Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate

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- 1 The pharmacokinetics of bismuth and ranitidine derived from oral doses of ranitidine bismuth citrate 800 mg given twice daily for 28 days were examined in this double-blind, placebo-controlled, parallel-group study in 27 healthy subjects.
- 2 Bismuth accumulation in plasma reflected its multicompartmental disposition, achieving the majority of predicted steady state within 14–28 days. Bismuth absorption from ranitidine bismuth citrate is limited ($<0.5\%$ of the dose), and bismuth elimination is predominantly renal secretion. Peak plasma concentrations did not exceed 19 ng ml^{-1} , remaining well below those associated with bismuth toxicity. Bismuth was measurable at low concentrations in plasma and urine for up to 5 months after the last dose. Plasma bismuth concentration-time data and urinary excretion data were best described by separate multicompartmental models, with terminal half-lives averaging 21 days and 45 days, respectively.
- 3 The pharmacokinetics of ranitidine derived from ranitidine bismuth citrate were similar to those of ranitidine administered alone. Ranitidine did not appreciably accumulate in plasma.
- 4 Ranitidine bismuth citrate was well-tolerated during 28 days of repeated dosing.

Keywords bismuth ranitidine pharmacokinetics

Introduction

Ranitidine bismuth citrate is a new antiulcerant that possesses both the acid-antisecretory activity of ranitidine [1] and the anti-*Helicobacter pylori* activity of bismuth [2, 3]. The pharmacokinetics of bismuth and ranitidine following single oral doses of this compound were described in the preceding paper. Following oral absorption, bismuth persists in the body with multiexponential elimination half-lives, respectively ranging from 1 to 4 h, 5 to 11 days, and 3 to 10 weeks. [4] This multiexponential behaviour raises the concern that prolonged, and possibly extensive, accumulation might occur with repeated dosing. Therefore, this study was conducted to determine the pharmacokinetics of bismuth and ranitidine derived from ranitidine bismuth citrate given orally in 800 mg doses twice daily for 28 days.

Methods

Subjects and procedures

This study was conducted at LAB and Co. GmbH, Neu Ulm, Germany, and the protocol was approved by the Freiburg Review Board. Twenty-seven healthy male subjects aged 20–49 years gave written informed consent and participated in this study. Restrictions on the use of other medications during the study were as described in the preceding paper. Each subject was admitted to the research unit 1 day prior to receiving the first dose, and remained there for 36 days. Subjects were randomly assigned to receive either 800 mg ranitidine bismuth citrate (18 subjects) or placebo (nine subjects) twice daily for 28 days (days 1 to 28), ending with the morning dose on day 28. Doses were given 30 min before a standard breakfast and 2 h after a standard dinner throughout the study. Subjects were monitored in the

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research unit for 7 days (days 29 to 35) after dosing was completed. Subjects receiving ranitidine bismuth citrate also participated in an unblinded post-dosing pharmacokinetic sampling period, beginning on day 36 and lasting approximately 6 months. Subjects receiving placebo completed the study on day 36.

Measurements

Blood samples for determination of plasma bismuth and ranitidine concentrations were collected prior to, and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after the morning dose on days 1, 14, and 28. Blood samples for determination of plasma bismuth concentration were also collected immediately prior to the morning dose on days 4, 7, 10, 18, 21, and 25. Blood samples for determination of plasma bismuth concentration were also collected 1, 2, 3, 4, 5, 6, 7, 11, 14, 18, 21, 28, 35, 42, 49, 56, 70, 84, 98, 112, 126, 140, 154, and 168 days after the last dose on day 28.

Twelve-hour urine samples for determination of urinary bismuth concentration were collected prior to dosing and after the morning dose on days 1, 7, 14, 21, and 28, and consecutively for 7 days after the last dose on day 28. Twenty-four hour urine samples for determination of urinary bismuth concentration were also collected 11, 14, 18, 21, 28, 35, 42, 49, 56, 70, 84, 98, 112, 126, 140, 154, and 168 days after the last dose on day 28.

Analytical methods

Ranitidine plasma concentrations and bismuth plasma and urine concentrations were determined using the same methods described in the preceding paper.

Data analysis

Peak plasma concentration ($C_{\max}$) and peak time ($t_{\max}$), trough plasma concentration ($C_{\min}$), and area under the plasma concentration-time curve ($AUC\tau$) during the 12 h dosing interval following the morning dose on days 1, 14, and 28 were determined for both bismuth and ranitidine. $AUC\tau$ was calculated by linear trapezoidal interpolation with extrapolation to 12 h where necessary. Urinary recovery ($A_u\tau$) of bismuth during the 12 h dosing interval following the morning dose on days 1, 7, 14, 21, and 28 was calculated as the product of urine volume and bismuth concentration. Renal clearance (CL_r) of bismuth on days 1, 14, and 28 was calculated as $A_u\tau/AUC\tau$.

