Risedronate Gastrointestinal Absorption Is Independent of Site and Rate of Administration

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Purpose. Two studies were conducted to compare the absorption of risedronate administered as a solution to three different gastrointestinal sites (study A) and to determine the extent of absorption of risedronate solution administered by rapid and slow infusion to the second part of the duodenum (study B).

Methods. Each study was designed as a single-dose, crossover (three periods, study A; two periods, study B) trial in healthy male subjects, with a 14-day washout period between dosing. Subjects fasted overnight before drug administration and for 4 hours after drug administration. In study A, a risedronate solution of 40 mg in 30 mL of water was administered directly into the stomach, the second part of the duodenum, or the terminal ileum over 1 minute via a nasoenteral tube in a three-period crossover design. In study B, a risedronate solution of 40 mg in 30 mL of water was administered directly into the second part of the duodenum over 1 minute and over 1 hour in a randomized, two-period crossover design. Serum and urine samples were obtained for 48 hours after dosing for risedronate analysis.

Results. Eight subjects completed each study. No statistically significant site-specific differences in any pharmacokinetic parameter were observed (study A). Based on the area under the serum concentration-time profile and the amount of drug excreted in the urine unchanged, the extent of risedronate absorption did not differ significantly following a rapid or a slow infusion (study B). Only minor symptomatic complaints were reported by subjects, such as headaches and body aches.

Conclusions. These studies indicate that the rate and extent of risedronate absorption are independent of the site of administration along the gastrointestinal tract, and that the extent of absorption is not affected by the rate of administration.

KEY WORDS: risedronate; gastrointestinal absorption; gastrointestinal site; bisphosphonate; administration rate; pharmacokinetics.

INTRODUCTION

Risedronate, or 1-hydroxy-2-(3-pyridinyl)ethylidene bisphosphonic acid monosodium salt, is a pyridinyl bisphosphonate (Fig. 1). It is a potent antiresorptive agent that inhibits osteoclast-mediated bone resorption (1). Clinical studies have demonstrated that it is effective in increasing bone mass at the hip and the spine in early postmenopausal women (2), decreasing pain and the biochemical indicators of disease activity in patients with Paget's disease of bone (3), increasing bone mass in patients with multiple myeloma (4), and decreasing serum calcium in patients with primary hyperparathyroidism (5).

Clinical pharmacokinetic studies have described risedronate absorption as relatively rapid (t_{max} ~ 1 h) (6–8) and low (0.65%) (unpublished data, Procter and Gamble Pharmaceuticals). Similar to other bisphosphonates, risedronate absorption is decreased when administered shortly before (0.5 to 1 h) or after (2 h) a meal (6), and as expected, a more pronounced effect has been observed when a delayed-release dosage form is administered shortly before a meal (7). Once risedronate is absorbed, the serum concentration-time profile is multiphasic, with an initial half-life of 1.5 h and a terminal exponential half-life of 230 h (8). This 230-h half-life is hypothesized to represent the dissociation of risedronate from the surface of the bone. Risedronate, similar to most bisphosphonates (9), is not metabolized (unpublished data, Procter and Gamble Pharmaceuticals).

At the time the current study was designed, it was thought that having the option of an enteric-coated dosage form might provide a benefit during drug development. Neither risedronate absorption from different gastrointestinal sites nor rate-dependent absorption of risedronate from the small intestine had been studied previously. Therefore, two pharmacokinetic studies were conducted to compare the absorption of risedronate administered as a solution to the stomach, duodenum, and terminal ileum (study A), and to determine the extent of absorption of risedronate solution administered by rapid and slow infusion to the second part of the duodenum (study B).

MATERIALS AND METHODS

Healthy male subjects between 18 and 40 years of age who were within 10% of their ideal body weight were recruited for both studies. Each study employed a single-dose (40 mg) crossover design. There was a 14-day washout period between each dose administration. Each 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

Subjects fasted overnight before drug administration and for 4 hours after drug administration. Study A was a three-period crossover design. Risedronate solution (40 mg in 30 mL of water) was administered directly into the stomach, the second part of the duodenum, or the terminal ileum via a nasoenteral tube (ENtube Plus, ENtech Inc, Lebanon, NJ) inserted within 24 hours prior to dosing. Final positioning of the nasoenteral tube was performed by fluoroscopic control. Maximum tube migration down the gastrointestinal tract was allowed in the first period, but final positioning was adjusted in subsequent periods to ensure that the three gastrointestinal sites were observed in each subject. A single dose of risedronate solution was administered over 1 minute and was followed immediately by 20 mL of deionized water. The nasoenteral tube was removed within 10 minutes after drug administration.

