the A_e normalized for dose.

Statistical Methods

AUC and C_{max} were adjusted for dose and log-transformed, and subjected to analysis of variance (ANOVA); the ANOVA included terms for sequence, subject within sequence, period, treatment, and first order carry-over effects. Least squares means, 90% confidence intervals and 95% confidence intervals were obtained for each treatment group.

Intrasubject and intersubject variability in risedronate pharmacokinetics were studied using a mixed effects model (SAS version 6.11 PROC MIXED), with allowance for heterogeneous variance across formulations (16). Pairwise Wald's tests were performed to test for differences in intrasubject variances. The estimate of the intersubject variance was the variance estimate associated with the subject term in the model.

RESULTS

The study population was comprised of 30 males and 3 females, with an ethnic composition (N) of caucasians (18), African Americans (13), and hispanics (2). The mean (SD) age of the subjects was 33.2 (8.0) years, and the mean weight (SD) was 75.3 (7.4) kg. Of the 33 subjects enrolled in the study, 25 completed four treatment periods. Of the remainder, three were withdrawn because of protocol violations, two withdrew at their own request, and three who were enrolled to replace withdrawn subjects were withdrawn prior to the fourth study period since 25 subjects had already completed the study.

Pharmacokinetic Data

Mean serum concentration-time profiles and urinary excretion rate-time profiles following intravenous and oral administration are shown in Figures 1 and 2, respectively. Profiles following intravenous and oral administration could be adequately characterized by a three and four-exponential function, respectively.

The pharmacokinetic parameters of risedronate after oral and intravenous administration are summarized in Tables I and II. After intravenous administration of risedronate, renal clearance accounted for 87% of total clearance (Table I), with 65% (SD = 16%) of the dose excreted within 24 hours and 83% (SD = 15%) of the dose excreted within four weeks. The mean (SD) V_{ss} was 6.3 (1.5) L/kg, which was approximately 25% of the mean [SD] V_z (27 L/kg [1.5]), and approximately 33 times greater than the mean [SD] V_c (0.19 L/kg [0.04]). The mean (SD) half-lives during the first ($t_{½,1}$) and second ($t_{½,2}$) exponential phases were 0.87 (0.18) and 12.8 (6.4) hours, respectively; the mean (SD) $t_{½,Z}$ was approximately 200 hours (39) (Table I), which was not significantly different among treatments ($p > 0.05$). The $t_{½,1}$, $t_{½,2}$ and $t_{½,Z}$ accounted for (mean, [SD]) 61.9% [7.8], 16.4% [3.9] and 22.4% [5.0], respectively, of the total AUC. The absolute bioavailability of risedronate was 0.63% after administration of the tablet form, and 0.61% after administration of the aqueous solution, and the relative bioavailability of the tablet formulation compared with the solution was 104% (Table II). The 90% confidence limits for AUC indicated that the two formulations were equivalent in terms of the extent of absorption (Table II). There were no significant differences in C_{max} after administration of the tablet and solution formulations, but t_{max} was significantly shorter with the tablet formulation (Table I).

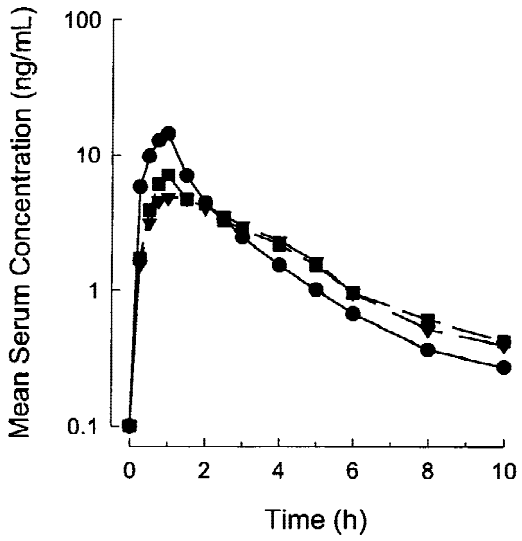

Fig. 1. Mean serum risedronate concentrations after single dose administration of a 30 mg tablet (■), 30 mg aqueous solution (▲), or 0.3 mg intravenous infusion (●).

