TAB B

MEMORANDUM

Department of Health & Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation & Research
Office of Drug Standards

DATE : 26 July 1989

TO : Stephen B. Fredd, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

FROM : C. T. Viswanathan, Ph.D.
Acting Director, Division of Biopharmaceutics (HFD-420)

SUBJECT : Biopharmaceutics Summary of NDA 19,810
LOSEC[R] (omeprazole) 20 mg and [redacted] mg capsules
Merck Sharp & Dohme

BACKGROUND

NDA 19,810 is the submission for LOSEC[R] (omeprazole) 20 mg and [redacted] mg capsules. Omeprazole is a substituted benzimidazole and is a member of a new class of anti-ulcer compounds. Omeprazole has been shown to inhibit H^+ ion formation by inhibiting the H^+/K^+ ATPase, the "proton pump", in the gastric parietal cell membrane. Although the drug is cleared from plasma in a few hours, it inhibits acid secretion in vivo for much longer and is to be administered once daily.

Omeprazole is extensively metabolized by the liver, with the metabolites exhibiting very low or no anti-secretory activity. Little, if any, of the drug is excreted unchanged in the urine.

Omeprazole is rapidly degraded under acidic conditions and exhibits relatively poor bioavailability when given orally without co-administration of pH-buffering agents or not enteric coated. LOSEC has been developed as an encapsulated (hard gelatin) enteric-coated granule formulation.

DISCUSSION

The sponsor has submitted numerous studies conducted during the development of LOSEC to assess the absorption, distribution, metabolism and excretion of omeprazole. These studies included pilot studies on formulation development, single-dose and multiple-dose pharmacokinetics, bioequivalence, disposition in the elderly, the renally impaired, and the hepatically impaired, and food and antacid interaction. The formulations used in the studies included intravenous dosing, buffered and unbuffered suspensions, buffered solutions, encapsulated uncoated granules, Phase II

and Phase III encapsulated enteric-coated granules, and the intended final market image formulation called LOSEC.

The disposition of omeprazole (after intravenous dosing) was characterized in several studies. The results of one study showed a mean (range) volume of distribution of 0.31 l/kg ([redacted]), a mean elimination half-life of 0.9 hours [redacted] and a mean clearance of 530 ml/min [redacted]. The mean total recovery from urine and feces (expressed as per cent of radioactive dose) was 98% [redacted]. The pharmacokinetics of omeprazole appear to be dose-dependent above 40 mg given intravenously, as was indicated by a non-linear increase in AUC in a study where doses of 10, 20, 40 and 80 mg IV were administered.

The mean bioavailability (F) of a 20 mg capsule (Phase III formulation) was 0.5 ([redacted]) when compared to a 20 mg intravenous dose. After repeated dosing (20 mg once daily for 5 days), the mean AUC increased from 0.73 micromol*h/L ([redacted]) on day 1 to 1.26 micromol*h/L ([redacted]) on day 5, the mean Cmax increased from 0.624 micromol/L ([redacted]) on day 1 to 0.794 micromol/L ([redacted]) on day 5, and these differences were not statistically significant. The mean bioavailability was 0.4 ([redacted]) on day 1 and 0.5 ([redacted]) on day 5 and the difference was not significant. However, in another multiple-dose study (20 mg once daily for 8 days), there was a statistically significant increase in AUC between day 1 (0.99 micromol*h/l, range: [redacted]) and day 8 (1.41 micromol*h/l, range: 0.15 - 6.56) but the mean Cmax on day 1 (0.607 micromol/L, range: [redacted]) was not significantly different from day 8 (0.79 micromol/L, range: [redacted]).

A bioequivalence study comparing Phase II (Lot No. H415-2-5) and Phase III (Lot No. H415-6-1) capsule formulations did not demonstrate the equivalence of the two formulations (90% confidence interval for AUC and Cmax were 68.4% - 122.2% and 87% - 158.2% respectively with Phase II capsule as reference). This lot of Phase II capsule formulation was used in the pivotal (sponsor's determination) duodenal ulcer dose response study (I-260).

A bioequivalence study comparing Phase III (Lot No. H431-7-7) and LOSEC (Lot No. H431-9-1) capsule formulations was equivocal and was determined as not demonstrating the bioequivalence of a clinical lot to the final market image formulation. The 90% confidence interval for AUC (log transformed) and Cmax were 93% - 123% and 85% - 133% respectively with the Phase III capsule as reference. The sponsor claimed bioequivalence based on AUC only and a wider confidence interval criteria (80% - 125%). Furthermore, the sponsor rationalized that discarding the data from one subject, whom they considered to be an outlier, narrowed the confidence interval.

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The disposition of omeprazole in the elderly was studied after the administration of an omeprazole solution. Comparison of the data to that obtained in young, healthy subjects indicated that the pre-systemic and systemic elimination of omeprazole is reduced in the elderly.

In a study in patients with chronic renal insufficiency, the pharmacokinetic constants for intact omeprazole were within the range of those reported in young, healthy subjects. However, the AUC of the hydroxy-metabolite were nearly tripled compared to young, healthy subjects. In patients with liver cirrhosis, the rate of elimination from plasma of omeprazole and two of its metabolites was substantially decreased as compared to young, healthy subjects.

The results of studies looking at the effect of food on omeprazole bioavailability were not definitive since subjects were not administered the dose under true fasting conditions.

Dissolution testing of omeprazole capsules involves the assessment of the integrity of the enteric-coated granules as well as the dissolution characteristics. Acid resistance is tested during a two hour exposure to 500 ml of gastric fluid (USP, without enzymes) at 37 degrees C in a USP dissolution apparatus (No. 2, paddle) at 100 rpm. The granules are then analyzed for residual omeprazole. To test drug release, the same exposure to gastric fluid is conducted for 2 hours (on different units since the units tested in the acid resistance phase are destroyed), but then 400 ml of phosphate buffer is added to change the pH to 6.8. Temperature and stirring are maintained for another 30 minutes (post neutralization) at which time samples are withdrawn for analysis. Samples are analyzed for omeprazole content using a reversed-phase HPLC analytical method with detection of omeprazole by UV absorbance at 280 nm.

CONCLUSION

I. In Vivo Studies:

In a submission dated February 6, 1989, the sponsor attempted to clarify the exact formulation which would be the final market image. From that submission it appeared that the final market image would be the Phase III formulation (which has also been called EOG III, formula J, and has batch numbers designated as H431-7-[redacted]). Several of the biopharmaceutic and clinical studies were conducted using this formulation of EOG III and the in vivo bioavailability of omeprazole from this formulation has been adequately demonstrated. Therefore, from a biopharmaceutic point of view, the Phase III formulation, formula J, was approvable. In a recent telephone conversation between Dr. James Holt (MS&D) and Nick Flaischer (Division of Biopharmaceutics), it was learned that the sponsor intends to market the LOSEC formulation. The difference between EOG III and LOSEC is a 20% increase, from 20 to 24 mg of [redacted]

[redacted], in one of the ingredients used in the enteric coating.

II. Dissolution:

The dissolution methodology, except for paddle speed, as specified by the sponsor, is acceptable. The paddle speed of 100 rpm is excessive and it is felt that a reduction to 50 rpm is more appropriate. Furthermore, a change in the final specifications to [redacted] remaining after [redacted] hours acid exposure and NLT [redacted] dissolved in [redacted] minutes (post acid exposure) would assure that all lots meet the dissolution specifications and provide adequate lot-to-lot quality control.

The sponsor is suggested to conduct a definitive food affect study (which could be conducted during Phase IV).

C.T. Viswanathan, Ph.D.

Prepared by Nicholas M. Fleischer, R.Ph., M.S.
PD Initialed by Tran for Mei-Ying Huang, Ph.D. 7-5-89
FT Initialed by Paul Hepp, Pharm.D. 7-21-89

cc: Orig. NDA 19-810, HFD-180(2), HFD-420(Vish, Johnson),
HFD-426(Fleischer), HFD-344(Turner), Chron., Drug, Reviewer files

NMF:rmf: PC; 7/5/89/rev.7-6-89/rev.7-20-89/rev.7-21-89/rev.7-26-89

Omeprazole
LOSEC® 20 mg and [illegible] mg capsules
NDA 19-810
Reviewer: Nicholas M. Fleischer
158,40,1D

Merck Sharp & Dohme
West Point, Pennsylvania
Submission Dates:
December 21, 1987
February 6, 1989

JUN 27 1989

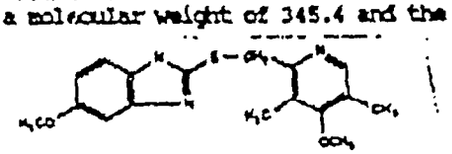
REVIEW OF AN ORIGINAL NDA

Background Information

Omeprazole is a substituted benzimidazole and is a member of a new class of anti-ulcer compounds. Capsules LOSEC 20 mg and [illegible] mg are enteric-coated formulations of omeprazole intended for oral administration. The enteric coating protects degradation of omeprazole by acidic gastric contents. LOSEC is to be administered once daily for the short-term treatment of documented duodenal ulcer, reflux esophagitis or pathological hypersecretory conditions.

Physicochemical Properties

Omeprazole (USAN) is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]-sulfinyl]-1H-benzimidazole and has also been referred to as MK-764 and H 168/68. It has a molecular weight of 345.4 and the following structural formula:



Omeprazole is a non-hygroscopic, crystalline powder which is very slightly soluble in water (ca. 0.13g/L), however, aqueous solubility increases with pH (exceeds 1000 g/L in 0.1M sodium hydroxide at room temperature). It is freely soluble in 95% ethanol and dichloromethane. The compound has pKa's of 8.8 and approximately 4.

LOSEC capsules have the following qualitative and quantitative composition:

Characteristic	Amount (mg) per 20-mg capsule
Core	
Omeprazole, micronized	20.0

The above outlined formulation was developed following several process changes involving the enteric-coated granule formulations that were used in Phase II and III clinical studies. In the Chemistry, Manufacturing and Controls section of the NDA, the composition of the omeprazole lists an alternate aqueous enteric coating method. In a meeting between MSAD and FDA on April 24, 1989, the alternate coating issue was discussed and MSAD was requested to submit bioequivalence data for the formulations from the two different coating procedures. The developmental summary is attached as Appendix I (2 pages). The tabulation below identifies the formulations of omeprazole used in definitive drug disposition studies and clinical studies of efficacy and safety. (See Summary Comment #10 for further clarification.)

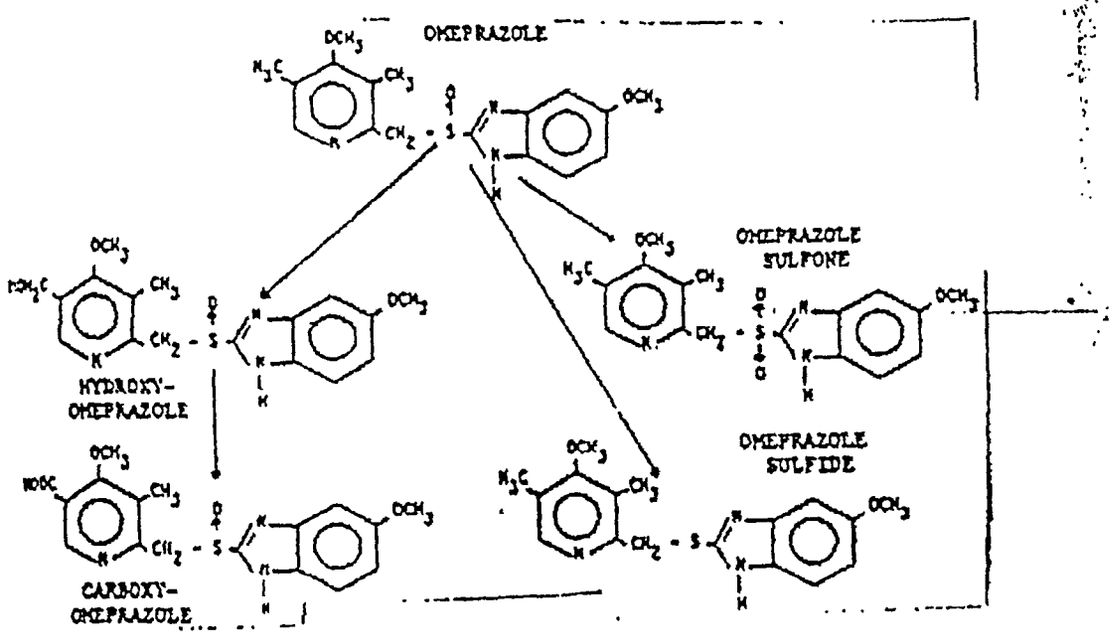
Drug Description or Purpose	Study No.(s)	Dosage Strength	Lot Number	Patients Rlzd
Dose-response pharmacokinetics for 30 and 60 healing	I-040	2 x 30 mg (DCE III)	[illegible]	12,[illegible]
Multiple-dose pharmacokinetics	I-130	30 mg (DCE III)	[illegible]	16,[illegible]
Bioequivalence of Phase II and Phase III Capsule Formulations	I-042	2 x 20 mg (DCE II) 2 x 30 mg (DCE III)	[illegible] [illegible]	5,[illegible] 7,[illegible]
Bioequivalence of Phase III Capsule Formulation and Capsule LOOSE 30 mg	I-116	30 mg (DCE III) 30 mg (LOOSE)	[illegible] [illegible]	[illegible] [illegible]
Effect of food on bioavailability	I-115 I-[illegible]	2 x 30 mg (DCE III) 30 mg (DCE III)	[illegible] [illegible]	17,[illegible] [illegible]
Effect of antacids on bioavailability	I-013	2 x 30 mg (DCE II)	[illegible] [illegible]	[illegible] [illegible]
	I-[illegible]	30 mg (DCE III)	[illegible]	[illegible]
Efficacy and tolerance in DU patients	I-[illegible]	30 mg (DCE III)	[illegible] [illegible]	1,[illegible] [illegible]
Rate of DU healing and relief of symptoms	I-[illegible]	30 mg (DCE II) 30 mg (DCE III)	[illegible] [illegible]	—[3] [illegible]
Comparison of ulcer healing rate with omeprazole and cimetidine in DU patients	I-301a	30 mg (DCE III)	[illegible]	[illegible]
Effect of 20 mg vs. 30 mg of omeprazole in DU healing	I-[illegible]	20 mg (DCE III) 30 mg (DCE III)	[illegible] [illegible]	[illegible] —
DU healing frequency and symptom relief after 2 and 4 weeks treatment with omeprazole and cimetidine	I-321	30 mg (DCE III)	[illegible]	—[3]
Treatment of DU patients resistant to H_2-receptor antagonists	I-314/315	30 mg (DCE III)	[illegible] [illegible] [illegible] [illegible]	[illegible] [illegible] [illegible] [illegible]
Omeprazole vs. cimetidine in the treatment of DU	I-331	30 mg (DCE III)	[illegible] [illegible]	[illegible] —
Comparison of DU healing rates between omeprazole and cimetidine in DU patients	I-321	30 mg (DCE III)	[illegible] [illegible]	—[3] [illegible]
Comparison of omeprazole and cimetidine in the treatment of active DU	I-322	30 mg (DCE III)	[illegible]	[illegible]
Omeprazole in patients with Zollinger-Ellison Syndrome	I-[illegible] ([illegible]) [illegible] [illegible]	60 mg (DCE III)	[illegible] [illegible] [illegible] [illegible] [illegible] [illegible]	[illegible] [illegible] [illegible] [illegible] —[illegible]
		30 mg (DCE II)	[illegible] [illegible] [illegible] [illegible]	[illegible] [illegible] [illegible] [illegible]
		30 mg (DCE III)	[illegible] [illegible] [illegible] [illegible] [illegible] [illegible]	[illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
		30 mg (DCE III)	[illegible]	[illegible]
Efficacy and safety of omeprazole on healing of erosive DU in outpatients	[illegible] through [illegible]	30 mg (DCE III)	[illegible]	[illegible]
Efficacy and safety of omeprazole vs. cimetidine and healing of erosive DU in outpatients	[illegible] through [illegible]	30 mg (DCE III)	[illegible]	[illegible]

