Effect of renal function on risedronate pharmacokinetics after a single oral dose

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Aims To determine the relationship between risedronate pharmacokinetics and renal function.

Methods Risedronate was administered to adult men and women ($n=21$) with various degrees of renal function (creatinine clearance 15–126 ml min⁻¹) as a single oral dose of 30 mg. Serum samples were obtained for 72 h after dosing, and urine samples were collected for 72 h after dosing and then periodically for 6 weeks. Risedronate concentrations were determined using an enzyme-linked immunosorbent assay (ELISA). Risedronate serum concentration–time and urinary excretion rate–time profiles were analysed simultaneously using nonlinear regression.

Results Renal clearance and volume of distribution were linearly related to creatinine clearance ($r^2=0.854$, $P<0.001$; and $r^2=0.317$, $P<0.01$, respectively). Decreases in predicted renal clearance and volume of distribution of 82 and 69%, respectively, were observed when creatinine clearance decreased from 120 to 20 ml min⁻¹. A 64% decrease in predicted oral clearance was observed when creatinine clearance decreased from 120 to 20 ml min⁻¹ ($P=0.064$). Iohexol clearance, a predictor of renal function, produced similar results to those observed with creatinine clearance. Risedronate was well tolerated by the study population.

Conclusions Risedronate renal clearance was significantly related to a decrease in renal function. There was a consistent reduction in oral clearance with a decrease in creatinine clearance. However, based on the regression analysis, generally no dosage adjustment appears to be necessary for most patients with mild or moderate renal impairment (creatinine clearance >20 ml min⁻¹).

Keywords: pharmacokinetics, renal function, renal impairment, risedronate

Introduction

Risedronate sodium (1-hydroxy-2-[3-pyridinyl] ethylidene bisphosphonic acid monosodium salt) is a pyridinyl bisphosphonate in development for the treatment and prevention of osteoporosis, and has recently been approved for the treatment of Paget's disease of bone by the US Food and Drug Administration. It is a potent antiresorptive agent that inhibits osteoclast-mediated bone resorption and has a high affinity for hydroxyapatite crystals in bone [1]. Risedronate has been shown to normalize bone turnover and increase bone mass in patients with multiple myeloma [2] and osteopenia [3],

prevent trabecular and cortical bone loss in women with menopause induced by chemotherapy for breast cancer [4], and decrease pain and biochemical indicators of disease activity in patients with Paget's disease of bone [5–7].

Risedronate bioavailability after oral administration is low (<1%) [8] and similar to that observed in clinical studies with other bisphosphonates [9–11]. Absorption of risedronate is relatively rapid ($t_{\max} \sim 1$ h) and is independent of the site of administration within the upper gastrointestinal tract [12]. Risedronate absorption is independent of the oral dose from 2.5 to 30 mg [13]. 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 [8, 13]. The long half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

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Osteoporosis and other diseases of bone affect a population with various degrees of renal function. A decline in renal function may affect drug therapy by altering the pharmacokinetic and/or pharmacodynamic characteristics of drugs. Drugs eliminated primarily by renal excretion may accumulate as a consequence of impaired renal function, leading to an accentuated response. Therefore, dosage adjustments for some drugs may be required in this population of patients. In common with other bisphosphonates [11, 14], risedronate is eliminated primarily by renal clearance, with the remainder incorporated into bone [15, 16]. Thus, patients with impaired renal function may have increased exposure following administration of risedronate, due to a decrease in renal clearance, and a dosage adjustment may be appropriate. The objective of this study was to determine the relationship between risedronate pharmacokinetics and renal function.

Methods

Study design

The study utilized a single-dose, balanced, parallel design in which adult men and women with various degrees of renal function received an oral 30 mg dose of risedronate. A local ethics review committee approved the study, and a written informed consent was obtained from each subject prior to enrolment.