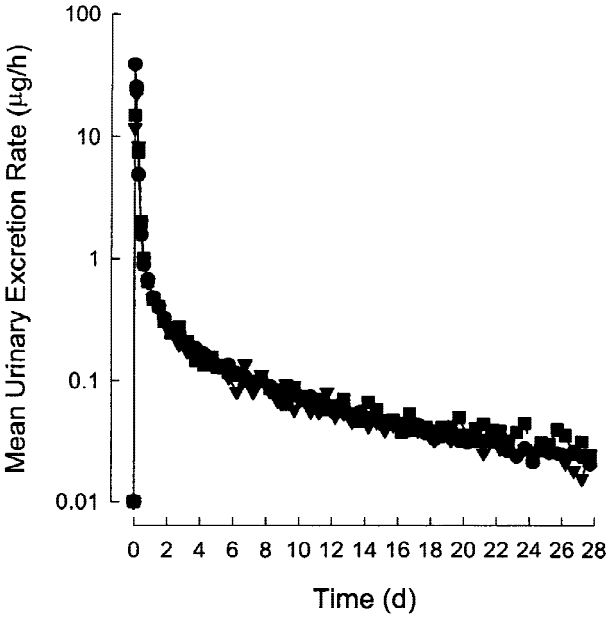

Fig. 2. Mean urinary risedronate excretion rate after single dose administration of a 30 mg tablet (■), 30 mg aqueous solution (▲), or 0.3 mg intravenous infusion (●).

Renal clearance varied by less than 10% among the three treatments (Table I). It was, however, significantly ($p = 0.038$) lower after intravenous administration than after administration of the oral solution (Table I).

Intrasubject and intersubject variations in pharmacokinetic parameters are summarized in Table III. Intrasubject variation after intravenous administration of risedronate was less than 20%. However, oral administration resulted in high intrasubject variability (45–83%) for parameters influenced by absorption. In general, intrasubject variation was not significantly different between the tablet and the oral solution.

DISCUSSION

The results of this study are consistent with those of previous studies (7,8), showing that the absolute bioavailability of risedronate after oral administration is less than 1%. The low absolute oral bioavailability is comparable with that of other bisphosphonates, including pamidronate (0.3–0.5%) (17), alendronate (0.7%) (18), clodronate (1–2%) (19), etidronate (2.3%) (20), and tiludronate (6%) (21). The extent of absorption of the tablet formulation was equivalent to that of the oral solution. Peak serum concentrations achieved with the two oral formulations did not differ significantly; the 90% confidence interval for this parameter (93–130%) was slightly greater than the current range for bioequivalence (80–125%), but was within the range proposed for highly variable drugs (70–143%) (22). These results indicate that the rate and extent of risedronate absorption are not limited by the dissolution of the tablet. In addition, the t_{max} for the tablet was less

Table I. Risedronate Pharmacokinetic Parameters Following Single-Dose Oral Administration of 30 mg and Intravenous Administration of 0.3 mg[a]

Pharmacokinetic parameter	Estimate of central tendency[b] (95% confidence interval)			Formulation comparison[c]
	Tablet (T)	Solution (S)	Intravenous (I)	
Dose-adjusted AUC (ng · hr/mL)	0.91 (0.77–1.07)	0.87 (0.73–1.04)	143 (119–172)	S T I
Dose-adjusted C_{max} (ng/mL)	0.16 (0.13–0.19)	0.14 (0.12–0.17)	50 (42–61)	S T I
A'_e (%)	0.59 (0.51–0.68)	0.56 (0.48–0.66)	87 (73–102)	S T I
t_{max} (hr)	1.03 (0.93–1.14)	1.23 (1.12–1.34)	0.99 (0.88–1.11)	I T S
$t_{1/2,Z}$ (hr)	218 (202–236)	204 (188–222)	200 (183–218)	I S T
CL (L/hr/kg)	—	—	0.092 (0.076–0.112)	—
CL_R (L/hr/kg)	0.086 (0.079–0.093)	0.087 (0.079–0.095)	0.080 (0.073–0.088)	I T S
V_z (L/kg)	—	—	27 (22–32)	—

[a] AUC, area under serum concentration-time curve from time 0 to ∞; C_{max}, maximum serum concentration; A'_e, percentage of the dose excreted in the urine from time 0 to ∞; t_{max}, time to maximum serum concentration; $t_{1/2,Z}$, terminal exponential half-life; CL, total clearance; CL_R, renal clearance; V_z, terminal volume of distribution. C_{max} and AUC were dose-normalized to 1 mg.

[b] AUC, C_{max}, A'_e, $t_{1/2,Z}$, CL_R, Cl and V_z are geometric means; t_{max} is an arithmetic mean.

[c] Groups are ordered from the smallest to the largest mean value; underlining indicates that there was no statistically significant difference between groups.

than that for the solution, also indicating that the rate of risedronate absorption is not affected by the rate of dissolution of the tablet. These results are consistent with previously reported results indicating that the extent of absorption is not affected by the rate of administration (6).