1 From same batch of omeprazole DC granules as [illegible].
2 From same batch of omeprazole DC granules as [illegible].
3 From same batch of omeprazole DC granules as [illegible], [illegible], and [illegible].
4 Prepared from a [illegible] batch of granules.

Pharmacologic Mechanism of Action

The parietal cells of the gastric mucosa secrete acid by means of a membrane pump, identified as an H^+,K^+-ATPase, that exchanges hydrogen ions for potassium ions. This gastric acid pump has also been referred to as a "proton pump." Omeprazole has been shown to inhibit H^+ ion formation by inhibiting the H^+/K^+ ATPase in the gastric parietal cell membrane. Although the drug is cleared from plasma in a few hours, it inhibits acid secretion in vivo for much longer.

Several in vivo metabolites of omeprazole have been identified. These metabolites have very low or no anti-secretory activity. The metabolic scheme is depicted below:



IN VITRO DISSOLUTION

Dissolution testing of LOSEC involves assessment of the integrity of the enteric-coated granules as well as the dissolution characteristics. Acid resistance is tested during a two hour exposure to 500 ml of gastric fluid (USP, without enzymes) at 37 degrees C in a USP dissolution apparatus (No. 2, paddle) at 100 rpm. The granules are then analyzed for residual omeprazole. To test drug release, the same exposure to gastric fluid is conducted for 2 hours, but then 400 ml of phosphate buffer is added to change the pH to 6.8. Temperature and stirring are maintained for another 10-30 minutes at which time samples are withdrawn for analysis. Samples are analyzed for omeprazole content using a reversed-phase HPLC analytical method with detection of omeprazole by UV absorbance at 280 nm. The firm has proposed specifications of [redacted] acid resistance and [redacted] dissolution in [redacted] minutes.

A summary of the dissolution of different formulations is presented below:

Study No.	Capsule Description	Formulation No.	Mean % Acid Resistant	Mean % Dissolved in . . . min
I-244	20 mg ECG II	B431-4-2	83%	101% in 10 min[2]
I-278	20 mg ECG III	B431-7-1	90%	92% in 30 min
I-243	30 mg ECG II	B415-2-5	87%	94% in 15 min[2]
	30 mg ECG III	B415-4-1	96%	85% in 15 min
I-316	20 mg ECG III	B431-7-7	91%	90% in 30 min
	20 mg (LOSEC)	B431-9-1	93%	90% in 30 min
	20 mg (LOSEC)	B431-9-4	93%	83-91%[1] in 30 min
I-252	30 mg (ECG III)	B415-6-1	94%	85% in 15 min
I-298	20 mg (ECG III)	B431-7-7	91%	90% in 30 min
I-233	30 mg (ECG II)	B415-2-3	84%	92% in 10 min
		B415-2-4	90%	97% in 10 min
I-307	20 mg (ECG III)	B431-7-4	94%	94% in 30 min

[1] Range of six capsules [2] Not encapsulated

COMMENTS

1. The firm provided only the mean results of dissolution testing. For future submissions, the firm should be advised to provide the individual results of 12 dosage units from dissolution testing of lots used in bioavailability studies.

2. In the Chemistry, Manufacturing and Controls section of the NDA, the firm has proposed a drug release specification of NLT [redacted] dissolved in [redacted] minutes. The firm should clarify whether Q will be [redacted] or [redacted].

3. In two telephone conversations with the firm (on April 22 and April 25, 1988), this reviewer discussed the proposed dissolution method to clarify differences between the firm's method and the USP enteric-coated products method. A summary of the conversations follows:

Question 1. In the acid resistance test, why is 500 ml of gastric fluid and a paddle speed of 100 rpm used? The USP method calls for 750 ml of 0.1 N hydrochloric acid.

Question 2. At the end of the acid challenge, why does the firm analyze the granules for residual omeprazole whereas the USP method calls for the removal of an aliquot and testing it for drug released?

Question 3. The firm's continuation of the test for drug release called for the addition of 400 ml of phosphate buffer with paddle speed maintained at 100 rpm with a specification of 85% dissolved in 30 minutes. The USP method calls for the addition of 250 ml of phosphate buffer. Why is 100 rpm paddle used when that speed is considered to be excessive and not discriminatory to detect poor formulations?

Answer 1. MSAD analyzes the granules for residual omeprazole versus the USP method of analyzing an aliquot of bath fluid because of the instability of omeprazole in acid media. Any omeprazole that would be released in the acid bath would be immediately degraded and be unanalyzable.

Answer 2. The issue of using the paddle at 100 rpm originated from developmental work done by the firm in Sweden which originally discovered omeprazole. That firm felt that using the paddle at 100 rpm would be more of a test in the acid challenge phase and that speed was maintained for the drug release phase in phosphate buffer.

The conclusions of the telephone conversations were that since the firm had an automated method, the minor differences of fluid quality and quantity would not make a substantial difference. However, the firm agreed to generate dissolution data on the finished dosage form using the paddle at 50, 75 and 100 rpm and submit it to the Agency.

IN VIVO STUDIES

The firm has submitted 21 studies (referred to in this review as Study #'s 1-21) in support of the human pharmacokinetics and bioavailability section of this NDA. The studies, some of which included special populations (elderly, duodenal ulcer patients, renally impaired and hepatically impaired), are listed below.

Reference No.	Study No.	Formulation	Dosage Regimen	Formulation No.(s)	No. of Subj.	Conclusions
Pilot Studies:						
4	1-204-1	40-mg Oral Suspension (buffered)	S-D	[illegible]	6	The oral bioavailability of omeprazole from unbuffered suspension was reduced by gastric acid degradation to 44% as compared to the buffered suspension. When an enteric-coated omeprazole granule formulation was given orally with adequate pH-buffer protection, bioavailability approached that of the pH-buffered suspension. Granule dissolution rates exceeding 80% in 5 min or encapsulation of the granules had little effect on bioavailability. Oral doses were safe and well tolerated.
		40-mg Oral Suspension (unbuffered)	S-D	[illegible]		
		40-mg Oral BOCI capsule (buffered)	S-D	[illegible]		
5	1-204-4	40-mg Oral BOCI (rapid dissolution)	S-D	[illegible]	6	
		40-mg Oral BOCI (intermed. dissolution)	S-D	[illegible]		
		40-mg Oral BOCI capsule (rapid diss.)	S-D	[illegible]		
		40-mg Oral Suspension (all buffered)	S-D	[illegible]		
Single-Dose Pharmacokinetics:						
6	1-206	10 mg IV (^{14}C)	S-D	[illegible] (B347-1-1)	8	Clearance of omeprazole is rapid ($t_{1/2}$ = 0.5 hr) and eliminated by metabolism. Metabolites are excreted primarily in the urine. Omeprazole is completely absorbed from an oral solution, but a first-pass effect reduces bioavailability to 50%. The sulfone and sulfide metabolites were identified in plasma.
		40 mg Oral Solution (^{14}C, buffered)	S-D	[illegible] (B312-1-4)		
7	1-229	40-mg Oral Suspension (^{14}C, buffered)	S-D	[illegible]	16	Of the 80% ^{14}C recovered in urine, 64.1% was unchanged omeprazole. Of six potential metabolites, one were identified, namely OH-omeprazole (IX) and the corresponding carboxylic acid (XI).
8	1-225	10 mg IV	S-D	[illegible]	16	Omeprazole pharmacokinetics were not dose-dependent after i.v. administration. After oral administration, omeprazole AUC increased disproportionately faster than the dose. Oral bioavailability increased from 40% to nearly 100% as dose increased.
		40 mg IV	S-D	[illegible]		
		10 mg Oral Solution	S-D	[illegible]		
		40 mg Solution	S-D	[illegible]		
		80 mg (buffered)	S-D	[illegible]		
		[illegible]	S-D	[illegible]	10	The pharmacokinetics of omeprazole are

Reference No.	Study No.	Formulation	Dosage Regimen	Formulation No.(s)	No. of Subj.	Conclusions
Multiple-Dose Kinetics						
10	1-233	18 mg IV 19 mg IV	1-8 1-8	8135-3-1 (8135-3-1)	9	Pharmacokinetics of i.v. omeprazole are proportional to dose.
11	1-238	1[illegible] mg IV 40 mg IV	1-8 1-8	8431-7-14	6	Repeated administration of 40-mg i.v. dose may cause clearance to decrease.
12	1-244	2 x 20 mg Oral BCC II capsule	1-8	8431-4-1	8	Once daily or tw. pr dosing (5 days) revealed greater day 1 bioavailability and reduction in intragastric acidity for on dosing. Day 5 bioavailability was equal for each regimen both being higher and over day 1. A similar trend was noted for reduction in intragastric acidity.
13	1-278	^{14}C-labeled IV	1-8	8134-1-1 (8397-4-3)	10	The rate of elimination of omeprazole does not change following repeated oral administration of the drug. Increases noted in oral bioavailability following repeated administration of BCC capsules apparently result from changes in pre-systemic events such as increased acid degradation of the drug.
		20 mg Oral Solution (buffered)	1-8	8464-1-1		
		20 mg Oral BCC III capsule	1-8	8431-7-1		
Bioequivalence Studies						
14	1-261	1 x 20 mg Oral BCC II capsule 1 x 20 mg Oral BCC III capsule 40-mg Oral Suspension (buffered)	1-8 1-8 1-8	8415-7-1 8516-4-1 8418-1-4	12	BCC II and BCC III formulations are equally bioavailable although drug is absorbed slightly more rapidly from BCC III. Both formulations are 70% as bioavailable as oral suspension.
15	1-316	20-mg Oral BCC III capsule 20-mg Capsule LOSEC	1-8 1-8	8431-7-7 8431-4-1	20	Capsule LOSEC 20 mg are bioequivalent to the Phase III capsule formulation.
Special Studies						
17	1-296/ 301	20 mg IV (^{14}C)	1-8	8395-4-1 (8397-4-1) 8395-3-3 (8397-4-1)	16	In the elderly, omeprazole is completely absorbed and completely metabolized. Bioavailability (76%) and increased $t_{1/2}$ (1 hr) may just reduced pre-systemic and systemic clearance as compared to younger individuals. The decreased renal function actually attributed to individuals in this age group had no apparent effect on omeprazole disposition, but it did slow the excretion of metabolites.
		40 mg Oral Solution (^{14}C, buffered)	1-8	8464-4-1 8464-4-1		
18	1-336	18 mg IV 40 mg IV 20 mg Oral BCC III capsule	1-8 1-8 1-8	8795-1-3 8431-7-14	8	In unusual ulcer patients in remission, omeprazole is approximately 30% bioavailable from the BCC capsule. Repeated administration of 40 mg i.v. (QD) may cause the clearance of omeprazole to decrease. In 10 patients, the plasma clearance and $t_{1/2}$ of omeprazole averaged 250-400 ml/min and 0.7-0.8 hr, respectively.
19	1-265	20 mg IV (^{14}C)	1-8	8395-4-1 (8397-4-1)	13	In patients with chronic renal insufficiency (14 ml/min/1.73m^2 ≤ creatinine clearance ≤ 52 ml/min/1.73m^2), omeprazole is completely absorbed bioavailability and $t_{1/2}$ were similar to that in healthy volunteers indicating similar pre-systemic and systemic elimination of omeprazole. The elimination of omeprazole metabolites decreased in concert with the individual decrement in renal function.
		40 mg Oral Solution (^{14}C, buffered)	1-8	8464-4-1		
20	1-264	20 mg IV (^{14}C)	1-8	8395-4-1, 2,3,4 (8397-4-1, 3,4)	8	In patients with chronic hepatic impairment, the systemic elimination of omeprazole was slower as compared to healthy volunteers, but still exclusively via biotransformation. Absorption was complete and bioavailability was nearly 100%, indicating decreased pre-systemic elimination also. The elimination of omeprazole metabolites was somewhat slower indicating slowness by biotransformation as well as urinary excretion.
		40 mg Oral Solution (^{14}C, buffered)	1-8	8464-4-1, 2,3		