Drug administration procedures for study B were similar to those for study A. Study B was a two-period, randomized crossover design. Positioning of the nasoenteral tube in the sec-

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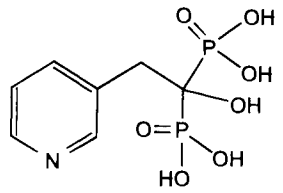

Fig. 1. Chemical structure of risedronate.

ond part of the duodenum was confirmed by fluoroscopic control. A single dose of risedronate solution (40 mg in 30 mL of water) was administered by rapid (over 1 minute) or slow (over 1 hour) infusion via the tube.

Blood samples were collected immediately prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, and 48 hours after dosing. Serum was harvested and frozen at –20°C until risedronate analysis. Urine was collected prior to dosing and at given intervals (0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–36, and 36–48 hours) after dosing for analysis of risedronate concentrations. Urine specimens were refrigerated at 4°C until the entire specimen for the interval was obtained. Aliquots of urine were frozen at –70°C until risedronate analysis.

Safety was monitored during the studies. Routine laboratory testing (clinical chemistry, hematology, coagulation studies, urinalysis) was performed at screening and at the end of the final study period. Vital signs (blood pressure, heart rate, respiration, and temperature) were measured at screening, prior to administering each dose of risedronate, and at the end of each study period. Adverse events and abnormal laboratory test results were followed until resolution.

Bioanalytical Methods and Pharmacokinetics Analysis

Serum risedronate concentrations were determined using an ultrafiltration procedure coupled with an enzyme-linked immunosorbent assay (ELISA). In this method, 1 mL of serum is acidified and ultrafiltered, and the ultrafiltrate 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 quantitation range of the four-parameter standard curve was 0.16 to 6.9 ng/mL. The interassay coefficients of variation for quality control samples ranged from 13% to 15% and 15% to 18% for study A and study B, respectively. The relative risedronate recovery for the quality control samples ranged from 82% to 104% and 85% to 90% for studies A and B, respectively.

Urine concentrations of risedronate were determined by capillary gas liquid chromatography/mass spectrometry (GC/MS) using selective ion monitoring. Risedronate and the internal standard (d_4-risedronate free acid) were isolated from urine (2 mL) by coprecipitation with calcium carbonate. Cation and anion exchange columns were used for sample clean-up, and the eluate was evaporated. The analyte and internal standard were derivatized by acetylation and silylation, and quantification was by GC/MS. The quantitation range of the linear standard curve was 11 to 539 ng/mL. The interassay coefficients of variation for quality control samples ranged from 6% to 10% and 5% to 11% for studies A and B, respectively. The extraction efficiency (absolute) was 94%.

The maximum risedronate serum concentration (C_{max}) and the time of the maximum serum concentration (t_{max}) were determined by visual inspection of the data. The area under the serum concentration-time curve from time 0 to the last quantifiable serum concentration at time t (AUC_t) was estimated by the linear trapezoidal rule. Urinary excretion of risedronate was calculated as the product of urine concentration and urine volume. The cumulative urinary excretion of risedronate (A_e) was the sum of the excreted amounts. Renal clearance (CL_R) was calculated as the quotient of A_e and AUC over the same time interval.

Statistical Methods

For study A, the extent and the rate of drug absorption were assessed by comparing the AUC_t and the C_{max}, respectively, among the three gastrointestinal sites. Analysis of variance (ANOVA) for a three-period crossover design was performed on the natural logarithmic transformations of AUC_t and C_{max}, with the level of significance at 0.05 for the main effects and 0.10 for carryover.

For study B, AUC_t and C_{max} were compared between the two infusion rates. ANOVA for a two-period crossover design was performed on the natural logarithmic transformations of AUC_t and C_{max}, with the level of significance at 0.05 for the main effects and 0.10 for carryover.

For each study, the least-squares means of log-transformed AUC_t and C_{max} and the corresponding 95% confidence intervals were calculated. The antilogs of the means and confidence intervals also were calculated to provide the geometric means and their corresponding intervals. The same ANOVA procedure was used to analyze t_{max}, A_e, and CL_R. The data for these variables were assessed for adherence to normality assumptions using the Shapiro-Wilks normality test for both the log-transformed and raw data. The logarithmic transformation of the variable was used if it better satisfied the normality assumptions. Based on these results, the CL_R values were log-transformed prior to analysis in study A, and the A_e values were log-transformed prior to analysis in study B.