Risedronate renal clearance accounted for 87% of total clearance, indicating that only a small proportion of a systemically available dose is incorporated, or "cleared", into bone. Urinary recovery of risedronate (65% in 24 hours, 85% in 28 days) was comparable with that reported for clodronate (73–81% in 24–48 hours) (19,23) after intravenous administration. In contrast, lower urinary recoveries (percentage recovered, time period) were reported for etidronate (52–55%, 24–96 hours) (20,24), alendronate (40%, 36 hours (18); 70%, 18 months (25)), tiludronate (50%, 13 days) (21), and pamidronate (24–50%, 48 hours) (17). These results suggest that risedronate and clodronate may dissociate from bone more readily than other bisphosphonates, and that drug accumulation in bone may be lower than for other bisphosphonates. The steady state volume of distribution was large (6.3 L/kg), probably due to distribution of risedronate to the bone. It was approximately 33 times greater than the volume of distribution of the central compartment (0.19 L/kg), thus large fluctuations in peak and trough serum concentrations can be expected during daily dosing (14). The finding that steady state volume of distribution was approximately a quarter of the terminal volume of distribution would be expected with a drug where most of the dose is eliminated relatively quickly, but a small proportion persists with a long half-life (14).

There was greater variability in risedronate pharmacokinetics after oral administration than after intravenous administration, possibly related to binding to divalent cations within

Table II. Comparison of the Ratios of Risedronate Pharmacokinetic Parameters Following Oral Administration of 30 mg, or Intravenous Administration of 0.3 mg[a]

Pharmacokinetic parameter	Point estimate (%) [90% confidence interval]			Formulation comparisons[b]
	Tablet/intravenous (TI)	Solution/intravenous (SI)	Tablet/solution (TS)	
Dose-adusted AUC (ng · hr/mL/mg)	0.63 [0.54–0.75]	0.61 [0.52–0.72]	104.2 [89.0–122]	SI TI TS
Dose-adjusted C_{max} (ng/mL/mg)	0.32 [0.27–0.38]	0.29 [0.24–0.34]	110.1 [93.2–130]	SI TI TS
A'_e (%)	0.68 [0.58–0.80]	0.65 [0.55–0.77]	104.3 [89.0–122]	SI TI TS

[a] AUC, area under serum concentration-time curve from time 0 to ∞; C_{max}, maximum serum concentration; and A'_e, percentage of the dose excreted in the urine from time 0 to ∞.

[b] Groups were ordered from the smallest to the largest mean; underlining indicates that there was no statistically significant difference between groups.

Table III. Intrasubject and Intersubject Coefficient of Variation (CV) for Risedronate Pharmacokinetic Parameters Following Oral Administration of 30 mg and Intravenous Administration of 0.3 mg[a]

Pharmacokinetic parameter	Intrasubject CV (%)			Formulation comparisons[b]	Intersubject CV (%)
	Tablet (T)	Solution (S)	Intravenous (I)		
AUC	74.3	53.2	7.0	I S T	15.1
C_{max}	82.2	45.6	12.4	I S T	9.9
A'_e	68.4	50.3	14.8	I S T	6.4
t_{max}	39.1	28.6	2.2	I S T	0[c]
$t_{1/2,Z}$	28.7	23.6	13.6	I S T	14.5
CL_R	14.2	15.6	19.3	T S I	21.4
CL	—	—	8.6	—	14.9
V_z	—	—	13.1	—	17.3

[a] AUC, area under serum concentration-time curve; C_{max}, estimated maximum serum concentration; A'_e, percentage of the dose excreted in the urine; t_{max}, time to maximum concentration; $t_{1/2,Z}$, terminal exponential half-life; CL_R, renal clearance; CL, total clearance; V_z, terminal volume of distribution.

[b] Groups are ordered from smallest to largest CV; underlining indicates no significant difference between groups.

[c] Restricted maximum likelihood estimate of intersubject variance is zero.

the intestine. In general, there was no significant difference in intrasubject variability between the two oral formulations. Moreover, pharmacokinetic variability after oral administration was primarily due to intrasubject variations. Similar findings have been reported with other bisphosphonates (17–19,26).

In conclusion, this study has established that the absolute bioavailability of risedronate after oral administration is less than 1%, and that the bioavailability for the tablet formulation and the oral solution is equivalent. The urinary recovery of risedronate (87% of dose) is greater than that reported for most bisphosphonates, which suggests that risedronate may dissociate from bone more readily than other bisphosphonates leading to less drug accumulation in bone. Variability in risedronate pharmacokinetics is primarily due to intrasubject variation in drug absorption.

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