Bismuth plasma concentration (C) *vs* time data obtained during and after dosing were fit to multiple oral dose equations derived by convolution [7] for two or more compartments, where the absorption rate constant was assumed equal to the first elimination rate constant. Best-fit estimates for coefficients and distribution/elimination rate constants (λ_i) were obtained using a weighting factor of $1/C^2$ and dosing interval (τ) of 12 h for doses 1 through 55. These estimates, together

with selection of the optimal number of compartments for an individual subject's data were based on Akaike's Information Criterion. Bismuth plasma half-life estimates were calculated as $\log 2/\lambda_i$. Predicted steady-state plasma bismuth concentrations (C_{ss}) during a dosing interval were determined using these best-fit parameters. These predicted C_{ss} were then used to calculate predicted steady-state $C_{\max}$, $C_{\min}$, and $AUC\tau$ for each subject.

Bismuth urinary excretion ($A_u\tau$) *vs* collection start time data obtained during and after dosing were fit to multiple oral dose equations derived by convolution [7] for two or more compartments, where the absorptive phase was assumed to be too rapid for distinction using urinary excretion data. Best-fit estimates for coefficients and distribution/elimination rate constants (λ_i) were obtained using a weighting factor of $1/(A_u\tau)^2$, urine collection durations of 12 and 24 h, and dosing intervals (τ) of 12 h for doses 1 through 55. These estimates, together with selection of the optimal number of compartments for an individual subject's data, were based on Akaike's Information Criterion. Bismuth urinary excretion half-life estimates were calculated as $\log 2/\lambda_i$. Steady-state urinary bismuth excretion during a dosing interval ($A_u\tau_{ss}$) was determined using these best-fit parameters.

Analysis of variance (ANOVA) was used to assess temporal differences in ranitidine $C_{\max}$, $C_{\min}$, and $AUC\tau$, as well as log-transformed values of bismuth $C_{\max}$, $C_{\min}$, $AUC\tau$, $A_u\tau$, and CL_r . These bismuth parameters were log-transformed to satisfy the assumption of equal variances on each day. The Wilcoxon Signed-Rank test was used to assess temporal differences in $t_{\max}$ for both ranitidine and bismuth.

Results

Ranitidine pharmacokinetics

Plasma ranitidine concentrations during the 12 h interval after the morning dose on days 1, 14, and 28 are described in Table 1. Arithmetic mean values of $C_{\max}$, $C_{\min}$, and $AUC\tau$, and median values of $t_{\max}$ were not significantly different on day 28 from the values on days 1 or 14. Plasma concentration parameters did not increase more than 15% above day 1 values with repeated dosing for 28 days.

Table 1 Ranitidine pharmacokinetic parameters (arithmetic means $\pm$ s.d.)

Parameter	Day 1	Day 14	Day 28
$AUC\tau$ (ng ml ⁻¹ h)	2696 $\pm$ 905	3106 $\pm$ 960	2794 $\pm$ 1219
$C_{\max}$ (ng ml ⁻¹)	681 $\pm$ 237	762 $\pm$ 256	737 $\pm$ 293
$t_{\max}$ (h) ^a	2.0 (1.3–2.0)	2.0 (1.5–2.0)	1.0 (1.0–1.5)
$C_{\min}$ (ng ml ⁻¹)	40 $\pm$ 16	42 $\pm$ 18	34 $\pm$ 20

^a Median and 95% CI

Bismuth pharmacokinetics

Median plasma bismuth concentrations during the 12 h interval after the morning dose on days 1, 14, and 28 are shown in Figure 1. Plasma bismuth concentrations exhibited a large degree of both inter- and intra-subject variability. Geometric mean values of $C_{\max}$ and $AUC\tau$ on day 28 were significantly ($P < 0.05$) greater than on day 1, but not day 14 (Table 2). The geometric mean value of $C_{\min}$ on day 28 was significantly ($P < 0.05$) greater than on day 1 and on day 14 (1.2-fold). Median values of $t_{\max}$ did not significantly differ between days 1, 14, or 28.

The geometric mean value of $A_u\tau$ on day 28 was significantly ($P < 0.05$) greater than on day 1, but not day 14 (Table 2). Values of $A_u\tau$ on days 7 and 21 (not shown) were consistent with this pattern of accumulation. Geometric mean values of CL_r did not significantly differ between days 1, 14, or 28.