Reference No.	Study No.	Formulation	Dosage Regimen	Protocol Section No.(s)	No. of Subj.	Conclusions
31	[illegible]	1 x 30-mg Oral BCC III capsule 40-mg Oral Suspension (Reference)	S-D S-D	[illegible]	12	Omeprazole capsules administered 15 min or 45 min before breakfast afforded equal bioavailability. Drug is one-third as bioavailable as from an oral suspension given under fasting conditions.
32	[illegible]	20-mg Oral BCC III capsule 20-mg IV	S-D S-D	[illegible]	12	Administration of omeprazole capsules once daily (a 7 days) before or immediately after breakfast afforded similar AUC for omeprazole but drug was absorbed more rapidly when given before breakfast. Bioavailability increased from 40% following the 1st dose to nearly 70% following the 7th dose.
33	[illegible]	1 x 30-mg Oral BCC II capsule	S-D	[illegible]	6	Administration of omeprazole capsules with single or repeated doses of antacid (Maalox or Rowalcid) has no or a slight enhancing effect on the bioavailability of omeprazole.
34	[illegible]	20-mg Oral BCC III capsule	S-D	[illegible]	12	

S-D = single dose
M-D = multiple dose
BCC = uncoated granules

BCC II = Phase II enteric-coated granule formulation
BCC III = Phase III enteric-coated granule formulation

In addition to the studies listed supra, the firm has also submitted several supportive studies (mainly in the form of reprints of journal articles) which contain information regarding the measurement of omeprazole levels in biological fluids. The supportive studies will be referred to in this review as such. The different formulations used in the above listed studies is explained in Appendix I. The 30 mg strengths of some BCC II and III formulations were made by adding more of the enteric coated pellets to a large capsule.

I. Supportive Study 1.

Title:

Mechanism of Action of Omeprazole. Scand J Gastroenterol 1986;21(Suppl 118):11-16

Comment

This study was not reviewed.

II. Supportive Study 2.

Title:

Effect of Omeprazole on Gastric Acid Secretion in Man. Scand J Gastroenterol 1986;21(Suppl 118):105-107

Comment

This study was not reviewed.

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III. Supportive Study 3.

Title:

Acid inhibitory characteristics of omeprazole in man. Scand J Gastroenterol 1985;20(suppl 108):105-12.

Clinical Investigator(s) and Study Site(s)

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Results

In six healthy subjects given 20-80 mg omeprazole suspension orally, plasma concentrations of omeprazole increased rapidly with peak levels occurring within 30-40 minutes after which they declined rapidly with a half-life of about 50 minutes. The area under the plasma omeprazole concentration-time curve (AUC) was significantly correlated to the percentage reduction of acid secretion measured 2-4 hours after dose.

In eight healthy subjects given placebo, 30, 60 and 90 mg omeprazole uncoated granules in random order, there was a significant correlation between the AUC and percentage inhibition of acid output.

IV. Study 1. (Study Code I-204-1)

Title:

Bioavailability of H 168/68 from suspension and uncoated granules.

Objective

To study the magnitude of pre-absorption degradation of omeprazole after oral administration of an unprotected dose and to study the influence of dissolution rate of a solid dosage form on the bioavailability of omeprazole.

Drug Dosage Forms Used

A. Omeprazole buffered suspension (2 mg/ml) containing 60 mg omeprazole and 8 mmol sodium bicarbonate in 30 ml (pH adjusted to 9 with NaOH). Lot # H 362-1-3.

B. Omeprazole unbuffered suspension (2 mg/ml) containing 60 mg omeprazole in 30 ml (pH adjusted to 9 with NaOH). Lot # H 362-5-1.

C. Sodium bicarbonate solution (13.7 mg/ml) containing 8 mmol sodium bicarbonate in 50 ml (pH adjusted to 9 with NaOH). Lot # H 322-2-8.

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D. Omeprazole uncoated granules in paper capsules containing 40 mg omeprazole. Lot # K 370-1-1.

The dissolution of the uncoated granules was tested in phosphate buffer, pH=6.5, using the paddle at 40 rpm. The mean % dissolved was nearly 100% at 30 minutes.

Clinical Investigators and Study Site

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Study Protocol

Six healthy male subjects (ages 23-26 years, weighing 68-85 kg) completed the study. All the subjects met the following exclusion criteria: a.) significant illness within the preceding two weeks, b.) receipt of an investigational drug within the preceding four weeks, c.) need for concomitant therapy, d.) illness which may influence gastrointestinal absorption, e.) history of severe allergic diseases, f.) history of significant cardiac, renal, hepatic and/or gastrointestinal disease and g.) history of drug addiction or alcohol abuse.

In a randomized cross-over design, omeprazole was given as a buffered suspension, an unbuffered suspension and uncoated granules. Fifty ml of a sodium bicarbonate solution was taken prior to, together with and 10, 20, and 30 minutes after administration of omeprazole as a buffered suspension and as uncoated granules. Fifty ml of water was given with the unbuffered suspension at the same time intervals.

Specimens Collected

Blood samples were taken at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180 and 240 minutes post-dosing of each treatment.

Bioanalytical Methodology

The analytical site is assumed to be the same as the clinical study site.

The blood samples were analyzed by HPLC for omeprazole.

Pharmacokinetic Methodology

The AUC up to four hours was calculated by the trapezoidal rule and the residual area was calculated by dividing the last measured plasma omeprazole concentration by the slope of the log-lin plasma concentration-time curve from 1-4 hours. Statistical evaluations of the pharmacokinetic parameters (Cmax, Tmax, AUC, relative AUC) were made using Wilcoxon's matched pairs signed rank test with $p<0.05$ being regarded as statistically significant.

Results

	Buffered suspension	Unbuffered suspension	Uncoated granules
AUC (μmol·l⁻¹·h)	4.78±0.676	2.15±0.565*	3.44±0.783
AUC (% rel susp)	100	44±3.9*	72±10
C_{max} (μmol·l⁻¹)	5.8±0.78	3.3±0.37*	3.9±0.46*
t_{max} (min)	131±7	171±3	240±1

* p<0.05 (compared to buffered suspension)
AUC: area under the plasma omeprazole concentration-time curve
C_{max}: peak plasma omeprazole concentration
t_{max}: time to C_{max}
AUC, C_{max} and t_{max} are given as mean±SEM

Sponsor's Conclusions

1. The bioavailability of the unbuffered suspension was reduced to 44% of the buffered suspension, however, the Tmax and decay were similar. The reduced bioavailability is most probably due to degradation of omeprazole in the acid environment of the stomach.

2. The bioavailability of the uncoated granules was reduced to 73% of the buffered suspension and Tmax was longer due to low dissolution rate of the uncoated granules.

Comments

1. Assay validation data were not provided with this study.

2. Metabolite concentrations were not analyzed in this study. However, since it has been stated that the identified metabolites have no pharmacological effect and the aim of this study was to look at absorption phenomena, the omission of metabolite analysis appears justified.

3. The firm did not provide documentation to support their conclusion that the decay of the plasma concentration-time curve from the buffered and unbuffered suspension proceeded at the same rate.

4. The use of a nonparametric statistical test may not be warranted and the firm should provide justification for using it. ANOVA with comparison of means (Duncan's multiple-range test) indicates that the AUC from the three treatments are different.

V. Study 2. (Study Code I-204-4)

Title:

Bioavailability of H 168/68 from uncoated granules with different in vitro dissolution rates compared with buffered suspension.

Objective

To measure the bioavailability of omeprazole given as two different formulations of uncoated granules and as a buffered suspension.

Drug Dosage Forms Used

A. UCG 2 - (a 10%) uncoated granule formulation of omeprazole with high in vitro dissolution rate. Lot # H 370-9-1.

B. UCG 2 in hard gelatin capsules (size 1), 30 mg omeprazole/capsule. Lot # H 415-1-1.

C. UCG 3 - (a 10%) uncoated granule formulation with intermediate dissolution rate. Lot # H 370-8-1.

D. Buffered suspension - a suspension of micronized omeprazole in sodium bicarbonate solution, 60 mg/50 ml. Lot # H 410-1-1.

In Vitro Drug Release

Dissolution rate was determined using a modified beaker method. 500 ml of phosphate buffer (pH=6.5) stirred at 100 rpm was used and the amount dissolved was determined from the continuous recording of the absorbance at 300 nm in a spectrophotometer using 1 cm flow cells. Disintegration time of the filled capsules was determined by placing the capsules in water and observing the time required for the capsules to open at both ends.

The solid particles of the suspension dissolved almost immediately. More than 90% of UCG 2 dissolved within 5 minutes, while about 70% of UCG 3 dissolved in the same time. UCG 3 was nearly 100% dissolved in 20 minutes. The capsules disintegrated within 5 minutes.

Clinical Investigator and Study Site

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Study Protocol

The four dosage forms (as a single 60 mg dose) were tested in six healthy, male subjects (age 20-26 years, weight 74-86 kg) in a randomized, cross-over design with at least five days between administrations. The exclusion criteria were the same as in the previous study.

After an overnight fast, the granule formulations were taken together with 100 ml of a sodium bicarbonate buffer solution and the 50 m' of suspension was taken together with 50 ml of the buffer solution. In addition, 50 ml of a sodium bicarbonate solution was taken prior to, and 10, 20, and 30 minutes after administration of each formulation.

The study protocol was approved by the Ethical Committee of the University of Gothenburg, Sweden.

Specimens Collected

Blood sampling was performed via an indwelling cannula in a forearm vein and 10 ml samples were collected in heparinized tubes at 0, 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes post-dosing. After cooling for at least five minutes and centrifugation for 10 minutes, the plasma was separated, mixed with 1 M sodium bicarbonate and frozen until analysis.

Bioanalytical Methodology

The concentrations in plasma of omeprazole were determined by an HPLC method similar to one used in previous studies at the Department of Analytical Chemistry at AB Hässle. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 30 nmole/L with a relative standard deviation of less than 10-15%), linear (30 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole in plasma were 1.1-9.7%. The mean intra-day CV of single concentration standard sets was 0.8% (range 0.4-2.3%) and the mean CV of inter-day quality control samples was 2.5% (range 94.5-107% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Methodology

The individual plasma concentrations were plotted on a logarithmic scale as a function of time and the final log-linear phase was fitted by eye and half-life calculated from the slope of the line, as ln 2/(-slope). The computer program CSTRIP was also used to fit the experimental data. The AUC from time zero to the last sampling point was calculated by the trapezoidal rule and the residual area was calculated by dividing the last measured concentration by the elimination rate constant (-ln 2/half-life) using the median plasma half-life. Friedman's method was used to test for possible significant differences between mean values for AUC, Cmax and Tmax.

Results

	Buffered suspension	BCO 1	BCO 2 in capsules	BCO 3
AUC (μmol l⁻¹ h)	4.9±1.01	4.3±0.58	4.3±1.21	4.5±0.84
AUC (% rel susp)	100	93±13	81±13	92±4
C_{max} (μmol l⁻¹)	5.7±1.02	4.1±0.37	4.0±0.96	4.4±0.41
t_{max} (min)	20	20	30	30

AUC: area under the plasma omeprazole concentration-time curve
C_{max}: peak plasma omeprazole concentration
t_{max}: time to C_{max}
AUC and C_{max} are given as mean±SEM, t_{max} is given as median

There were no statistically significant differences between the four treatments.

Comments

1. The use of a nonparametric statistical test (the Friedman Two-Way Analysis of Variance by Ranks used in this study to test for significant differences) may not be warranted. The firm should provide justification for using a nonparametric test.

2. ANOVA with comparison of means (Duncan's multiple-range test) indicates that the AUC of the four treatments are not significantly different.

3. The in vitro drug release methodology used in this study is not relevant to the proposed drug release testing method to be used for the dosage form which is the subject of this NDA.

VI. Study 3. (Study Code I-208)

Title:

Pharmacokinetic Study with ^{14}C-Labelled H 168/68 Administered Orally and Intravenously

Objective

To evaluate the absorption and disposition characteristics of a single intravenous and oral omeprazole dose.