Study population

Men and women were eligible for enrolment if they were at least 18 years of age, in stable medical condition, and within 30% of their ideal body weight (1983 Metropolitan Height and Weight Tables [17]). Women had to be surgically sterile or at least 1 year postmenopausal. Subjects had to have stable renal function, defined by two 24 h ambulatory collected creatinine clearances (CL_{CR}) within 20% of the mean of the two values, during the 4 weeks prior to study. Glomerular filtration rate was assessed using iothexol clearance [18]. Renal function was classified by creatinine clearance according to the following ranges, with three to six subjects enrolled per group: Group I $>80 \text{ ml min}^{-1}$; Group II $50\text{--}80 \text{ ml min}^{-1}$; Group III $30\text{--}49 \text{ ml min}^{-1}$; and Group IV $<30 \text{ ml min}^{-1}$.

Ages of participants in Group I were matched with those in the other groups. Subjects were excluded if they had received bisphosphonates within 1 year of study entry, required any medications within 8 h before or 4 h after dosing (except antihypertensive and diuretic drugs, which were withheld for 2 h before and 4 h after dosing), or had active ulcer disease. Inclusion of subjects with

chronic use of prescribed medications was based on the likelihood of an effect on risedronate pharmacokinetics.

Study conduct

Prestudy screening evaluation consisted of: medical and medication history; physical examination including weight and vital signs; 12-lead electrocardiogram; routine urinalysis; and fasting blood samples for clinical chemistry and haematology. Serum and urine were collected for two CL_{CR} determinations separated by at least 7 days, with the second determination within 7 days of starting the study. A plasma sample for determination of iothexol clearance (CL_{IO}), a marker of glomerular filtration rate, was obtained at the time of the second CL_{CR} determination.

Each subject received one risedronate 30 mg cellulose film-coated tablet, administered orally with 240 ml of water after an overnight, 10 h fast and 4 h prior to a meal in the morning. Venous blood samples were collected at the following times: before the dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 40, 48, 60 and 72 h after the dose. The samples were allowed to clot for a minimum of 30 min at room temperature and then centrifuged. Serum was harvested from the samples and frozen at -25°C until assayed for risedronate. An additional blood sample was collected 12 h after the dose, processed to obtain serum, and stored at -20°C until determination of serum creatinine.

Urine was pooled over the following time intervals: $-12\text{--}0$ (blank), $0\text{--}1$, $1\text{--}4$, $4\text{--}8$, $8\text{--}12$, $12\text{--}16$, $16\text{--}24$, $24\text{--}32$, $32\text{--}40$, $40\text{--}48$, $48\text{--}60$, $60\text{--}72$ h after the dose, and twice a week for 6 weeks (8 h urine collections). Urine specimens were refrigerated (4°C , not frozen) until the entire specimen for the interval was obtained. Urine volume and pH for each interval were recorded. Aliquots of urine were then frozen at -25°C until assayed for risedronate. A 10% aliquot of each pooled sample obtained from 0 to 24 h was pooled and analysed for creatinine.

Safety evaluations included routine urinalysis and clinical laboratory tests (clinical chemistry and haematology) on the day prior to dosing and at exit. Blood samples were analysed for ionized calcium on the day prior to dosing, before the dose, 2, 6, 12, 24, 48 and 72 h after the dose, and at exit. Blood samples were also analysed for parathyroid hormone before the dose and 72 h after the dose. In addition, vital signs, 12-lead electrocardiogram and physical examination were reviewed.

Bioanalytical analysis

Serum 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 by absorbance detection of colour development. The quantitative ranges of the four-parameter standard curves were 0.19–6.0 ng ml⁻¹ and 0.28–4.7 ng ml⁻¹ for serum and urine, respectively. The interassay coefficients of variation for quality control samples ranged 12–15% for serum and 11–14% for urine. The relative risedronate recovery for the quality control samples ranged 91–106% and 97–107% for serum and urine, respectively.

Pharmacokinetic analysis

Risedronate serum concentration–time and urinary excretion rate–time data were simultaneously analysed using PCNONLIN, version 4.2 [19], and the following equations:

$$C = \sum_{i=1}^n C_i e^{-\lambda_i t} \quad (1)$$

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

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

where C is the serum concentration of risedronate 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, n is the number of exponents necessary to characterize serum concentration–time and urinary excretion rate–time profiles, C_i is the i th coefficient, λ_i is the i th exponent, CL_R is the renal clearance of risedronate, and C_n is the coefficient associated with λ_n . Initial parameter estimates were obtained from a previous study conducted in healthy volunteers [20]. Predicted serum concentrations and urinary excretion rates were weighted (1, $1/p$ or $1/p^2$, where p is the predicted value for that function) for use in data analysis. 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 [21]. Maximum serum concentration (C_{max}) and time that C_{max} occurred (t_{max}) were derived from the model based on the equations listed above. Area under the serum concentration–time curve (AUC), terminal exponential half-life ($t_{1/2,z}$), oral clearance