RESULTS

Study A

Demographic characteristics of the eight healthy male subjects in study A included a mean age ± SD of 30.8 ± 6.6 years and a mean weight ± SD of 72.4 ± 4.7 kg. There were no significant differences in any of the pharmacokinetic parameters (AUC_t, C_{max}, t_{max}, A_e, and CL_R) following administration of risedronate to the stomach, duodenum, and terminal ileum (Table I). The mean serum risedronate concentration-time profiles following administration of a 40-mg dose to the three gastrointestinal sites are depicted in Figure 2, and the mean cumulative urinary excretion is depicted in Figure 3.

Study B

Demographic characteristics for the eight healthy male subjects in study B included a mean age ± SD of 25.1 ± 4.5 years and a mean weight ± SD of 78.4 ± 8.0 kg. Following administration of risedronate by rapid or slow infusion, the only

Table I. Pharmacokinetic Parameters Following Single-Dose Oral Administration of 40 mg Risedronate to Three Different Gastrointestinal Sites

Pharmacokinetic parameter	Least-squares geometric mean[a] (95% confidence interval)			*P* value for overall F-test
	Stomach	Duodenum	Terminal ileum	
AUC_t (ng•h/mL)	36.0 (19.9, 65.0)	35.0 (19.7, 62.0)	43.2 (23.9, 78.0)	0.8863
C_{max} (ng/mL)	13.9 (7.0, 27.5)	13.3 (6.9, 25.7)	21.3 (10.8, 42.1)	0.5831
t_{max} (h)	1.01 (0.27, 1.76)	0.69 (0, 1.41)	0.63 (0, 1.37)	0.1868
A_e (μg)	242 (154, 330)	182 (97, 267)	226 (139, 314)	0.6363
CL_R (L/h/kg)	0.0730 (0.055, 0.097)	0.0533 (0.040, 0.071)	0.0575 (0.043, 0.077)	0.3478

[a]Values for t_{max} and A_e are arithmetic means.
AUC_t = area under the serum concentration-time curve from time 0 to last quantifiable concentration; C_{max} = maximum serum concentration; t_{max} = time of occurrence of maximum serum concentration; A_e = cumulative urinary excretion; CL_R = renal clearance.

pharmacokinetic parameter demonstrating a significant treatment effect was t_{max} (Table II and Fig. 4). The 25% lower C_{max} and the 1-hour longer t_{max} with the slower infusion rate were expected findings, reflecting the delivery rate of risedronate to the duodenum. The mean cumulative urinary excretion is depicted in Figure 5.

Safety Results

Risedronate solution was well tolerated by subjects in both studies. Two subjects had mild adverse events considered related to study drug by the investigator: general malaise and muscle cramps; backache, myalgia, and lower abdominal cramps; respectively. Both patients recovered and completed the study.

DISCUSSION

The results of these studies indicate that the absorption of risedronate administered as an aqueous solution to the stomach, the second part of the duodenum, or the terminal ileum is not significantly different. Although not statistically different, the 50% greater C_{max} following administration to the ileum may be

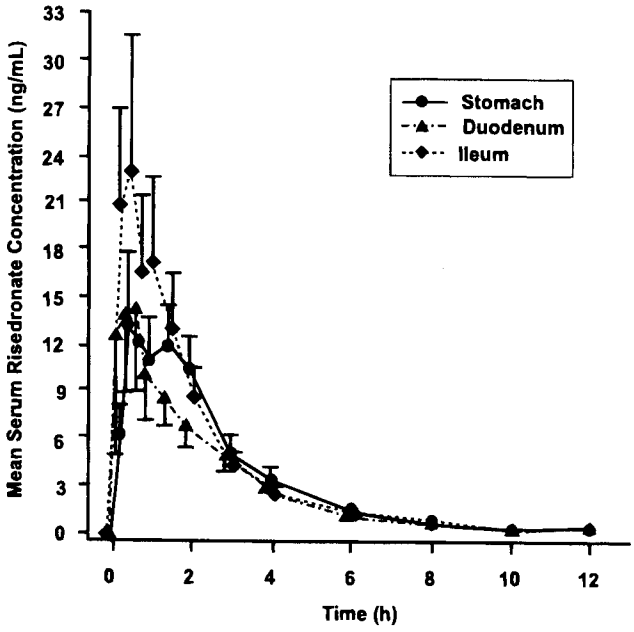

Fig. 2. Mean (± SE) serum concentration-time profiles following single-dose oral administration of 40 mg risedronate to the stomach, duodenum, and terminal ileum.