Drug Dosage Forms Used

The intravenous dosage form was a specially prepared solution of radioactive omeprazole in polyethylene glycol 400 which was diluted with sodium bicarbonate solution immediately prior to the experiment. The final solution (combination of batch #'s H 394-2-1 and H 397-1-1) contained 10 mg of omeprazole in 10 ml and had specific radioactivity of 2.08 microCi/mg.

The oral dosage form was a specially prepared solution of radioactive omeprazole in polyethylene glycol 400 which was diluted with a sodium bicarbonate solution immediately prior to the experiment. The final solution (combination of batch #'s H 404-1-1 and H 322-2-8) contained 20 mg of omeprazole in 51 ml and had a specific radioactivity of 1.05 microCi/mg.

Clinical Investigator(s) and Study Site

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Carl Gunnar Regardh, Ph.D.

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Study Protocol

Eight healthy male volunteers (mean age of 27.1, range 24-31 years; mean

weight of 74.2, range 64-86 kg; mean height of 184.3, range 178-192 cm) were enrolled and completed the study. The study protocol was approved by the Drug Department of the Swedish National Board of Health and Welfare, The Ethical Committee of the Medical Faculty of the University of Gothenburg and the Isotope Committee of Sahlgren's Hospital, Goteborg. After an overnight fast, subjects were treated with 10 mg of omeprazole intravenously or 20 mg orally given in a randomized, cross-over design with 1 to 4 weeks between treatments. The IV dose was administered over 5 minutes. 100 ml of an 8 mmol $NaHCO_3$ solution was administered with both the oral and IV doses in addition to 50 ml of the $NaHCO_3$ solution given 5 minutes prior to dosing and 10, 20 and 30 minutes post-dosing. Standardized meals were served at 2.5, 6 and 10 hours.

Specimens Collected

Blood samples were drawn from an antecubital vein at 5, 8, 11, 15, 20, 25, 30, 40, and 50 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours post-dosing and collected in heparinized tubes. The plasma was separated and stored at -20 degrees centigrade until analysis.

Urine was collected prior to dosing and at intervals of 0-1, 1-2, 2-4, 4-6, 6-9, 9-12, 12-24, 24-48, 48-72 and 72-96 hours post-dosing. Urine samples were adjusted to pH 7-8 with 1 M Na_2CO_3 and frozen until analysis.

Faces were collected quantitatively in 4 daily portions and stored frozen until analysis.

Bioanalytical Methodology

The concentrations in plasma of omeprazole and the sulfone metabolite of omeprazole (H 168/66), were determined in human plasma and urine using a specific, sensitive, linear, accurate and reproducible HPLC method published in J. Chromatogr., 309 (1984) 347 (analytical site was not specified). The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 30 nmole/L with a relative standard deviation of less than 10-15% and sensitivity for hydroxy-omeprazole in urine was 200 nmole/L), linear (plasma method was 30 nmole/L-100 micromole/L and urine method was 200 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole in plasma and hydroxy-omeprazole in urine were 2.1 to 5.8% and 1.5 to 3.2% respectively. The mean intra-day CV of single concentration standard sets was 1.2% (range 0.4-4.5%) and the mean CV of inter-day quality control samples was 2.7% (range 95-103% of recovered spike) for omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 1.3% (range 0.6-1.8%) and the mean CV of inter-day quality control samples was 3.8% (range 97-108.5% of recovered spike) for omeprazole sulphone in plasma. The mean intra-day CV of single concentration standard sets was 2.5% (range 1.1-5.0%) and the mean CV of inter-day quality control samples was 4.3% (range 91.5-101.5% of recovered spike) for hydroxy-omeprazole in urine.
Total radioactivity was determined in plasma, urine and fecal samples by liquid scintillation counting. The total radioactivity in plasma was the sum of the radioactivity of omeprazole, the sulfone metabolite and unidentified metabolites.

The blood and urine samples which were obtained for a laboratory screen, were analysed by the Department of Clinical Chemistry, Sahlgren's Hospital, Gothenburg, Sweden.

Pharmacokinetic Analytical Methods

The pharmacokinetic constants of the two-compartment model were derived in each individual from the computer fitted bi-exponential function of plasma concentration vs. time curve of the intravenous dose using the NONLIN program. Total body clearance (TBC) was calculated as

$$TBC = \frac{Dose_{i.v.}}{\frac{A}{alpha} + \frac{B}{beta}}$$

F was determined by the ratio of the AUC's of the unchanged drug after the oral and intravenous dose, after adjustment for the difference between doses. AUC(i.v.) was calculated as

$$AUC(i.v.) = \frac{A}{alpha} + \frac{B}{beta}$$

AUC(oral) was determined by the use of the linear, after one hour the log-linear, trapezoidal rule and extrapolation to infinity by the term Cp-last/beta. The half-life of omeprazole after oral administration was determined from the individual regression lines of the log plasma concentration vs. time curve in the post-absorptive phase.

Student's t-test for paired observations and the nonparametric Wilcoxon matched-pairs signed-ranks test were used to test the level of significance.

Results

The disposition characteristics of omeprazole calculated from the plasma levels following a single intravenous dose of 10 mg (28.95 micromol) are tabulated below:

Subject nr	A nmol·l^{-1}	B nmol·l^{-1}	$t_{1/2\,\alpha}$ min	V_c l·kg^{-1}	V_β l·kg^{-1}	k_{10} h^{-1}	$t_{1/2\,\beta}$ h	Clearance ml·min^{-1}
1								
2								
3								
4								
5								
6								
7								
8								
N	4374.0	979.0	3.83	0.0787	0.3133	5.39	0.867	529.0
mean	± 681.5	± 256.2	± 0.89	± 0.0171	± 0.0338	± 1.26	± 0.263	± 102.4

a) no distribution phase discernible

After the 20 mg (57.9 micromol) oral dose, maximum omeprazole concentrations were attained relatively quickly (Tmax of 13.8 ± 1.7 min, Cmax of 1813.8 ± 496.1 nmol/l, mean ± SEM). The average absolute bioavailability was 54% (range 25-117%) when calculated as omeprazole, however, after 96 hours, the total radioactivity recovered in the urine was nearly identical after oral and intravenous dosing. The mean elimination half-lives of omeprazole following intravenous and oral dosing were 0.867 ± 0.263 and 1 ± 0.357 hours respectively and the difference was not significant.

The plasma concentrations of the sulfone metabolite of omeprazole were close to the minimum detectable concentration and not detectable after 3 hours in six subjects after i.v. dosing while high concentrations measurable for at least 12 hours were found in the two remaining subjects. After oral dosing, the concentrations of the sulfone metabolite were substantially higher in all the subjects.

The mean plasma concentrations of the total pool of radioactive metabolites were almost the same as those of the parent drug during the first two hours after the oral dose when all of the subjects had measurable levels of omeprazole as well as of the metabolites. Omeprazole could barely be detected in the urine and after neither route of administration did recovery exceed 0.1% of the administered dose. Recovery of the sulfone metabolite ranged from 0.24-1.5% of the administered intravenous dose and from 0.13-0.9% of the oral dose. The difference between the means (0.68% for i.v. and 0.36% for oral) was not significantly different. Urinary recovery of radioactive metabolites was 78.2 ± 0.9% of the i.v. dose and 75.7 ± 0.9 of the oral dose after 96 hours with the bulk of the excretion occurring in the first 24 hours. A plot of the mean urinary excretion rate of each collection interval against the midpoint of the collection interval showed that the rate declined in a multi-exponential fashion with at least three distinct phases with half-lives corresponding to 1.5, 10 and >17 hours.

The mean fecal recovery of the radioactive dose after 96 hours was 19% (range 15-24%) and 18% (range 14-21%) for the i.v. and oral dose respectively.

The mean total recovery from urine and feces (expressed as per cent of radioactive dose) was 98% for the i.v. dose and 94% for the oral dose and the difference was significant.

Sponsor's Conclusions

1. The mean systemic availability of omeprazole was about 50% and varied about fourfold between different individuals with the reduction in this parameter probably due to pre-systemic elimination. However, the entire radioactive dose seems to have been taken up from the gastrointestinal tract as the urinary recovery of radioactivity was virtually the same for the i.v. and oral dose.

2. The plasma levels (after IV dosing) of omeprazole exhibited two-compartment model kinetics with a very rapid distribution into a relatively small volume of distribution with about 25% of the total body content localized in the blood. Data from a previous study indicated that binding to plasma proteins was greater than 95%.

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3. The half-life of omeprazole is short and varies about tenfold between individuals.

4. Omeprazole is eliminated entirely by metabolism which varies quantitatively and the formation of the sulfone metabolite was related to the route of administration and inter-individual variation.

5. The major fraction of the metabolites are excreted by the kidneys and about one-fifth is excreted by biliary and/or gastrointestinal secretion.

Comments

1. The assay validation report of this study (attachment 3) included information for the analysis of another omeprazole metabolite in urine, i.e., hydroxy-omeprazole, however the study report did not contain any data relating to this metabolite. Analysis of urine for this metabolite would have provided valuable information to clarify the "mixed bag" of urine data results from measuring total radioactivity.

2. The limit of determination of the omeprazole assay in plasma was 30 nmole/L, however, numerous results were reported which were below the limit of determination. The use of those results should not have a significant impact on the conclusions from the study.

3. The reported time of blood sampling after intravenous dosing was not the accepted method and resulted in the times being five minutes early. The intravenous dose was administered as an infusion over five minutes and at the end of the infusion a blood sample was obtained. This sample should have been reported as a five minute sample and not a zero minute sample. Correct reporting would have made the i.v. and oral blood sampling times identical. Analysis of the data by this reviewer using the corrected times did not change the parameter estimates significantly.

4. Tables 9 and 10, which are plasma levels of 'total radioactivity' after i.v. and oral dosing respectively expressed as equivalents of omeprazole, have values reported which are less than the values reported in tables 2 and 4, which are plasma levels of omeprazole after i.v. and oral dosing respectively. This result is most probably do to the inaccurate conversion of radioactivity to omeprazole equivalents.

5. Subjects 1 and 2 were definite outliers as evidenced by significantly different pharmacokinetic parameters. Excluding subjects 1 and 2, the mean value for clearance was 671.7 ml/min and the mean F was 0.367 with % C.V.'s of 29 and 26 respectively compared to 529.8 ml/min (%C.V. = 55) and 0.536 (% C.V. = 62). This may be suggestive of a bimodal metabolic pattern and may warrant further investigation.

6. The table (#18) which reported the 'total radioactivity' excreted in urine and feces had an incorrect total for subject #1. The correct total after i.v. dosing should be 99.5.

VII. Study 4. (Study Code I-229)

Title:

Omeprazole Metabolites in Urine After Oral Administration of ^{14}C-labelled Compound to Healthy Subjects.

Objective

To elucidate the structure of the two main urinary metabolites of omeprazole in healthy subjects given ^{14}C-labelled omeprazole orally.

Drug Dosage Form Used

60 mg of omeprazole was suspended in 50 ml of a sodium bicarbonate solution (8 mmol $NaHCO_3$/50 ml). The suspension contained 25 microCi of ^{14}C-labelled omeprazole (0.5 mg). The batch number was H 410-2-2.

Clinical Investigator and Study Site

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Study Protocol

Ten healthy male subjects of median age 34 years (range 27-39), median weight 74 kg (range 65-84) and median height 183 cm (range 174-192) were enrolled in and completed the study. The inclusion and exclusion criteria were similar to the previous study. Alcohol and all medication, including over the counter drugs were not permitted for two days prior to and during the study. After at least a 10 hour fast, a 60 mg omeprazole dose was administered. To protect the drug from exposure to gastric acid, 50 ml of a sodium bicarbonate solution was given 5 minutes prior to, together with and 10, 20 and 30 minutes after administration of the dose.

Specimens Collected

Five of the subjects collected all excreted urine in 24 hour portions, samples of which were stored frozen for determination of excreted radioactivity. The other five subjects collected urine at intervals of 0-1, 1-2, 2-4, 4-6, 6-9, 9-12, 12-24, 24-48, 48-72 and 72-96 hours after dosing. The samples from this group were used both for determination of radioactivity and for identification of metabolites.

Bioanalytical Methodology

Samples were analyzed at the Department of Analytical Chemistry and Department of Pharmacokinetics and Drug Metabolism, [redacted]

Description of Analytical Methods

Radioactivity measurements were conducted by liquid scintillation

counting.

Metabolite separation and identification were performed by multiple HPLC methods, ^{1}H-NMR measurements and mass spectrometry.

Results

On average, 47% of the given dose was excreted in the first 2 hours and within 96 hours, 79% of the radioactive dose was recovered.

The HPLC system was able to separate at least six metabolites which accounted for approximately 91% of the radioactivity. Unmetabolized omeprazole was not detected in urine samples. The most lipophilic metabolite accounted for 28% of the radioactivity and the next most abundant metabolite accounted for 23% of the radioactivity.

VIII. Study 5. (Study Code I-225)

Title:

Omeprazole Pharmacokinetics in Healthy Subjects After I.V. and Oral Administration of Different Doses.

Objective

The aim of this investigation was to study the influence of the dose on the absorption and disposition of omeprazole in healthy subjects.

Drug Dosage Form Used

A. Intravenous solution (Batch #'s H 394-4-1 and H 404-2-1)

Omeprazole was dissolved in 8.0 g of PEG 400 and prior to use was diluted to 20 ml with a sodium bicarbonate solution. The final solution contained 1 or 4 mg/ml of omeprazole.