(CL_o) and terminal volume of distribution uncorrected for bioavailability (V_Z/F) were calculated from coefficients and exponents using standard equations [22, 23]. Cumulative urinary excretion (A_e) of risedronate was calculated as the product of AUC and CL_R . The percentage of the dose excreted in urine (A_e) was calculated as the A_e normalized for dose.

Predicted pharmacokinetic parameters were based on the linear relationships with CL_{CR} , and percentage decrease in CL_R , V_Z/F and CL_o was based on the equation (for example using CL_o):

$$\text{Percentage decrease} = \left(1 - \left(\frac{CL_{o20 \text{ ml min}^{-1}}}{CL_{o120 \text{ ml min}^{-1}}} \right) \right) \cdot 100 \quad (4)$$

Oral bioavailability (F) was estimated using the method of Hinderling & Shi [24]. Briefly, the method uses regression analysis of CL_o and CL_R (CL_o = nonrenal clearance (CL_{NR})/ F + $(1/F)$ (CL_R)). Assumptions of the method include first-order kinetics, and that bioavailability and nonrenal clearance (CL_{NR}) are independent of the renal function.

Statistical methods

The relationship between pharmacokinetic parameters and renal function (CL_{CR} and CL_{IO}) was assessed using a linear M-regression method [25]. The M-estimates for the slopes and intercepts of the regression lines were obtained using Huber weights, due to the observed variability in the data. A nonparametric Spearman's correlation between CL_o and CL_{CR} was also calculated and the relationships between CL_o and CL_R , and CL_{IO} and CL_{CR} were assessed. A P value of less than 0.05 was considered significant using a two-tailed test.

Results

Study population

Twenty-one subjects were enrolled: six in Group I (no renal impairment, with $CL_{CR} > 80 \text{ ml min}^{-1}$); six in Group II ($CL_{CR} = 50–80 \text{ ml min}^{-1}$); six in Group III ($CL_{CR} = 30–49 \text{ ml min}^{-1}$); and three in Group IV ($CL_{CR} < 30 \text{ ml min}^{-1}$). All participants completed the study. Demographic characteristics of the 21 participants (seven females, 14 males) are presented in Table 1. The mean age and weight at screening were 59.7 years (s.d. = 13.3) and 80.0 kg (s.d. = 15.6).

Pharmacokinetics

Serum concentration–time and urinary excretion rate–time profiles for individual subjects were adequately

Demographic characteristics	Group I	Group II	Group III	Group IV
Age (years)	62.0 (9.9)	69.3 (9.3)	49.5 (15.6)	56.0 (8.9)
Weight (kg)	81.0 (17.1)	65.1 (9.4)	88.1 (11.0)	92.0 (8.9)
Height (cm)	169.0 (11.0)	158.3 (7.6)	173.8 (6.9)	171.3 (1.2)
n (Female/male)	6 (2/4)	6 (5/1)	6 (0/6)	3 (0/3)
CL _{CR} (ml min ⁻¹)	107.2 (15.2)	66.2 (16.5)	42.5 (2.7)	18.4 (4.4)
CL _{IO} (ml min ⁻¹)	97.8 (16.9)	57.0 (8.5)	34.2 (5.3)	19.3 (2.1)

CL_{CR}: creatinine clearance on the day of dosing (enrolment into groups was based on two creatinine clearance determinations during screening); CL_{IO}: iothexol clearance determined during screening. Group I: creatinine clearance >80 ml min⁻¹; Group II: 50–80 ml min⁻¹; Group III: 30–49 ml min⁻¹; Group IV: <30 ml min⁻¹.

Table 1 Mean (s.d.) demographic and renal function characteristics of the study population.

characterized by a 3- or 4-exponential function using a weighting of $1/p^2$. Risedronate pharmacokinetic parameters are listed in Table 2.

