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

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- 1 The pharmacokinetics of bismuth and ranitidine derived from ranitidine bismuth citrate given in single oral doses ranging from 200 mg to 1600 mg were evaluated in healthy subjects.
- 2 Bismuth was only minimally absorbed ($<0.5\%$ of the amount dosed) after administration of ranitidine bismuth citrate, and peak plasma concentrations never exceeded 33 ng ml^{-1} in any subject. Plasma concentrations and urinary recoveries of bismuth at doses up to and including 800 mg were relatively constant and not proportional to dose. Bismuth absorption was increased more than proportionally with the dose at 1600 mg.
- 3 The pharmacokinetics of ranitidine after administration of ranitidine bismuth citrate were dose-proportional and consistent with previous observations for ranitidine administered alone.
- 4 Ranitidine bismuth citrate was well-tolerated in single oral doses of up to 1600 mg.

Keywords bismuth ranitidine pharmacokinetics

Introduction

Recent advances in gastroenterology indicate that the pathophysiology of peptic ulcer disease is multifactorial, involving both the corrosive effect of stomach acid on the gastric mucosa and the impairment of mucosal defense by factors such as *Helicobacter pylori* infection [1]. Although drug therapy for peptic ulcer disease has proven effective, new drugs for peptic ulcer disease must target multiple pathophysiological mechanisms to achieve increased healing and reduce the occurrence of relapse [2]. Ranitidine bismuth citrate possesses both the activity of ranitidine to inhibit secretion of gastric acid by blocking the action of histamine at the acid-secreting parietal cell [3,4], and the antimicrobial activity of bismuth against *Helicobacter pylori* [5]. Bismuth may also provide cytoprotection [6–8] and inhibit pepsin activity [9].

Because bismuth acts locally in the gut, systemic absorption does not appear to be necessary for efficacy. Thus, the pharmacokinetics of bismuth are of interest primarily for toxicological reasons. Although the pharmacokinetics of ranitidine alone have been previously well-documented [10], the pharmacokinetics of bismuth have only recently been described [11–13].

Similarly, while ranitidine has been demonstrated to

be safe in broad therapeutic application [14], bismuth, in most salt forms, has not. Investigations into the safety of bismuth have led to the proposal of threshold blood concentrations as an indicator of potential toxicity [15]. Although these threshold concentrations are probably too low [13], there appears to be a relationship between the degree of systemic exposure and toxicity to bismuth. Therefore, this study was conducted to determine the pharmacokinetic profiles of both ranitidine and bismuth after administration of single oral doses of ranitidine bismuth citrate.

Methods

Subjects and procedures

This study was conducted at Harris Laboratories, Lincoln, Nebraska, USA and the protocol was approved by the Harris Institutional Review Board. Sixty (60) healthy male subjects aged 19 to 40 years gave written informed consent and participated in this study. Subjects were not allowed to participate if they had ingested any bismuth-containing medications for at least 1 month

prior to the study. The use of tobacco, caffeine, or any medications was also prohibited during the study.

Four groups of 15 subjects each were assigned to receive the same single dose of ranitidine bismuth citrate (200, 400, 800, or 1600 mg), and groups were dosed in order of ascending dose. Each subject participated in only one group. Within each dose group, subjects were randomly assigned to receive either ranitidine bismuth citrate ($n=12$) or placebo ($n=3$). Subjects were admitted to the research unit and fasted from the evening before drug administration until 4 h post-dose on the following day.

Doses were administered in the morning with 240 ml of water. From each dose group ($n=15$), six subjects receiving ranitidine bismuth citrate and two subjects receiving placebo were randomly selected to continue in the study through 29 days post-dose in order to characterize the disposition of bismuth. The remaining subjects completed the study 48 h post-dose.

Measurements

Blood samples for determination of plasma ranitidine, plasma bismuth, and blood bismuth concentration were taken predose, and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 30, 36, and 48 h post-dose. Blood samples for determination of plasma and blood bismuth concentration were also taken 5, 7, 9, 11, 13, 15, 16, 19, 21, 23, 25, 27, and 29 days post-dose in those subjects continuing in the study. Urine samples for determination of bismuth concentration were collected in intervals for 48 h post-dose in all subjects, and for 29 days post-dose in those subjects continuing in the study.