B. Oral solution (Batch #'s H 361-3-1, H 452-1-1 and H 458-1-1)

Omeprazole was dissolved in 11.2 g of PEG 400 and prior to use was diluted with 50 ml of a sodium bicarbonate solution. The final solution contained 10, 40 or 90 mg/60 ml of omeprazole.

Clinical Investigator and Study Site

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Study Protocol

Ten healthy, male subjects with a mean age of 25 years (range 19-27), a mean weight of 78 kg (range 70-86) and a mean height of 184 cm (range 178-192) participated in the study. The inclusion and exclusion criteria were

similar to previous studies. Study medications were administered in a randomized, five-way cross-over design (i.v. doses of 10 and 40 mg and oral doses of 10, 40 and 90 mg) after a minimum 10 hour fast with at least 6 days between experiments. Sodium bicarbonate solutions were given orally with both the i.v. and oral doses of omeprazole as in previous studies. The i.v. dose was administered over five minutes. The subjects remained semi-recumbent for the first three hours of each treatment and then were allowed to move about freely though strenuous exercise as well as sleeping was prohibited. Two standardized meals were served during the eight hours the subjects stayed at the laboratory.

Specimens Collected

Blood samples (5 ml) were collected in heparinized tubes via indwelling cannulae 5 minutes prior to and 5, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 480 minutes after the start of i.v. infusion of omeprazole or oral administration with the exception of the 7 minute sample after oral dosing. After cooling and centrifugation, the plasma was transferred to tubes containing Na_2CO_3 and frozen until analysis.

Urine was collected quantitatively over the first 24 hours of each experiment and stored frozen until analysis.

Bioanalytical Methodology

Omeprazole, the sulfone metabolite of omeprazole (H 168/66), the sulfide metabolite of omeprazole (H 168/22) and OH-omeprazole were determined in human plasma and urine using a specific, sensitive, linear, accurate and reproducible HPLC method published in J. Chromatogr., 309 (1984) 347 at the Department of Analytical Chemistry, [redacted]. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole and omeprazole sulphone in plasma was 50 nmole/L with a relative standard deviation of less than 10-15% and the corresponding value for hydroxy-omeprazole was 100 nmole/L), linear (50 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole, hydroxy-omeprazole and omeprazole sulphone in plasma were 0.5 and 6.6%, 1.6 and 8.7%, and 1.2%, respectively. The mean intra-day CV of single concentration standard sets was 1.9% (range 0.6-5.4%) and the mean CV of inter-day quality control samples was 6.9% (range 95.5-119.5% of recovered spike) for omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 2.8% (range 1.4-5.2%) and the mean CV of inter-day quality control samples was 5.9% (range 88.5-112% of recovered spike) for hydroxy-omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 4.7% (range 1.1-14.7%) and the mean CV of inter-day quality control samples was 7.4% (range 82.5-120% of recovered spike) for omeprazole sulphone in plasma. Assay validation for the detection of the sulphide metabolite in plasma was not included with the report.

Description of Pharmacokinetic Analytical Methods

Methods used were similar to methods used in Study 3. The level of significance of the influence of dose on the various pharmacokinetic parameters studied was determined by Student's t-test for paired

observations or by two-sided ANOVA followed by Sheffe's contrast U-test with $p < 0.05$ considered statistically significant.

Results

1. The mean (and % C.V.) of the pharmacokinetic constants after 10 and 40 mg intravenous dosing are below:

PARAMETER	10 mg	40mg
A (micromol/L)	3.75 (114)	8.71 (47)
B (micromol/L)	0.829 (45)	2.97 (45)
$t_{1/2}$ alpha (min)	5.31 (104)	5.9 (77)
$t_{1/2}$ beta (hours)	0.482 (26)	0.593 (42)
K_{el} (hours^{-1})	4.48 (100)	3.98 (53)
V_c (L/kg)	0.139 (61)	0.147 (39)
V_{beta} (L/kg)	0.34 (34)	0.373 (43)
AUC (micromol/L*hour)	0.754 (18)	3.18 (23)
Cl (ml/min)	658 (18)	633 (21)

The dose had no significant influence on V_c, Vbeta, half-life and total body clearance.

2. After oral dosing of 10, 40 and 90 mg of omeprazole the following results were obtained:

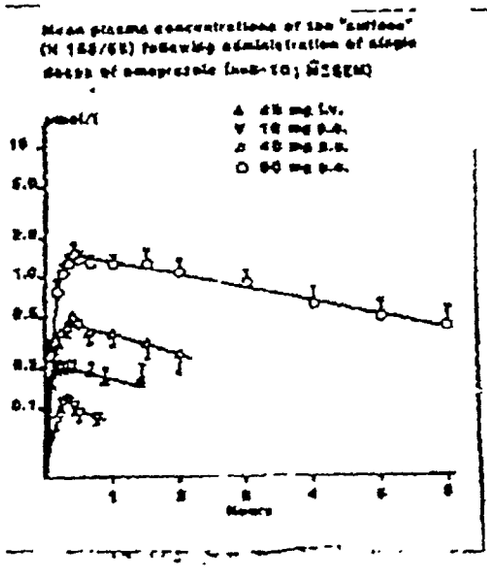
	10 mg	40 mg mean ± S.E.M. (range)	90mg
Tmax (hours)	0.209 ± 0.019	0.275 ± 0.028	0.325 ± 0.056
Cmax (micromoles/L)	0.553 ± 0.118	3.0 ± 0.51	9.4 ± 1.54
AUC (micromoles/L*h)	0.307 ± 0.066	2.0 ± 0.42	7.35 ± 1.41
F	0.403 ± 0.076	0.582 ± 0.079	0.969 ± 0.124
Half-life (hours)	0.40 ± 0.05	0.49 ± 0.05	0.75 ± 0.11

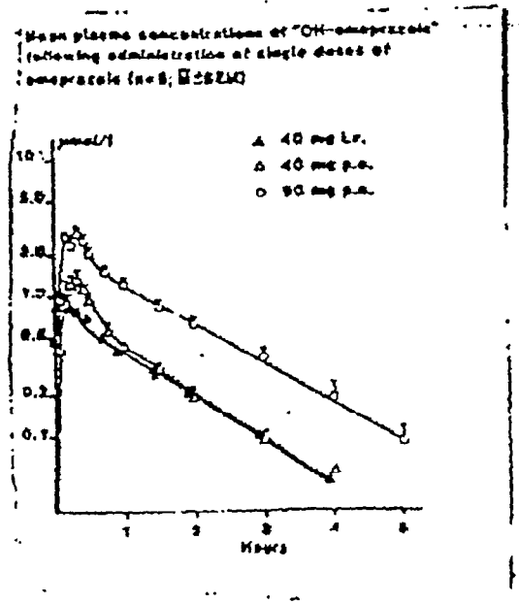
The tendency of increasing Tmax with increasing dose was not statistically significant, however, Cmax, AUC and F increased nonlinearly with increasing oral doses. Half-life after the 90 mg dose was significantly

longer than for the lower doses. There was, however, no significant differences between the half-life of identical i.v. and oral doses.

3. Plasma levels of the sulfone metabolite after the 10 mg intravenous dose were close to the minimum determinable concentration. The mean plasma concentration-time curves after the i.v. and oral doses are shown in the figure below on the left. The maximum levels were reached within 25 minutes and the half-life of the elimination phase was found to be about 3 hours. The mean AUC for the 40 and 90 mg dose were 1.9 ± 0.3 and 6.8 ± 1.3 micromol/L/h respectively and increased in a non-linear way with increasing dose.

4. The mean plasma concentration-time curves of OH-omeprazole following i.v. administration of 40 mg and oral administration of 40 and 90 mg are shown in the figure below on the right and the AUC's were 1.31 ± 0.07, 1.31 ± 0.14 and 3.66 ± 0.24 micromol/L/h respectively. The half-life for the elimination phase of the metabolite was about one hour. The ratio of the dose corrected AUC of the metabolite to omeprazole decreased from 0.94 to 0.58 when the dose was raised from 40 to 90 mg.





5. No detectable amounts of the sulfide could be seen after the 90 mg oral

dose.

6. Negligible amounts of omeprazole and the sulfone metabolite were recorded in urine after all the doses. The amounts of OH-omeprazole recovered in the urine after 24 hours was practically the same after identical i.v. and oral doses as shown in the following table:

	OH-omeprazole (micromoles)	
	i.v.	p.o.
10 mg	1.83 ± 0.27	1.65 ± 0.28
40 mg	9.53 ± 0.76	9.7 ± 0.9
90 mg		28.7 ± 1.6

The fraction of the dose recovered as metabolite was 5.3, 8.7 and 11% after 10, 40 and 90 mg oral doses. Adjusted to the systemic availability, the recoveries decreased from 25 to 20 to 15% with increasing dose.

Sponsor's Conclusions

1. Omeprazole is rapidly distributed into a relatively small volume of distribution and eliminated with a half-life of about 30 minutes.

2. No significant dose-related change in any parameters calculated from the i.v. experiments was detected.

3. The mean systemic availability of omeprazole after oral administration was dose dependent and ranged from 40-97% in a dose interval of 10-90 mg.

4. The increased fraction available of unchanged drug seems not to be due to decreased oxidation or reduction to the corresponding sulfone or sulfide or hydroxylation to OH-omeprazole.

Comments

1. The limit of determination of omeprazole and omeprazole sulfone in plasma was 50 nmole/L and of OH-omeprazole was 100 nmole/L, however, in several of the tables of individual plasma levels, there were reported values less than the limit of determination.

2. The sponsor's recording of the time of blood sampling was not appropriate. The i.v. dosing was accomplished using a five minute infusion. The sponsor recorded the first blood sample (at the end of infusion) as "0" time, however, this is more often recorded as the actual time after dosing began and should have been a 5 minute sample. Subsequently, all of the i.v. dosing blood sample times have a slight discrepancy. The timing of the sampling after oral dosing was appropriate and it is felt that the discrepancy from the i.v. dosing is not substantial.

3. The sponsor used a model dependent method for calculating AUC which means that the estimates of AUC are only as good as the estimates of the coefficients and exponents (A, B, alpha, beta) of the bi-exponential equation of the two-compartment model. The sponsor did not provide information on the goodness-of-fit of their non-linear regression analysis, in fact, they stated that plasma data of a few individuals would possibly have fitted better to a one- or three-compartment model. The

mean AUC after the 10 mg intravenous dose calculated by this reviewer (using trapezoidal rule from t=0 to t=last measured concentration) was significantly different (p=0.018) when compared to the AUC as calculated by the sponsor. The AUC values (as determined by alternate methods) for the other doses and routes did not appear to be significantly different. Furthermore, it is felt the differences in the AUC values would not impact on conclusions from the study.

4. The sponsor concluded that there was no statistically significant differences in half-life or clearance between the 10 and 40 mg intravenous dose. However, as in the previous comment, this may be dependent upon the goodness-of-fit of the parameter estimation routine because this reviewer's finding is that there was a statistically significant difference (p = 0.0145) in half-life when half-life was estimated by another method. It is remarkable how closely the estimates for systemic clearance coincided using different parameter estimation routines. Furthermore, it is this reviewer's observation that systemic clearance appears to remain relatively constant (independent of dose or route) except for the 10 mg oral dose which was significantly different.

5. This reviewer's analysis of the sulfone metabolite data appears to show a significant effect (decrease after i.v. dosing) of route of administration on the formation of this metabolite. Comparison of the ratio of AUC sulfone to AUC parent after 40 mg i.v. and 10, 40 and 80 mg orally showed that the mean ratios of the oral dosing were not significantly different (Duncan's Multiple Range Test). The hydroxy metabolite appears not to exhibit route dependency as the AUC's (after 40 mg dose given i.v. and orally) were nearly identical (p = 0.27).

IX. Study 6. (Study Code I-303) Abstract #601 at III World Conference on Clinical Pharmacology & Therapeutics, 1986

Title:

Dose-Response Relationship for I.V. Omeprazole on Pentagastrin-Stimulated Gastric Acid Secretion. Comparison with Oral Omeprazole.

Objective:

To study the maximal (2-3 h after i.v. and 6.5-7.5 h after oral dosing) and minimal (24.5-25.5 h after i.v. and oral dosing) effect on pentagastrin-stimulated gastric acid secretion of single doses of 10-80 mg i.v. and 20 mg oral omeprazole in healthy subjects.

Drug Dosage Form Used

Intravenous omeprazole consisted of freeze-dried omeprazole (batch No. H-529-3-1) dissolved immediately before use in a solvent (polyethylene glycol 400 40%, sodium dihydrogen phosphate 1.3 mg/ml and disodium hydrogen phosphate 0.3 mg/ml; batch Nos. H-530-2-2, H-530-2-1) to a concentration of 4 mg omeprazole/ml. The dose was infused over 5 minutes and the rate was adjusted to 4, 2, 1 and 0.5 ml/min to deliver 80, 40, 20 and 10 mg omeprazole respectively. The pure solvent was used as placebo. Enteric-coated granules of omeprazole (batch No. H-431-7-7) in hard gelatin capsules were used for oral dosing and identical capsules

containing enteric-coated granules without omeprazole (batch No. K-499-3-4) were used as placebo.