Regression analysis indicated that CL_R (Figure 1) and V_Z/F (Figure 2) were linearly related ($P=0.0001$ and 0.0079 , respectively) to CL_{CR}. Decreases in predicted CL_R and V_Z/F of 82 and 69%, respectively, were observed when CL_{CR} decreased from 120 to 20 ml min⁻¹ ($r^2=0.854$, $CL_R=0.811 \cdot CL_{CR} + 1.38$; and $r^2=0.317$, $V_Z/F=28.4 \cdot CL_{CR} + 713$, respectively).

The relationship between CL_O and CL_{CR} was of borderline significance ($P=0.064$; Figure 3). Consistent with CL_R, the trend toward a lower CL_O was observed with a 64% decrease in predicted CL_O when CL_{CR} decreased from 120 to 20 ml min⁻¹ ($r^2=0.169$, $CL_O=128 \cdot CL_{CR} + 4580$). Regression analysis using CL_{IO} as a predictor of glomerular filtration rate produced similar results to those obtained using CL_{CR}, which was not unexpected since CL_{IO} and CL_{CR} were highly correlated in these study participants ($r=0.967$, $CL_{IO}=0.883 \cdot CL_{CR} + 0.325$; Figure 4). No other pharmacokinetic parameters were significantly related to CL_{CR} or CL_{IO}.

Estimation of the oral bioavailability by the method of Hinderling & Shi [24] resulted in a significant linear relationship between CL_O and CL_R ($P=0.0093$; Figure 5). The mean (95% confidence interval) oral bioavailability of risedronate was estimated at 0.61% (0.37, 2.21), and CL_{NR} was estimated to be 19.6 ml min⁻¹ (−29.8, 69.1).

Adverse events

Of the 21 participants, 11 (52.4%) experienced 22 adverse events. Headache was the most frequently reported adverse event (three subjects, one per group in Groups I, III and IV). Twenty of the adverse events were assessed by the investigator as having a doubtful relationship to the drug. Two adverse events were assessed as possibly

drug-related: single episodes of headache experienced in Subject 22 (Group III) and Subject 25 (Group IV). Both subjects recovered from the events. Of the 22 events, 15 were mild in severity, six were moderate, and one was severe. The severe event was experienced by Subject 26 (50 year-old black male, Group IV), who had a left hip dislocation 30 days after dosing. The subject recovered from the event, which the investigator assessed as being severe but having a doubtful relationship to risedronate.

Clinical laboratory evaluation and other safety measurements

As is common in patients with renal insufficiency, laboratory abnormalities such as anaemia, hyperphosphataemia, hyponatraemia/hypernatraemia, hyperkalaemia, hyperuricaemia, hyperparathyroidism, proteinuria, and haematuria were observed. No evidence of drug-related changes in any of the laboratory parameters, including ionized calcium and parathyroid hormone, were observed following risedronate administration.

Vital signs (oral temperature, blood pressure, respiratory rate, and heart rate) were normal for the population. There were no clinically significant changes in the electrocardiograms of the participants during the study.

Discussion

Bisphosphonates are recommended for the treatment and prevention of osteoporosis, and other diseases of bone (such as Paget's disease of bone) [26, 27]. These diseases affect a population with various degrees of renal function. Elderly patients, in whom osteoporosis is most common, are particularly susceptible to impairment of renal function. A decline in renal function may affect bisphosphonate therapy by altering pharmacokinetic and/or pharmacodynamic characteristics, as these drugs are eliminated primarily by renal clearance, with the remainder of the drug incorporated into bone [11, 14, 16].

Table 2 Risedronate pharmacokinetic parameters after single dose oral administration of 30 mg to volunteers.