Analytical methods

Ranitidine plasma concentrations were determined by high performance liquid chromatography (h.p.l.c.) with ultraviolet absorbance detection [16]. The assay was linear ($r \geq 0.99$) over the 10–250 ng ml⁻¹ concentration range, and precision was within 8%. Bismuth plasma, blood, and urine concentrations were determined by inductively coupled plasma mass spectrometry (ICPMS) [17]. The plasma and blood assays were linear ($r^2 \geq 0.999$) over the 0.2–64 ng ml⁻¹ concentration range, and precision was within 13.2%. The urine assay was linear ($r^2 \geq 0.999$) over the 1–500 ng ml⁻¹ concentration range, and precision was within 9.7%.

Data analysis

Ranitidine plasma concentration data were analysed to determine observed peak concentration ($C_{\max}$) and time ($t_{\max}$), linear trapezoidal area under the concentration *vs* time curve extrapolated to infinity (AUC), and log-linear regression elimination half-life ($t_{1/2}$).

Bismuth plasma concentration data from all subjects were analysed to determine observed peak concentration

($C_{\max}$) and time ($t_{\max}$), linear trapezoidal area under the concentration *vs* time curve to 12 h post-dose (AUC(0,12 h)), and renal clearance (CL_r) calculated from 12-h urinary recovery and AUC(0,12 h). Plasma and urine $t_{1/2}$, mean residence time (MRT), and total urinary recovery (A_u), were determined in those subjects followed for 29 days post-dose.

Analysis of variance (ANOVA) was used to compare ranitidine dose-normalized AUC, dose-normalized $C_{\max}$, $t_{\max}$, and $t_{1/2}$ between doses. Bismuth $C_{\max}$, AUC(0,12 h), A_u , and CL_r were log-transformed prior to statistical analysis to satisfy the assumption of equal variances between doses. ANOVA with piece-wise linear regression was used to compare log-transformed bismuth $C_{\max}$, AUC(0,12 h), and A_u between doses, testing for zero intercepts and slopes of unity. The piece-wise linear regression equation was: $\log(\text{Parameter}) = \text{Intercept} + \text{Slope} \cdot \log(\text{Dose}) + \text{Slope} \cdot [\log(\text{Dose}) - \log(800)] \cdot I$, where $I=0$ when $\text{Dose} \leq 800$, and $I=1$ when $\text{Dose} > 800$. ANOVA was also used to compare log-transformed bismuth CL_r between doses. The Wilcoxon Signed-Rank test was used to compare $t_{\max}$ between doses for both ranitidine and bismuth.

Results

Ranitidine pharmacokinetics

Mean ranitidine plasma concentration-time curves are shown in Figure 1. Dose-normalized AUC, dose-normalized $C_{\max}$, $t_{\max}$ and $t_{1/2}$ of ranitidine did not significantly differ between doses. Observed values of these parameters are summarized in Table 1. Ranitidine plasma concentrations increased proportionally with increasing dose of ranitidine bismuth citrate over the dose range examined in this study.

Bismuth pharmacokinetics

Bismuth blood/plasma concentration ratios (C_b/C_p), calculated for all samples collected, were concentration-

Figure 1 Ranitidine mean plasma concentrations in 12 healthy subjects following oral administration of 200 mg (■), 400 mg (●), 800 mg (▲), or 1600 mg (□) ranitidine bismuth citrate.

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

	Dose ^a			
	200 mg	400 mg	800 mg	1600 mg
AUC (ng ml ⁻¹ h)	1214 $\pm$ 213	2626 $\pm$ 480	4607 $\pm$ 1079	8572 $\pm$ 3493
C _{max} (ng ml ⁻¹)	182 $\pm$ 39	480 $\pm$ 126	956 $\pm$ 418	1983 $\pm$ 1895
t _{max} (h) ^b	2.5 (1.0–5.0)	2.0 (2.0–3.0)	2.5 (2.0–3.0)	3.0 (2.0–3.0)
t _{1/2} (h)	2.66 $\pm$ 0.42	2.58 $\pm$ 0.45	3.14 $\pm$ 0.95	2.96 $\pm$ 0.70

^a equivalent to 80, 160, 320, and 640 mg ranitidine, respectively. ^b median (95% CI)

independent. The median C_b/C_p was 0.61, suggesting that bismuth resides in plasma and does not enter red blood cells. Thus, pharmacokinetic analyses were carried out using plasma concentration data.