Clinical Investigator and Study Site

Cornelis B H W Lamers, Prof

Dept of Internal Medicine
St. Radboud Ziekenhuis
NIJMEGEN
The Netherlands

Study Protocol

Ten healthy male subjects with a median age of 25 years (range 22-33), median weight of 73.6 kg (range 64.2-82.3) and a median height of 179 cm (range 172-187) were enrolled in and completed the study. The inclusion and exclusion criteria appeared to be adequately met (except for subject No. 6 whose weight of 64.2 kg was below the inclusion criteria minimum of 66 kg). This study was an open, cross-over, randomised trial consisting of seven experiments. In each experiment either a single i.v. dose of placebo, 10, 20, 40 or 80 mg omeprazole or a single oral dose of placebo or 20 mg omeprazole was given. Two gastric secretion tests were conducted in each experiment. The pre-study protocol called for a one week washout period between experiments, however, this was not adhered to and several subjects had less than 7 days between treatments.
After a minimum 10 hour fast, the dose was administered either i.v. or orally. The oral dose was taken with 150 ml of water. Indwelling cannulas were inserted in each forearm to keep intravenous infusions and sampling of venous blood separate.

Specimens Collected

Blood samples (7 ml) were collected in heparinised tubes 5 minutes prior to and 0.0, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 2.5, 3 and 24 hours after i.v. dosing and 5 minutes prior to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 24 hours after oral dosing.

Bioanalytical Methodology

The plasma samples were analysed at the Department of Analytical Chemistry, Bioanalytical Laboratory, [redacted] using HPLC similar to methods used in previous studies.

Pharmacokinetic Analytical Methodology

The terminal half-life of i.v. omeprazole was determined from the individual regression lines of the log plasma concentration-time curves during the elimination phase. The AUC was calculated using the trapezoidal rule and for i.v. dosing, adding the area to infinity (last measured concentration x half-life/0.693). Systemic availability (F) of oral omeprazole was calculated by

$$F = \frac{AUC_{20\ mg\ p.o.}}{AUC_{20\ mg\ i.v.}}$$

Statistical evaluations of the terminal half-life were made using Wilcoxon's matched-pairs signed-rank test.

Pharmacodynamic Methodology

A dose-response curve for the maximal effect on pentagastrin-stimulated acid secretion of IV omeprazole was calculated using EISFIT. This was done by fitting the % reduction in mean peak acid output (PAO) to a sigmoid Emax model. The IV dose that was equipotent to 20 mg oral omeprazole was estimated by inserting the maximal reduction in PAO caused by the oral dose in the equation for the calculated dose-response curve.

Results

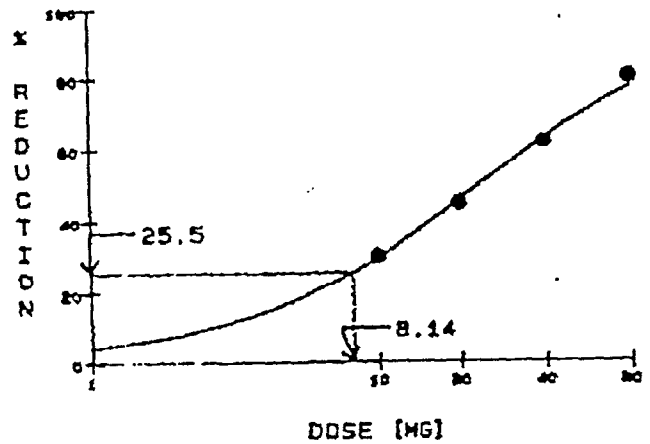
1. The individual and summarized pharmacokinetic parameters are tabulated below:

Area under the plasma concentration-time curve(AUC(mg/h/l))terminal half-life(t½h) and systemic availability(F) after administration of omeprazole single doses in (on healthy subjects

Subject No	Intravenous								Oral	
	10mg		20mg		40mg		80mg		20mg	
	AUC	t	AUC	t	AUC	t	AUC	t	AUC	F
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
Median	[illegible]	.69	1.82	.64	4.00	.79	9.30	.84	.91	.30
Max	3.68	1.08	3.12	.92	6.81	1.10	26.74	1.31	1.67	.95
Min	.79	.44	1.15	.37	2.94	.61	6.96	.67	.38	.12

The terminal half-life was significantly increased after the 80 mg i.v. dose. There was a linear increase in the median AUC with increasing i.v. dose although a disproportionately greater increase was seen between 40 mg and 80 mg for some subjects.

2. The dose-response curve for the maximal inhibitory effect of IV omeprazole is shown in the following figure. The dose giving 50% reduction in PAO was calculated to be 24 mg. The IV dose having the same maximal effect (25.5% inhibition) as 20 mg oral omeprazole was calculated to be 8 mg.



Sponsor's Conclusions

1. I.V. administration of omeprazole resulted in a dose-dependent inhibition of peak acid output and an i.v. dose of about 10 mg was equipotent to 20 mg oral omeprazole.

2. The apparent difference in potency was fully accounted for by the smaller amount absorbed from the oral formulation (F=0.5).

3. The pharmacokinetics of i.v. omeprazole appear to be dose-dependent at doses somewhere above 40 mg.

Comments

1. Dissolution data of the oral dosage formulation used in this study were not provided. (The batch no. of the capsules used in this study is the same as that used in several other studies for which dissolution data were provided.)

2. ANOVA of normalized AUC indicated that the means of the four i.v. doses were not significantly different (Duncan's Multiple Range Test).

3. Assay validation data were not provided with this study report or in the Summary of Analytical Techniques.

4. The demographic data table has the maximum and minimum values reversed.

5. The sponsor's attempt at establishing a pharmacokinetic-pharmacodynamic relationship should be commended. However, a better approach would have been to relate plasma concentrations with effect.

X. Study 7. (Study Code I-321) Abstract #601 at III World Conference on Clinical; Pharmacology & Therapeutics, 1986

Title:

Effect of Repeated Administration of I.V. and Oral Omeprazole of Gastric Acid Secretion in Healthy Subjects
(N.B. The pharmacodynamic portion of this study is not included in this review since the sponsor did not attempt to model the PK-PD relationship as was done in study I-303.)

Objective:

To study the maximal and minimal effects on pentagastrin-stimulated gastric acid secretion as well as the pharmacokinetics, during repeated intravenous administration of 10 mg and 20 mg omeprazole and compare with repeated oral administration of 20 mg.

Drug Dosage Form Used

Same as in previous study.

Clinical Investigator and Study Site

Per Lundborg, MD

Clinical Pharmacology Laboratory
AB Hässle
S-431 83 MÖLNDAL
Sweden

Study Protocol

Nine healthy male subjects with a median age of 25 years (range 22-32), median weight of 79.5 kg (range 66-84) and a median height of 185 cm (range 173-191) were enrolled in and completed the study. Inclusion and exclusion criteria as per protocol were met. During study days 1-5, the subjects either took the daily oral omeprazole at home before breakfast or came to the laboratory for the daily dose of the i.v. omeprazole. On the 6th day, the subjects came to the laboratory for both the oral and i.v. doses. The study periods (20 mg oral and 10 and 20 mg i.v dosing) were conducted in random order at intervals of at least one week. Indwelling cannulas were inserted in separate forearms to keep intravenous infusions and sampling of venous blood separate.

Specimens Collected

Blood samples (7 ml) for determination of omeprazole in plasma were collected in heparinized tubes 10 minutes prior to end of drug infusion and 0, 10, 20, 30, 45, 60, 90, 120, 150, 180 and 240 minutes after the end of drug infusion for the i.v. dose and at 5 minutes prior to oral dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 8 hours after dosing.

Bioanalytical Methodology

The plasma samples were analyzed at the Department of Analytical Chemistry, Bioanalytical Laboratory, [redacted] using HPLC similar to methods used in previous studies.

Pharmacokinetic Analytical Methodology

The terminal half-life of i.v. omeprazole was determined from the individual regression lines of the log plasma concentration-time curves during the elimination phase (the same time interval was used for any given subject). The AUC was calculated using the trapezoidal rule and in the case of i.v. omeprazole, adding the area to infinity.

In some experiments with i.v. omeprazole, the last measurable concentration was higher than in the preceding sample. These values were excluded from the calculation of half-life and AUC.

The systemic availability (F) for oral omeprazole was calculated by the following equation:

$$F = \frac{AUC_{20\ mg\ p.o.}}{AUC_{20\ mg\ i.v.}}$$

Statistical evaluations of the terminal half-life were made using Wilcoxon's matched-pairs signed-rank test.

Results

In one subject (No. 5), the highest plasma omeprazole concentration after 10 mg i.v. was taken 2 hours after administration. The results of this subject have been excluded from the pharmacokinetic calculations. The individual and summarized pharmacokinetic parameters are tabulated below:

Area under the plasma concentration-time curve (AUC; umol*h/l), terminal halflife ($t_{1/2}$; h) and systemic availability (F) after repeated administration of omeprazole in nine healthy subjects.

Subject No	Intravenous				Oral	
	6*10mg		6*20mg		6*20mg	
	AUC	$t_{1/2}$	AUC	$t_{1/2}$	AUC	F
1						
2						
3						
4						
5						
6						
7						
8						
9						
Median	.86	.48	2.86	.53	.55	.30
Max						
Min						

Sponsor's Conclusions

1. Great variation exists between individuals in their ability to metabolize omeprazole.

2. The pharmacokinetics following 10 and 20 mg omeprazole i.v. once daily after repeated dosing were linear.

3. The unexpected increase of the last measurable plasma concentration in some subjects may be due to analytical error or some other unknown factor.

4. The high plasma concentration occurring at 2 hours in subject No. 5 after i.v. dosing was probably due to sample mix up.

Comments

1. Assay validation data were not provided with this study report or in the Summary of Analytical Techniques.

2. Dissolution data of the oral dosage formulation used in this study were not provided but this batch no. has been used in other studies which had dissolution data.

XI. Study E. (Study Code I-338)

Title:

Comparison between the effects of IV and oral omeprazole on 24-hour intragastric acidity in healthy subjects.
(N.B. The pharmacodynamic portion of this study is not included in this review since the sponsor did not attempt to model the PK-PD relationship as was done in study I-303.)

Objectives:

To compare the effects of single doses and repeated once-daily administration of oral (20 mg) and i.v. (10 and 40 mg) omeprazole on 24-hour intragastric acidity in healthy subjects aged between 35 and 65.

Drug Dosage Form Used

Oral omeprazole (20 mg) was given as enteric coated granules in hard gelatin capsules (batch No. H 431-7-14).

The i.v. dose consisted of an ampul of lyophilized omeprazole sodium (equivalent to 40 mg, batch No. H 705-1-3) which was mixed immediately before use in 100 ml of commercially available 0.9% NaCl (Travenol) infusion bag. The amount infused was 25 and 100 ml for the 10 and 40 mg dose, respectively, over 30 minutes.

Clinical Investigator and Study Site

Per Lundborg, Prof MD

Clinical Pharmacology Laboratory
AB Hässle
S-431 83 MÖLNDAL, Sweden

Study Protocol

Five males and four females with a median age of 40 years (range 35-49), median weight of 65 kg (range 52-87) and median height of 174 cm (range

155-190) were enrolled in and completed the study. Inclusion and exclusion criteria as detailed in the protocol appeared to have been met. The study was conducted as an open, cross-over trial. Each subject took part, in random order, in three study periods extending over 5 days and separated by at least a 10 day washout period. The study periods were a.) 20 mg orally once daily for 5 days, b.) 10 mg i.v. once daily for 5 days and c.) 40 mg i.v. once daily for 5 days. Doses were given in the morning after an overnight fast and on study days 1 and 5 (when subjects remained in the laboratory) standardized meals were served 0.5, 4.5 and 10.5 hours after dosing.

Specimens Collected

Blood samples (5 ml) were collected in heparinized tubes at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210 and 270 minutes after the start of i.v. infusion and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after the oral dose.

Bioanalytical Methodology

The plasma samples were analyzed for omeprazole at the Department of Bioanalytical Chemistry at [redacted] using similar HPLC methods as in previous studies. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 15-25 nmole/L with a relative standard deviation of less than 10-15%), linear (20 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves were 0.5-10% and 1.1-8.5%. The mean intra-day CV of single concentration standard sets was 1.6% (range 0.3-4.4%) and the mean CV of inter-day quality control samples was 3.6% (range 94-110% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Analytical Methodology

The terminal half-life of i.v. omeprazole was determined from the individual regression lines of the log plasma concentration-time curves during the elimination phase. The AUC was calculated using the trapezoidal rule and in the case of i.v. omeprazole, adding the area to infinity. The total plasma clearance for each i.v. dose was calculated as dose/AUC. The bioavailability of the first and fifth oral dose of 20 mg was calculated using the AUC for the corresponding 10 mg i.v. dose multiplied by two.
Wilcoxon matched-pairs signed-rank test was used in the statistical evaluation.

Results

The individual and mean AUC, F, clearance, clearance ratio and terminal half-life are presented in the following tables:

Table III. Area under the plasma concentration-time curve (AUC, umol·h/l) and bioavailability (F) during repeated oral and intravenous administration of omeprazole in nine healthy subjects.