Subject	CL_{CR} ($ml\ min^{-1}$)	CL_{IO} ($ml\ min^{-1}$)	BW (kg)	AUC ($ng\ ml^{-1}\ h$)	C_{max} ($ng\ ml^{-1}$)	t_{max} (h)	$t_{1/2,z}$ (h)	CL_O ($ml\ min^{-1}$)	CL_R ($ml\ min^{-1}$)	V_Z/F (l)	A_e (μg)	A'_e (%)
01	81.6	72	58.4	22.41	4.27	0.63	98.25	22319	75.14	189790	101.05	0.3368
02	109.9	106	94.7	24.97	4.64	0.74	214.73	20013	86.65	372126	129.78	0.4326
03	107.8	95	86.0	61.85	8.04	1.64	253.36	8084	74.82	177298	277.88	0.9263
04	100.6	88	64.9	25.13	4.38	1.10	143.67	19892	83.18	247450	125.38	0.4179
05	126.0	105	102.8	29.49	4.55	1.08	247.55	16962	96.46	363347	170.78	0.5693
06	117.2	121	79.3	16.94	3.81	0.68	275.87	29513	95.29	704821	96.92	0.3231
09	71.3	50	60.7	26.77	4.71	0.77	177.91	18675	123.22	287592	197.94	0.6598
10	49.1	52	62.3	20.04	3.04	1.13	132.65	24951	58.15	286466	69.92	0.2331
11	69.7	58	72.8	52.53	8.11	0.81	174.29	9513	80.44	143594	253.62	0.8454
12	65.3	66	50.2	15.55	3.90	0.70	88.01	32161	103.24	245035	96.34	0.3211
13	93.1	68	68.2	90.80	14.38	1.03	273.30	5501	77.29	130275	421.11	1.4037
14	48.6	48	76.1	65.28	7.44	0.93	258.70	7661	77.62	171515	304.15	1.0138
17	42.5	36	76.1	40.16	5.98	1.15	235.01	12455	41.47	253248	99.85	0.3328
18	42.2	39	104.3	128.49	7.23	1.52	335.09	3894	24.68	112870	189.64	0.6321
19	41.8	38	90.9	40.43	4.02	0.77	211.45	12362	32.42	226383	78.59	0.2620
20	38.1	32	90.0	350.38	86.85	0.46	284.08	1425	24.30	35091	511.43	1.7048
21	44.3	26	92.5	48.04	4.60	1.60	228.61	10406	33.61	205951	97.02	0.3234
22	46.2	—	75.0	295.80	79.60	0.68	326.81	1688	32.13	47818	570.51	1.9017
25	23.4	20	82.2	144.03	21.97	0.32	322.05	3466	16.44	96776	142.61	0.4754
26	16.2	17	99.5	14.19	1.89	0.33	30.19	35240	8.96	92069	7.69	0.0256
27	15.5	21	94.3	110.31	6.15	1.74	165.27	4526	9.90	64844	65.89	0.2196

CL_{CR} , creatinine clearance on the day of dosing; CL_{IO} , iothexol clearance; BW, body weight; AUC, area under the serum concentration-time profile from time $0 \rightarrow \infty$; C_{max} , maximum serum concentration; t_{max} , time that the maximum serum concentration occurs; $t_{1/2,z}$, half-life of the terminal exponential phase; CL_O , oral clearance; CL_R , renal clearance; V_Z/F , terminal volume of distribution, uncorrected for bioavailability; A_e , cumulative amount of drug excreted in urine from $0 \rightarrow \infty$; A'_e , cumulative amount of drug excreted in urine normalized for dose and expressed as a percentage. Iothexol clearance was not conducted in subject 22 due to allergy to iodine.

Figure 1 Relationship between renal clearance of risedronate (CL_R) and creatinine clearance (CL_{CR}), including 95% confidence intervals (.....) ($r^2=0.854$, $CL_R=0.811 \cdot CL_{CR} + 1.38$, slope $P=0.0001$).

Figure 2 Relationship between volume of distribution uncorrected for bioavailability (V_Z/F) and creatinine clearance (CL_{CR}), including 95% confidence intervals (.....) ($r^2=0.317$, $V_Z/F=28.4 \cdot CL_{CR} + 713$, slope $P=0.0079$).

Therefore, dosage adjustments for some bisphosphonates may be required in patients with impaired renal function. The present study characterized risedronate pharmacokinetics in this target population.

Figure 3 Relationship between oral clearance of risedronate (CL_O) and creatinine clearance (CL_{CR}), including 95% confidence intervals (.....) ($r^2=0.169$, $CL_O=128 \cdot CL_{CR} + 4580$, slope $P=0.064$).