Median bismuth plasma concentration-time curves are shown in Figure 2. Bismuth plasma concentrations were quantifiable for up to 96 h after the 200, 400, and 800 mg doses, and for up to 29 days after the 1600 mg dose. Median bismuth plasma concentration profiles were nearly superimposable following the 200, 400, and 800 mg doses.

Bismuth AUC(0,12 h) did not increase as the dose increased from 200 mg through 800 mg, remaining independent of dose in this range (linear regression of log AUC(0,12 h) as a function of log dose resulted in a slope that was not significantly different from zero). However, bismuth AUC(0,12 h) increased more than proportionally as the dose increased from 800 mg to 1600 mg, more than doubling in this range (linear regression of log AUC(0,12 h) as a function of log dose resulted in a slope that was significantly greater than one). The relationship between AUC(0,12 h) and dose is shown in Figure 3. Similar relationships to dose were observed for both C_{max} and A_u.

Considerable variability was observed between individuals in bismuth plasma concentration profiles. However, at the highest dose administered in this study, peak bismuth plasma concentrations did not exceed 33 ng ml⁻¹ in any subject. The time at which peak bismuth plasma concentration occurred did not differ between the doses administered in this study (Table 2).

Figure 2 Bismuth median plasma concentrations in 12 healthy subjects following oral administration of 200 mg (■), 400 mg (●), 800 mg (▲), or 1600 mg (□) ranitidine bismuth citrate.

Figure 3 Relationship between bismuth plasma AUC(0,12 h) and oral dose of ranitidine bismuth citrate, described by the piece-wise regression equations: log AUC(0,12 h) = 1.295 + 0.172 · log Dose (when Dose $\leq$ 800) with a slope not significantly different from zero ($P=0.384$), and log AUC(0,12 h) = -3.452 + 1.807 · log Dose (when Dose > 800), with a slope significantly greater than one ($P=0.002$).

Urinary recovery of bismuth over 29 days post-dose was less than 0.5% of the dose, ranging from 28 μ g to 1.16 mg, or from 0.02% to 0.41% of the amount of bismuth administered as ranitidine bismuth citrate (Table 2). Bismuth CL_r was relatively constant, exhibiting no significant differences between the doses administered in this study (Table 2).

Values of terminal t_{1/2}, in both plasma and urine, as well as MRT appeared to increase as the dose increased to 1600 mg (Table 2). However, this was most likely an artefact of concentrations in the terminal phase falling below the limit of bioanalytical quantitation, and truncating the data to a lesser extent as the dose increased. Therefore, between-dose statistical comparisons of these parameter values were not carried out. Terminal t_{1/2} and MRT estimates ranging up to 461 h (19.2 days) were observed after the highest dose.

Safety and tolerability

All subjects completed the study as planned, and no clinically significant drug-related biochemical abnormalities or adverse events were observed during the study. Ranitidine bismuth citrate was well-tolerated compared with placebo in these subjects.

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

	Dose ^a			
	200 mg	400 mg	800 mg	1600 mg
$C_{\max}$ (ng ml ⁻¹)	2.89 (1.47–5.67)	2.85 (1.95–4.17)	3.31 (1.97–5.56)	11.60 (7.54–17.83)
$t_{\max}$ (h) ^b	0.50 (0.50–0.50)	0.50 (0.25–1.00)	0.50 (0.50–1.00)	0.75 (0.50–1.00)
AUC(0,12 h) (ng ml ⁻¹ h)	8.98 (5.43–14.85)	10.40 (7.36–14.70)	11.39 (7.74–16.77)	40.23 (25.64–63.11)
A_u (μg) ^c	105.4 (47.5–233.6)	58.5 (27.4–124.8)	102.7 (44.5–237.1)	400.0 (181.3–882.7)
CL_r (ml min ⁻¹)	41.2 (32.9–51.5)	39.1 (31.6–48.4)	45.3 (38.2–53.7)	42.2 (32.2–55.2)
Urine $t_{1/2}$ (h) ^{b,c}	72.2 (31.6–284.8)	75.4 (45.6–291.8)	159.8 (52.6–397.3)	140.5 (76.9–373.6)
Plasma $t_{1/2}$ (h) ^{b,c}	2.8 (2.5–78.8)	5.0 (2.3–13.6)	9.3 (4.7–176.3)	114.3 (10.6–387.8)
MRT (h) ^{b,c}	4.1 (3.4–58.1)	6.7 (3.5–20.6)	12.1 (5.2–249.3)	105.4 (10.6–461.1)