Subj.	20 mg po Day 1		20 mg po Day 5		10 mg iv Day1	10 mg iv Day 5	40 mg iv Day1	40 mg iv Day 5
No	AUC	F	AUC	F	AUC	AUC	AUC	AUC
1(M)*		0.14		0.37				
2(F)		0.38		0.88				
3(F)		0.31		0.35				
4(M)		0.40		0.24				
5(F)		0.67		0.95				
6(M)		0.25		0.30				
7(M)		0.44		0.42				
8(F)		0.35		0.17				
9(M)		0.30		0.81				
* M= Male F= Female								
Geom. mean	0.62	0.33	0.84	0.42	0.93	0.59	4.25	6.59
95 % confidence interval								
Upper	0.99	0.46	1.74	0.68	1.25	1.32	5.22	10.03
Lower	0.39	0.23	0.41	0.27	0.70	0.74	3.45	4.33

Table IV. Omeprazole clearance (ml/min) and clearance-ratio day 5/day 1

Subj no	10mg iv day1	10mg iv day5	ratio	40mg iv day1	40mg iv day5	ratio
1			1.06			0.91
2			0.90			0.46
3			1.05			0.63
4			0.87			0.78
5			0.68			0.46
6			0.92			1.09
7			0.94			0.74
8			1.02			0.46
9			1.13			0.53
Geom mean	516	488	0.94	454	292	0.64
95% confidence interval						
upper	692	653	1.06	558	445	0.82
lower	386	364	0.84	369	192	0.50

Table V. Terminal half-life of omeprazole (h) following iv-administration of omeprazole

Subj no	10mg iv day1	10mg iv day5	40mg iv day1	40mg iv day5
1				
2				
3				
4				
5				
6				
7				
8				
9				
Median	.51	.59	.74	.58

Sponsor's Conclusions

1. The AUC following oral administration of 20 mg omeprazole increased in 7 of the 9 subjects from day 1 to day 5 but this difference was not statistically significant (p=0.11). The geometric mean of the individual ratios $AUC_{Day\ 5}/AUC_{Day\ 1}$ was 1.35 (0.84-2.18; 95% C.I.)

2. The geometric mean of bioavailability from Day 1 and Day 5 were not significantly different (p=0.139).

3. The increase in AUC from Day 1 to Day 5 was not significant (p=0.441) after the 10 mg i.v. dose, however, after the 40 mg dose the increase was significant (p=0.011). The geometric mean of the individual ratios $AUC_{Day\ 5}/AUC_{Day\ 1}$ was 1.06 (0.94-1.19; 95% C.I.) for the 10 mg dose while the corresponding value for the 40 mg dose was 1.56 (1.22-1.99).

4. The 36% (18-50; 95% C.I.) decrease in clearance during repeated i.v. administration of 40 mg was significant (p=0.011) but was not significant for the 10 mg dose (p=0.441). It has been suggested that the decrease in clearance may be the result of metabolic inhibition in combination with non-linear kinetics.

5. The terminal half-life was not significantly changed during repeated i.v. administration of either 10 mg (p=0.374) or 40 mg (p=0.139).

Comments

1. Dissolution data of the oral dosage formulation used in this study were not provided.

2. The study protocol indicated that hemoglobin levels were to be checked at the end of each study period. However, in the case report tabulations, hemoglobin levels are presented only as "before" and "after". Furthermore, a statistically significant decrease in hemoglobin and s-creatinine were found after the last study period.

3. Analysis (by paired T-Test) of the AUC data following oral administration of 20 mg omeprazole indicated that the increase from day 1 to day 5 approached significance ($p = 0.058$).

4. The significant increase in AUC from day 1 to day 5 after the 40 mg intravenous dose appeared to show a difference between males and females. Analysis (by paired T-Test) of males only ($N = 5$) indicated no significant difference ($p = 0.15$), however, the increase among the females ($N = 4$) was significant ($p = 0.02$). This sex difference was also evident in the half-life estimate, males having no change and females having a significant increase ($p = 0.0039$). It is difficult to attribute these findings to a sex effect solely, since there was a remarkable difference between the weights of male and female subjects participating in the study. The mean weights (% C.V.) of the males and females were 75.6 (10.8%) and 55.8 (5.2%) kg respectively which was significantly different ($p = 0.002$). These findings may be an artifact of all subjects receiving an identical dose instead of being dosed by body weight.

XII. Study 9. (Study Code I-246)

Title:

Morning or evening dosing of omeprazole: acute and steady state pharmacokinetics and effects on 24 hour gastric acid profiles in healthy volunteers.
(N.B. The pharmacodynamic portion of this study is not included in this review since the sponsor did not attempt to model the PK-PD relationship as was done in study I-303.)

Objectives: (pharmacokinetic)

To investigate the acute and steady-state pharmacokinetics of omeprazole administered as a morning or evening dose.

Drug Dosage Forms Used

Omeprazole (and matching placebo) was formulated as an encapsulated, enteric-coated granulate (Formulation No. H431-4-2).

Clinical Investigator(s) and Study Site

W.J. Louis, M.D.
R.A. Smallwood, M.D.
N. D. Yeomans, M.D.

Austin Hospital, Melbourne
Australia

Study Protocol

Eight non-smoking healthy male volunteers with a mean age of 22 years (range 20-26), mean weight of 74 kg (range 60-116) and a mean height of 178 cm (range 170-183) completed the study. The study was conducted as a double-blind, cross-over. Each subject completed two active treatment periods lasting 5 days, with an intervening 14 day washout period. In one period, two capsules (20 mg each of omeprazole) were taken each

morning at 0900 and in the other period two capsules were taken each evening at 2100.

Specimens Collected

Blood samples were obtained prior to dosing and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10 and 12 hours after each dose on days 1 and 5 of each period. Urine was collected during the 12 hour blood sampling interval.

Bioanalytical Methodology

Plasma and urine samples were analyzed for omeprazole and the sulphone metabolite.

Pharmacokinetic Analytical Methodology

AUC, C_{max}, t_{max} and terminal half-life were calculated and compared using two-way ANOVA and Student's two-tailed t-test. Statistical significance was claimed if p was less than or equal to 0.05.

Results

Omeprazole and omeprazole sulphone AUC, C_{max}, T_{max} and plasma half-life of omeprazole are tabulated below:

TABLE [illegible]: OMEPRAZOLE AUC

Area under the plasma omeprazole concentration - time curve (AUC; umol.h/L) in 6 healthy subjects given 40 mg omeprazole orally for 5 days.

Subj.	Day 1 a.m.	Day 5 a.m.	D1:D5	Day 1 p.m.	Day 5 p.m.	D1:D5
[illegible]						
MEAN	1.45	6.66	1.9	2.62	6.77	1.9
SEM	0.36	1.32	0.2	0.64	1.34	0.2

[illegible] p < 0.01 — [illegible] p < 0.01

[illegible] p = 0.025

NS

TABLE [illegible]: OMEPRAZOLE SULPHONE AUC

Area under the plasma omeprazole sulphone concentration - time curve (AUC; umol.h/L) in 6 healthy subjects given 40 mg omeprazole orally for 5 days.

Subj.	Day 1 a.m.	Day 5 a.m.	D1:D5	Day 1 p.m.	Day 5 p.m.	D1:D5
[illegible]						
MEAN	3.54	7.07	2.1	3.61	8.67	2.9
SEM	0.93	1.70	0.2	0.71	1.73	0.6

TABLE [illegible] [illegible] PEAK PLASMA CONCENTRATIONS

Peak plasma [illegible] concentrations (mmol/L) in 8 healthy subjects given [illegible] [illegible] orally for 5 days.

Subject	Day 1 a.m.	Day 5 a.m.	95% CI	Day 1 p.m.	Day 5 p.m.	95% CI
1						
2						
3						
4						
5						
6						
7						
8						
Mean	[illegible]	2.31	1.1	0.86	2.04	1.7
SD	[illegible]	0.55	0.3	0.30	0.36	0.5

[illegible] p < 0.05 [illegible] 0.07 < p < 0.025

[illegible] 0.004 < p < 0.01

[illegible]

TABLE [illegible] [illegible] SULPHONE PEAK PLASMA CONCENTRATIONS

Peak plasma [illegible] sulphone concentrations (mmol/L) in 8 healthy subjects [illegible] [illegible] orally for 5 days.

Subject	Day 1 a.m.	Day 5 a.m.	95% CI	Day 1 p.m.	Day 5 p.m.	95% CI
1						
2						
3						
4						
5						
6						
7						
8						
Mean	[illegible]	1.35	1.1	0.35	0.95	2.1
SD	[illegible]	0.37	0.3	0.41	0.37	0.4

[illegible] 0.07 < p < 0.025

[illegible] 0.025 < p < 0.01

[illegible] TIME TO PEAK PLASMA [illegible] CONCENTRATION

Time to peak plasma [illegible] concentration (h) in [illegible] subjects given 10 mg [illegible] orally for 5 days

Subject	Day 1 a.m.	Day 3 a.m.	Day 1 p.m.	Day 3 p.m.
1				
2				
3				
4				
5				
6				
7				
8				
MEAN	1.0	1.9	[illegible]	1.2
SEM	0.4	0.6	[illegible]	0.3

[illegible] p < 0.05 [illegible]
[illegible] 0.01 < p < 0.02 [illegible]
[illegible] p: [illegible]

[illegible] TIME TO PEAK PLASMA [illegible] SULPHATE CONCENTRATION

Time to peak plasma [illegible] sulphate concentration (h) in [illegible] subjects given 10 mg [illegible] orally for 5 days

Subject	Day 1 a.m.	Day 3 a.m.	Day 1 p.m.	Day 3 p.m.
1				
2				
3				
4				
5				
6				
7				
8				
MEAN	3.4	4.6	3.6	4.3
SEM	0.3	0.5	0.5	0.3

[illegible] 0.01 < p < 0.02 [illegible] < 0.01 < p < 0.02 [illegible]
[illegible] 0.01 < p < 0.02 [illegible]
[illegible] p: [illegible]

[illegible]

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Sponsor's Conclusions

1. The 2 to 3 fold increase in AUC for omeprazole, which occurred in all subjects irrespective of treatment, is suggestive of increased absorption of the drug during prolonged treatment.

2. Omeprazole was absorbed more slowly and less completely after a single evening dose than after a single morning dose.

Comments

1. The study report did not address subject inclusion and exclusion criteria.

2. Assay validation data for the sulfone metabolite in plasma or urine were not included with the study report. Furthermore, the Summary Section of Analytical Techniques for Biological Fluids indicated validation data for hydroxy-omeprazole in urine but the study synopsis did not indicate that the hydroxy metabolite was included in the study.

3. Blood sample volumes and sample handling were omitted from the study report.

4. The analytical [illegible] were not reported.

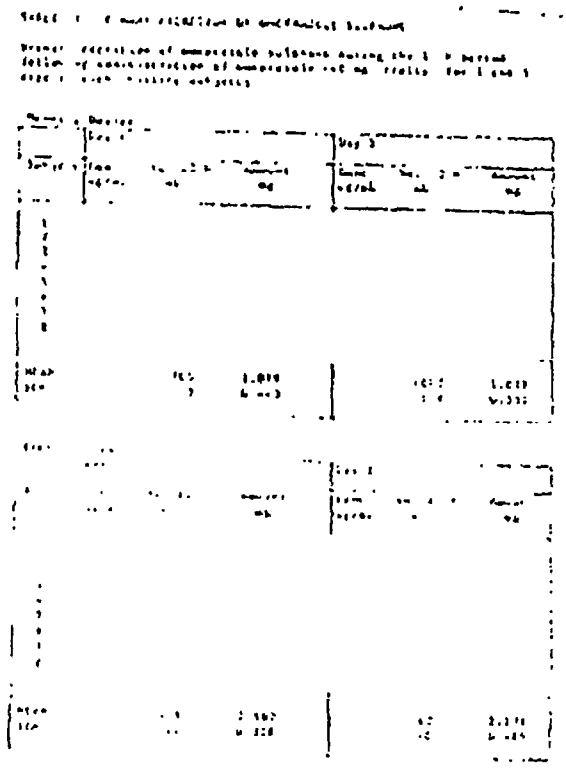
5. The method of calculating pharmacokinetic parameters was omitted.

6. Subjects 1 and 8 were pronounced outliers in almost every pharmacokinetic parameter except Tmax. Subject 8 (weight of 116 kg) was a definite outlier in the comparison of weights. Since subject 1 was nearly identical in demographic details to the other subjects, the possibility of biphasic metabolism of omeprazole may be evident.

7. The experimental [illegible] was described as a [illegible] crossover study. However, the [illegible] of the order of the experiments was omitted from the study [illegible].

8. The study synopsis includes the collection of urine samples as part of the investigational method. However, the results section of the report did not include any urinary recovery data. The case report tabulations (which were not included with the original NDA submission and were requested by this reviewer and received under separate cover on July 14, 1988) did contain tabulated urinary excretion data (copy below). This reviewer's analysis of the data indicates that the amount of the sulfone metabolite excreted in the urine was significantly greater when dosing was in the evening (Duncan's Multiple Range Test). This effect may be related to the urinary volume of the study period, since the volumes of urine collected during the evening dosing phase were significantly smaller. A weak relationship of increased amount in urine with decreased volume is implied by the linear regression ($r^2 = 0.21$) of amount in urine on urine volume which has a negative slope and does not go through the origin.

9. Regard's sponsor's conclusion #1 the suggestion of increased absorption of the drug during prolonged treatment cannot be validated based on AUC alone.



XIII. Study 10. (Study Code I-278)

Title:

Pharmacokinetics and Bioavailability of Omeprazole Before and After Repeated Oral Administration in Healthy Subjects.

Objective:

To explore the potential mechanisms for the increased area under the plasma concentration-time curve, AUC, observed after the repeated administration of omeprazole as EC granules.