Figure 4 Correlation between iothexol clearance (CL_{IO}) and creatinine clearance (CL_{CR}), including 95% confidence intervals (.....) ($r=0.967$, $CL_{IO}=0.883 \cdot CL_{CR} + 0.325$, $P=0.0001$).

Regression analysis of renal clearance and creatinine or iothexol clearance, indicated a significant linear relationship between glomerular filtration and renal clearance of risedronate. Renal clearance of risedronate was reduced (82%), with a decrease in creatinine clearance (120–20 ml min^{-1}). Consistent with declining renal

Figure 5 Relationship between oral and renal clearance of risedronate (CL_O and CL_R , respectively) including 95% confidence intervals (.....) ($r^2 = 0.306$, $CL_O = 163 \cdot CL_R + 3200$, slope $P = 0.0093$).

clearance was a 64% decrease in oral clearance of risedronate. Thus, the results of this study suggest that a dosage adjustment may be necessary in patients with severe renal impairment (creatinine clearance $\leq 20 \text{ ml min}^{-1}$), though currently there are no safety or efficacy data to support a recommendation for a dosage adjustment in this population. However, based on the regression analysis, no dosage adjustment appears necessary for patients with mild or moderate renal impairment (creatinine clearance $> 20 \text{ ml min}^{-1}$) as the increase in risedronate exposure is neither statistically nor clinically significant. These results are consistent with a study of the treatment of Paget's disease of bone (30 mg day $^{-1}$ for 2 months), where risedronate was found to be efficacious and well tolerated [28] in patients with creatinine clearances as low as 30 ml min^{-1} (data on file, Procter & Gamble Pharmaceuticals).

The renal clearances of other bisphosphonates have also been reported to decrease with declining renal function. The renal clearance of tiludronate [29, 30], clodronate [31, 32], and pamidronate [33] decreased with declining creatinine clearance. As observed with risedronate, the C_{max} values for tiludronate, clodronate and pamidronate in subjects with impaired renal function were not significantly different from the control groups [30, 32, 33], with the exception of one group ($CL_{\text{CR}} = 50\text{--}80 \text{ ml min}^{-1}$) in the clodronate study [32]. In common with risedronate, the clearance (oral or total) of tiludronate, clodronate and pamidronate is reduced in

renally impaired patients. On the basis of the clodronate studies, others have recommended a dosage adjustment in patients with renal impairment [31, 32]. Saha *et al.* [32] recommended a clodronate dosage reduction dependent on the patient's creatinine clearance, beginning with a creatinine clearance of less than 80 ml min^{-1} (i.e. $CL_{\text{CR}} = 50\text{--}80 \text{ ml min}^{-1}$, 75–100% of normal dose; $CL_{\text{CR}} = 12\text{--}50 \text{ ml min}^{-1}$, 50–75% of normal dose; $CL_{\text{CR}} < 12 \text{ ml min}^{-1}$, 50% of normal dose). Although the area under the pamidronate plasma concentration–time curve was two fold greater in renally impaired patients ($CL_{\text{CR}} < 30 \text{ ml min}^{-1}$) than in patients with normal renal function, Berenson *et al.* [33] suggested that no reduction in dose would be necessary in renally impaired cancer patients as successive doses of pamidronate are generally separated by several weeks.

Hinderling & Shi [24] have proposed a method to determine the absolute bioavailability and nonrenal clearance using only oral data. This method is based on the use of subjects with various degrees of renal function, and the collection of serum and urine data. Based on this method, the oral bioavailability of risedronate was 0.61%, which is similar to that reported previously for risedronate (0.65%) [8] and to that observed in clinical studies with other bisphosphonates [9–11, 34, 35]. The use of this method to estimate the bioavailability of bisphosphonates appears valid, provided that the drug investigated meets the necessary assumptions (i.e. nonrenal clearance is independent of renal function).

In conclusion, renal clearance of risedronate was significantly related to a decrease in renal function (creatinine or iothexol clearance). Consistent with renal clearance, oral clearance was reduced by 64% with a decrease in creatinine clearance from 120 to 20 ml min^{-1} . Therefore, generally no dosage adjustment appears to be necessary for most patients with mild or moderate renal impairment (creatinine clearance $> 20 \text{ ml min}^{-1}$).

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