^a equivalent to 64, 128, 256, and 512 mg bismuth, respectively. ^b median and 95% CI. ^c $n=6$ at each dose ($n=12$ for all other parameters).

Discussion

The pharmacokinetics of ranitidine after administration of single oral doses of ranitidine bismuth citrate are comparable with the pharmacokinetics previously reported for ranitidine administered alone [10]. Plasma ranitidine concentrations increased proportionally with increasing dose. Plasma ranitidine concentrations after ranitidine bismuth citrate doses of 400 mg and 800 mg were similar to plasma ranitidine concentrations produced by comparable doses of 150 mg and 300 mg ranitidine as the hydrochloride salt [10].

Plasma bismuth concentrations were not dose-proportional. The $C_{\max}$, AUC(0,12 h), and A_u of bismuth derived from ranitidine bismuth citrate were comparable and independent of dose at or below 800 mg. The mechanism underlying this disproportionality is unknown, although the fact that renal clearance did not vary with dose indicates that renal elimination is not responsible and suggests an absorptive mechanism that is perhaps saturable.

Bismuth plasma concentrations and urinary recovery after administration of the 1600 mg dose increased more than proportionally with dose. A possible explanation for this unusual pattern of absorption may be achievement of a threshold in ranitidine dose-related elevation of gastric pH following the 1600 mg dose capable of increasing bismuth solubility, and a corresponding increase in bismuth absorption. Bismuth absorption has been shown to increase with elevated gastric pH resulting from H_2 -receptor blockade [18].

Following the highest dose, where characterization was optimized, bismuth terminal $t_{1/2}$ and MRT were quite prolonged, reaching values as high as 19 days. Bismuth has been reported to exhibit multicompartmental behaviour with 1 to 4 h, 5 to 11 day, and 3 to 10 week half-lives [13].

Elimination of bismuth is presumed to occur primarily through renal excretion. The observed values of renal clearance, together with the extensive plasma albumin binding of bismuth [19], indicate net tubular secretion. It has been suggested that bismuth also undergoes biliary excretion [20]. We have recently confirmed this as a minor route of elimination in a separate study

involving two patients undergoing nasobiliary drainage, who demonstrated biliary clearance that was 12% of renal clearance for bismuth from ranitidine bismuth citrate.

Although these data indicate that bismuth derived from ranitidine bismuth citrate is absorbed orally, the extent of bismuth absorption was minimal, comprising less than 0.5% of the amount administered. Because bismuth absorption was minimal, it is not surprising that it was also quite variable, as reflected in pharmacokinetic parameters other than renal clearance. The vast majority of bismuth passes unabsorbed in the faeces, leading to a commonly reported side effect in these and other studies: darkened stools. Limited absorption of bismuth has also been observed from bismuth citrate administered alone [21,22].

Because the pharmacological activity of bismuth occurs within the gastrointestinal tract, absorption is not necessary for efficacy, but of interest for its potential toxicity. The limited absorption of bismuth derived from ranitidine bismuth citrate is advantageous in the context of previously reported bismuth toxicity occurring with other bismuth salts administered at high doses for long periods of time [15,22]. Bismuth concentrations of 50–100 ng ml⁻¹ blood (80–160 ng ml⁻¹ plasma) have been proposed as a threshold for toxicity based on poorly documented clinical experience [15]. Subsequent review of this experience has indicated that these proposed thresholds are too low [13]. The maximum plasma concentrations observed in this study were well below this threshold, consistent with the observed tolerability of this compound.

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