Bismuth plasma concentration-time data for each subject observed during dosing and measurable for up to 154 days after the last dose were best fit by a three-

Figure 1 Bismuth median plasma concentrations in 18 healthy subjects on days 1 (●), 14 (▲), 28 (■), and at projected steady-state (---) with twice daily dosing of ranitidine bismuth citrate 800 mg (equivalent to 256 mg bismuth) for 28 days.

compartment model in most subjects. Data from three subjects were not used due to an inadequate duration of sampling. In the remaining 15 subjects, correlation coefficients for the relationship between observed and predicted concentration ranged from 0.618 to 0.974. The relationships between day 1, day 14, day 28, and predicted steady-state values of bismuth plasma $C_{\max}$, $AUC\tau$, and $C_{\min}$ are shown in Figure 2. The geometric mean predicted steady-state $C_{\max}$ was essentially equivalent to that observed on day 28, while geometric mean predicted steady-state $AUC\tau$ and $C_{\min}$ were 1.3- and 1.5-fold higher, respectively, than those observed on day 28. Half-lives for the three phases of bismuth disposition averaged 20 min, 11.1 h, and 20.7 days (Table 3). A plot of bismuth plasma concentrations during the post-dosing period in a representative subject is shown in Figure 3.

Bismuth urinary excretion data for each subject observed during dosing and measurable for up to 168 days after the last dose were best fit by a two-

Figure 2 Bismuth geometric mean $C_{\max}$ (● scaled $\times 20$), $C_{\min}$ (▲ scaled $\times 70$), $AUC\tau$ (■ scaled $\times 4$), and $A_u\tau$ (□) observed during dosing and projected to steady-state in 18 subjects receiving ranitidine bismuth citrate 800 mg (equivalent to 256 mg bismuth) twice daily for 28 days.

Table 2 Bismuth pharmacokinetic parameters (geometric means and 95% CI)

Parameter	Day 1 Observed ^a	Day 14 Observed ^a	Day 28 Observed ^a	Steady state Predicted ^b
$C_{\max}$ (ng ml ⁻¹)	2.30* 1.56–3.39	5.33 3.88–7.33	5.85 4.08–8.37	5.51 4.20–7.25
$t_{\max}$ (h) ^c	0.50 0.38–0.75	0.50 0.38–0.75	0.50 0.38–0.63	—
$C_{\min}$ (ng ml ⁻¹)	0.31* 0.27–0.36	1.87* 1.49–2.36	2.32 1.74–3.11	3.42 2.50–4.68
$AUC\tau$ (ng h ml ⁻¹)	7.9* 6.2–10.1	31.7 25.1–40.1	36.5 27.7–48.3	47.1 35.4–62.6
$A_u\tau$ (μg)	24.1* 18.3–31.7	115.4 94.1–141.5	127.3 97.8–165.6	129.4 104.5–160.3
CL_r (ml min ⁻¹)	50.9 43.3–59.7	60.6 52.3–70.3	58.0 45.2–74.5	—

^a All subjects ($n = 18$)

^b Subjects with sufficient data for modelling ($n = 15$)

^c Median and 95% CI

* Significantly lower than day 28 ($P < 0.05$)

Table 3 Bismuth curve-fit half-life values (geometric means and 95% CI)

Plasma concentration ^a			Urinary excretion ^a	
Initial phase (min)	Intermediate phase (h)	Terminal phase (days)	Initial phase (days)	Terminal phase (days)
20	11.1	20.7	4.0	45.1
16–25	6.5–19.0	17.8–24.1	2.6–6.1	29.7–68.4

^a Subjects with sufficient data for modelling ($n=15$) **Figure 3** Bismuth plasma concentrations (Δ) and urinary recoveries ($\circ$) observed in subject 4 during the post-dosing period (following 28 days of dosing) showing best-fit model predictions.

compartment model in most subjects. Data from three subjects were not used due to an inadequate duration of sampling. In the remaining 15 subjects, correlation coefficients for the relationship between observed and predicted excretion ranged from 0.902 to 0.992. The relationship between day 1, day 14, day 28, and predicted steady-state values of bismuth $A_{u\tau}$ are depicted in Figure 2. The geometric mean predicted steady-state $A_{u\tau}$ was essentially equivalent to that observed on day 28. Half-lives for the two terminal phases of bismuth disposition averaged 4.0 days and 45.1 days (Table 3). A plot of bismuth urinary recoveries during the post-dosing period in a representative subject is shown in Figure 3.