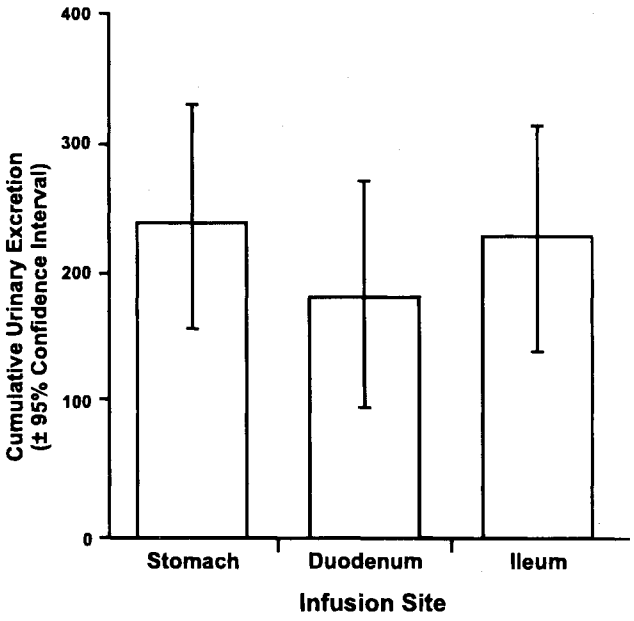

Fig. 3. Mean (± 95% confidence interval) cumulative urinary excretion following single-dose oral administration of 40 mg risedronate to the stomach, duodenum, and terminal ileum.

Table II. Pharmacokinetic Parameters Following Single-Dose Oral Administration of 40 mg Risedronate Solution as a Rapid or Slow Infusion Into the Duodenum

Pharmacokinetic parameter	Least-squares geometric mean[a] (95% confidence interval) Rapid infusion (over 1 minute)	Slow infusion (over 1 hour)	*P* value for treatment effect
AUC_t (ng·h/mL)	43.5 (23.4, 80.9)	39.9 (21.5, 74.2)	0.6609
C_{max} (ng/mL)	14.2 (7.6, 26.4)	10.7 (5.8, 20.0)	0.2467
t_{max} (h)	0.78 (0.21, 1.36)	1.84[b] (1.27, 2.42)	0.0303
A_e (μg)	235 (132, 421)	192 (108, 344)	0.2230
CL_R (L/h/kg)	0.0670 (0.0556, 0.0785)	0.0594 (0.0479, 0.0709)	0.2107

[a] Values for t_{max} and CL_R are arithmetic means.
[b] t_{max} was significantly longer than the rapid infusion.
Abbreviations as on Table I.

reflective of an increase in the rate of absorption, as the surface area in the ileum is much greater than the stomach or duodenum (10). However, no clear trend in the extent of absorption (AUC_t, A_e) was observed among the three gastrointestinal sites. Furthermore, the extent of absorption does not differ significantly following rapid or slow infusion of risedronate into the duodenum. Therefore, alternative drug delivery forms of risedronate are feasible, such as an immediate-release or enteric-coated dosage form.

Few studies have investigated the absorption of bisphosphonates from different gastrointestinal sites. In nonclinical studies, absorption of etidronate (an alkyl-bisphosphonate) was three times greater in the duodenum and the jejunum of rats than in the stomach (11). Alendronate (an amino-bisphosphonate) absorption in rats was five, nine, and two times greater than oral gavage following intraduodenal, intrajejunal, and intraileal administration, respectively (12). In a clinical study with alendronate, achlorhydric conditions were simulated by infusion of the H_2-receptor antagonist ranitidine (13). Alendronate bioavailability was approximately two times higher at a gastric pH of 6.0 following infusion of the H_2-receptor antagonist than at a fasting pH of 2.0.