Safety and tolerability

Twenty-six subjects completed the study as planned, and one subject withdrew from participation due to adverse events that were not typical of bismuth toxicity. No serious adverse events or clinically significant drug-related biochemical abnormalities were observed during the study. Ranitidine bismuth citrate was well-tolerated compared with placebo in these subjects.

Discussion

The results of this study indicate that the pharmacokinetics of ranitidine during and after 28 days of twice

daily dosing with 800 mg ranitidine bismuth citrate (≈ 320 mg ranitidine) are comparable with the pharmacokinetics of ranitidine administered alone, as previously reported [8]. Ranitidine displayed very little accumulation with repeated dosing of ranitidine bismuth citrate, consistent with administration of ranitidine alone.

Bismuth accumulated in plasma over 28 days of repeated twice-daily dosing with ranitidine bismuth citrate in a multi-compartmental fashion, consistent with data observed with shorter durations of dosing [9], as well as in duodenal ulcer patients [10]. Steady-state values of $C_{\max}$ were achieved by day 28 of dosing, while AUC_{τ} and $C_{\min}$ had achieved 77% and 68% of their respective predicted steady-state values. Thus, $C_{\max}$ reflected the more rapidly equilibrating compartments, while AUC_{τ} and $C_{\min}$ reflected the more slowly equilibrating compartments of bismuth distribution in the body. Because $C_{\max}$ was less representative of accumulation than of the more variable absorption process, less optimal model estimation was accepted for this parameter.

The multicompartmental distribution of bismuth was also readily apparent in the post-dosing phase, where prolonged elimination and re-distribution were observed. Bismuth was measurable at low concentrations in plasma for up to 5 months after the last dose on day 28. The half-lives observed for the three plasma elimination/distribution phases, averaging 20 min, 11.1 h, and 20.7 days, were comparable with values reported elsewhere for bismuth [4]. The terminal half-life accounted for more than 50% of the total plasma AUC, indicating that this half-life most reflected the elimination process governing accumulation of bismuth in plasma upon repeated dosing.

Urinary excretion is presumed to be the primary route of bismuth elimination. Assuming steady-state urinary recovery accounts for the majority of absorbed bismuth, it appears that 0.05% of the amount administered (≈ 256 mg bismuth) is bioavailable. During repeated dosing, the time course for accumulation of $A_{u\tau}$ resembled that for $C_{\max}$, essentially achieving steady state by day 28. Although urinary excretion data demonstrated multicompartmental behaviour as was observed in plasma, one fewer exponential term was needed in the best-fit model owing to less frequent early sampling of urine. The elimination phases of plasma and urine were not parallel, necessitating separate fitting of plasma and urine data. The reason for this discrepancy is unknown, but may involve an intervening compartment or non-linear binding of bismuth to metallothioneins in the kidney. Another hypothesis that remains to be investigated is whether speciation of bismuth occurs, leading to an apparent pharmacokinetic difference between plasma and urine, which is not discernible with current bioanalytical methods.

Bismuth CL_r was unaltered by time or concentration during repeated dosing. In general, individuals with the highest bismuth plasma concentrations also demonstrated the lowest CL_r , indicating the dominance of this route of elimination. Thus, caution is warranted in renally impaired patients.

The pharmacokinetics of bismuth derived from ranitidine bismuth citrate observed in this study are consistent with data reported for another bismuth-containing product, tripotassium dicitrate bismuthate (DeNol). Studies with DeNol indicate accumulation upon repeated dosing despite limited oral absorption [11–13].

The pharmacokinetics of bismuth are important in assessing the potential for toxicity associated with this metal. Therapeutic use of bismuth has had a history of sporadic failure, in part due to poor understanding of the factors that affect its absorption, distribution, and elimination. The work of Hillemand [14] to establish a blood concentration threshold for clinical toxicity initiated the search for a pharmacokinetically rational approach to understanding bismuth toxicity. While much of this work must focus on the extent of absorption from various bismuth compounds, an understanding of the systemic disposition of bismuth is also necessary.

The 50–100 ng ml⁻¹ blood (80–160 ng ml⁻¹ plasma) toxicity thresholds proposed by Hillemand [14] were based on the incidence of encephalopathy with overdose of bismuth subnitrate and subgallate salts, although other bismuth compounds have also produced osteoarthropathies and nephrotoxicity. Subsequent analysis of this data has indicated that the proposed threshold is too low [4]. In this study, plasma concentrations of bismuth derived from ranitidine bismuth citrate never exceeded 19 ng ml⁻¹ after dosing for 28 days at twice the recommended dose (400 mg twice daily). Although it is not clear whether peak or trough concentrations better represent the potential for toxicity, the relative exposure observed in this study was well within the accepted limits of tolerability for this metal.

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