The proposed mechanism for bisphosphonate absorption is by paracellular uptake (9,14,15); however, the mechanism

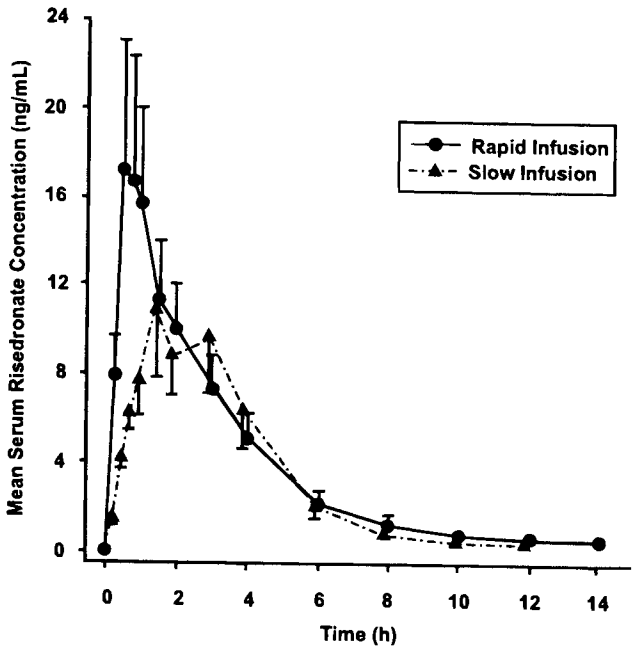

Fig. 4. Mean (± SE) serum concentration-time profiles following single-dose oral administration of 40 mg risedronate by rapid and slow infusion.

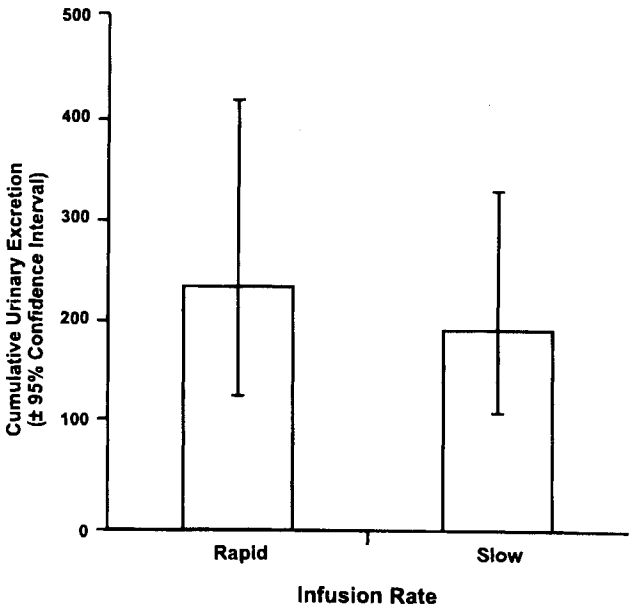

Fig. 5. Mean (± 95% confidence interval) cumulative urinary excretion following single-dose oral administration of 40 mg risedronate by rapid and slow infusion.

for the increased absorption from different gastrointestinal sites or at a higher pH has not been elucidated. Possible mechanisms for the increased absorption may include differences in gastrointestinal surface area, differences in gastrointestinal pH (ranging from pH 1 to 8) (10,16) affecting ionization/solubility of the bisphosphonates, or a change in tight junction permeability (14). Increased bisphosphonate concentrations, due to increased ionization and solubility, may result in increased tight junction permeability through bisphosphonate chelation of divalent cations present in tight junctions, and the widening of these junctions may lead to increased absorption as reported for tiludronate (14). This effect is consistent with the dose-dependent absorption reported for etidronate (11) and alendronate (9). Irrespective of the mechanism, studies indicate that the extent of absorption of some bisphosphonates, unlike risedronate, varies depending on the site of absorption, where pH varies. The 20% to 30% differences in rate and extent of risedronate absorption among the sites of administration in this study are small relative to the 50–70% intrasubject variability associated with risedronate (unpublished data, Procter and Gamble Pharmaceuticals), and as such should not have a clinical consequence. However, the high degree of variability associated with other bisphosphonate absorption and bioavailability (17–20), and the different incidences of toxicity associated with bisphosphonates (21,22), make it difficult to predict if the larger differences in absorption observed with other bisphosphonates would be of clinical significance.

In summary, these studies indicate that the rate and extent of risedronate absorption are independent of the site of administration along the gastrointestinal tract, and that the extent of absorption is not affected by the rate of administration.

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