Drug Dosage Forms Used

1. IV Tracer Dose (Batch no. H 574-1-1): 30 microCi ^{14}C omeprazole was dissolved in 6.13 g PEG 400 and diluted with 10 ml of a [redacted] solution (0.56 mg/ml, Batch no. H 397-4-1) to a total volume of 15 ml. Ten ml of this solution (20 microCi corresponding to 0.12 mg of omeprazole) was given intravenously (2 ml/min over 5 min).

2. Omeprazole oral solution (Batch no. H 404-5-1): 20 mg of omeprazole was dissolved in 2.0 g PEG 400 and stored deep frozen. The solution was diluted prior to use with 50 ml of a sodium bicarbonate solution (8 mmol/50 ml, Batches no. HD22-2-15 and -16). The final solution contained 40% PEG 400 and 20 mg of omeprazole per 52 ml. In order to protect the drug from exposure to gastric acid, 50 ml of the [redacted] solution was given 5 min before, together with, and 10, 20 and 30 min after administration of the omeprazole solution.

3. Omeprazole EC granules (Batch no. H 431-7-1): 20 mg of omeprazole as EC granules in a hard gelatin capsule.

Clinical Investigator and Study Site

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Study Protocol

Ten male subjects with a median age of 26 years (range 23-34 years), a median weight of 79 kg (range 68-85 kg) and a median height of 181 cm (range 171-194 cm) were enrolled in and completed the study. Inclusion and exclusion criteria as per protocol were met. Each subject participated in one study period, consisting of four separate experiments extended at least 17 days. Experiment 1 was administration of the omeprazole solution followed by at least a 7 days wash out. Experiment 2 was the administration of the EC granules and IV tracer dose on Day 1. Dosing with EC granules was continued once daily before breakfast for 7 more days at least. Experiment 3 (day 61) was a repeat of experiment 2 and

experiment 4 (day 9) was a repeat of experiment 1.

Specimens Collected

Exp. 1: After at least a 10 hour fast, a solution of 20 mg omeprazole was administered at about 8:00 a.m. Blood samples (5 ml collected in heparinized tubes) were taken before and 5, 10, 15, 20, 25, 30, 45 minutes and 1, 1.5, 2, 3, 4, 5 and 6 hours after dosing.

Exp. 2: After at least a 10 hour fast, a capsule of 20 mg omeprazole (as EC granules) was administered at about 8:00 a.m. Concomitant with the capsule dose, an IV tracer dose of omeprazole was given. Blood samples (8 ml) were taken before and 5, 7, 10, 15, 20, 25, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after dosing.

Exp. 3: Same as Exp. 2.

Exp. 4: Same as Exp. 1.

Bioanalytical Methodology

Plasma samples were analyzed for omeprazole and ^{14}C omeprazole by the Department of Bioanalytical Chemistry, [redacted] using HPLC combined with liquid scintillation counting by [redacted] scintillator. The HPLC method was similar to assay methods used in previous studies. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole was 30-50 nmole/L of plasma with a RSD of 10-15% and for ^{14}C omeprazole it was 2 nmole/L), linear (between 30 nmole/L and 100 micromole/L) and reproducible. The intra-day CV's of the standard curve were 2.6% for 170 nmole/L and 1.9% for 1700 nmole/L. The mean intra-day CV of single concentration standard sets was 2.0% (range 0.2-8.9%) and the CV of inter-day quality control samples was 3.3% (range 92.5-105.5% of recovered spiked concentration). The mean intra-day CV for ^{14}C omeprazole was 3.6% (range 0.5-22%)

Pharmacokinetic Analytical Methodology

The elimination half-lives, t1/2, of omeprazole following administration of the IV tracer dose and oral solution were calculated by linear regression analysis of the log plasma concentration-time curve (between time 20 min and the last determinable plasma concentration (Cp-last) for the IV dose and between time 30, 45 or 60 min (based on the individual regression lines) and the Cp-last for the oral solution). T1/2's were not calculated for the EC granule dosing because of erratic and continued absorption during the elimination phase.

The AUC was calculated by the trapezoidal rule between the time of administration and Cp-last. The residual AUC for the IV and oral solution were extrapolated using the beta (beta=ln2/t1/2) value from each individual curve. Total plasma clearance, CL, volume of distribution, Vbeta, and bioavailability, F, were calculated according to the following equations:

$$CL = \frac{dose(IV)}{AUC(IV)} \qquad Vbeta = \frac{CL}{beta}$$

$$F = \frac{AUC(oral)}{AUC(IV)} \times \frac{dose(IV)}{dose(oral)}$$

For the buffered solution, F before treatment was calculated using the AUC values of the IV tracer dose from the first day of treatment and F after treatment by using the AUC values of the IV tracer dose from the last day of treatment. For the EC granules, F was calculated using the AUC values determined for the simultaneously administered IV tracer dose.

95% confidence limits for the expected values of the logarithms (assumed to be normally distributed) of AUC and t1/2 were calculated. These were then transformed to 95% confidence intervals in the original scale. 95% confidence limits for the expected values of CL, Vbeta and F were also constructed. The change in the variables from before to after eight days' treatment was compared in terms of confidence intervals for the ratio between the geometric means for AUC and t1/2, and of confidence intervals for the ratio between arithmetic means for CL, Vbeta and F.

Results

The individual values of AUC, t1/2, CL and Vbeta and their summary statistics after the two IV tracer doses are shown below:

Table 1. Individual values of area under the plasma concentration-time curve (AUC) and elimination half-life (t½) of the i.v. tracer dose of omeprazole, determined on the first and last day of eight days' treatment with omeprazole, 20 mg o.m., in ten healthy subjects.

Subject No.	AUC (mg/l·h)		t½ (h)	
	First day of treatment	Last day of treatment	First day of treatment	Last day of treatment
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
Geometric mean	[illegible]	[illegible]	[illegible]	[illegible]
95% conf. limits	[illegible]	[illegible]	[illegible]	[illegible]
Ratio				
Geometric mean	[illegible]		[illegible]	
95% conf. limits	[illegible]		[illegible]	

Table 2. Individual values of plasma clearance (CL) and volume of distribution (V_β) of the i.v. tracer dose of omeprazole, determined on the first and last day of eight days' treatment with omeprazole, 20 mg o.m., in ten healthy subjects.

Subject No.	CL (l/h)			V_β (l/kg)		
	First day of treatment	Last day of treatment	Ratio	First day of treatment	Last day of treatment	Ratio
1			[illegible]			[illegible]
2			[illegible]			[illegible]
3			[illegible]			[illegible]
4			[illegible]			[illegible]
5			[illegible]			[illegible]
6			[illegible]			[illegible]
7			[illegible]			[illegible]
8			[illegible]			[illegible]
9			[illegible]			[illegible]
10			[illegible]			[illegible]
Arithmetic mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
95% conf. limits	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ratio						

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The individual values of AUC, t1/2 and F and their summary statistics after the two buffered solution doses are shown below:

Table 3. Individual values of area under the plasma concentration-time curve (AUC) and elimination half-life (t½) of the buffered solution of omeprazole administered one week before and one day after eight days' treatment with omeprazole as EC granules, 20 mg o.m., in ten healthy subjects.

Subj. No.	AUC (mg/l x h) before treatment (A)	AUC (mg/l x h) after treatment (B)	t½ (h) before treatment (A)	t½ (h) after treatment (B)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
Geometric mean	[illegible]	[illegible]	[illegible]	[illegible]
95% conf. interval	[illegible]	[illegible]	[illegible]	[illegible]
Ratio				
Geometric mean (A/B)	[illegible]		[illegible]	
95% conf. interval	[illegible]		[illegible]	

Table 4. Individual values of bioavailability (F) of the buffered solution of omeprazole administered one week before and one day after eight days' treatment with omeprazole as EC granules, 20 mg o.m., in ten healthy subjects.

Subj. No.	F before treatment (A)	F after treatment (B)	F A/B
1			[illegible]
2			[illegible]
3			[illegible]
4			[illegible]
5			[illegible]
6			[illegible]
7			[illegible]
8			[illegible]
9			[illegible]
10			[illegible]
Arithmetic mean	[illegible]	[illegible]	[illegible]
95% conf. interval	[illegible]	[illegible]	[illegible]
Range			

The individual values of AUC and F and their summary statistics after the EC granule doses are shown below:

Table 5. Individual values of the area under the plasma concentration-time curve (AUC) for the EC granules of omeprazole on the first and last day of eight days' treatment with 20 mg o.m., in ten healthy subjects.

Subj. No.	AUC (mg/l x h) first day of treatment (A)	AUC (mg/l x h) last day of treatment (B)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
Geometric mean	[illegible]	[illegible]
95% conf. interval	[illegible]	[illegible]
Ratio		
Geometric mean (A/B)	[illegible]	
95% conf. interval	[illegible]	

Table 6. Individual values of the bioavailability (F) of the EC granules of omeprazole on the first and last days of eight days' treatment with 20 mg o.m., in ten healthy subjects.

Subj. No.	F first day of treatment (A)	F last day of treatment (B)	F A/B
1			[illegible]
2			[illegible]
3			[illegible]
4			[illegible]
5			[illegible]
6			[illegible]
7			[illegible]
8			[illegible]
9			[illegible]
10			[illegible]
Arithmetic mean	[illegible]	[illegible]	[illegible]
95% conf. interval	[illegible]	[illegible]	[illegible]
Range			

Sponsor's Conclusion:

1. Estimations from the last determinable plasma concentration and t1/2 for each experiment indicate that no plasma concentrations of omeprazole could have been detected 24 hours after dose.

2. The results from the IV tracer dose experiments indicate that the pharmacokinetic parameters, including variables of systemic elimination of an IV dose omeprazole, are unaltered after repeated administration of EC granules. There were no significant changes in AUC, t1/2, CL or Vbeta between the two administrations.

3. The significant increase in omeprazole AUC and F observed during once-daily treatment with EC granules is unlikely to be due to any changes in the systemic elimination of the drug but caused rather by an increased systemic availabilit.

4. The t1/2 and F were not significantly changed between the two administrations of the buffered solution. However, the significant increase in AUC of the second treatment of buffered solution, although smaller than that of the EC granules, indicates that a decreased first pass elimination during treatment may be a further contributing factor.

Comments

1. Dissolution information (in summary format) for the capsule dosage form used in this study was provided in the Summary section of the Human Pharmacokinetics and Bioavailability Data section. The dosage form (EOG III) had a mean acid resistance of 90% and 92% dissolved in 30 min.
2. The study report indicated that the arithmetic mean of Vbeta of the first day of treatment was 288 ml/kg, however, recalculation showed the mean to be 277 ml/kg. This error does not change the conclusion of similar Vbeta's on the first and last day of treatment. However, this simple error in the summary statistics raises some uncertainty about the adequacy of the review of this data prior to submission to the Agency.

3. The analysis of plasma samples after the IV tracer dose was done by scintillation counting. Since the extensive metabolism of omeprazole has been well documented in previous studies and since no information was provided (such as TLC) that the assay of the tracer dose was specific for parent omeprazole, all calculations using the IV tracer dose data are suspect. The proper method (outside of documenting the specificity of the assay) would have been to collect the omeprazole peak of the HPLC assay and analyze it for radioactivity.

4. The extrapolated AUC (after Cp-last) of the IV tracer dose was on average 12% (range 5-22%) and 9.4% (range 5-16%) greater than the AUC(0 to Cp-last) for the first and last day of treatment respectively.

5. One subject (No. 7, in the study was a definite outlier in almost every parameter examined throughout the four experiments. Analysis of the data by this reviewer with the exclusion of subject 7 did not change any of the sponsor's conclusions. However, in view of the comment in the study report that subject 7 had abnormal liver function tests, an evaluation by a medical [illegible] may be warranted as to the possible

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correlation between compromised liver function and decreased clearance of omeprazole.

XIV. Study 11. (Study Code I-243)

Title:

Bioavailability of Omeprazole From Two Formulations of Enteric-Coated Granules Given as a Single Dose

Objective:

To compare EOG II and EOG III with respect to bioavailability and to study the correlation between plasma AUC and the 24 hour urinary excretion of the hydroxy-omeprazole.

Drug Dosage Form Used

Hard gelatin capsules containing 30 mg of omeprazole were used (EOG II, batch no. H 415-2-5 and EOG III, batch no. H 415-6-1). The buffered suspension contained 60 mg omeprazole per 50 ml (batch no. H 410-1-4). The sodium bicarbonate solutions used as buffer were batch nos. H 322-2-12 and H 322-2-14.

Clinical Investigator and Study Site

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Sweden

Study Protocol

Twelve male subjects (meeting the appropriate inclusion and exclusion criteria) with a mean age of 24 years (range 20-27), a mean weight of 79 kg (range 71-86) and a mean height of 184 cm (range 173-190) were enrolled in and completed the study. Each subject participated in three experiments with a single dose of omeprazole given under fasting conditions. The EOG formulations were given double-blindly. The six possible orders of experiments were allocated at random to the twelve subjects in such a way that each order occurred only twice. Omeprazole was given in doses of 60 mg in one of the dosage forms described above. Sodium bicarbonate solution (50 ml) was given 5 minutes before, with and 10, 20 and 30 minutes after the administration of the suspension. The capsules were given with 200 ml of water. Subjects stayed at the laboratory during blood sampling and were given standardized meals. They were allowed to sit and walk around but not to lie down for periods of more than ten minutes.

Specimens Collected

Blood samples (5 ml) were collected in heparinized tubes via a plastic cannula inserted in a forearm vein at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5,

6, 7, 8, 9, 10, 11, 12 and 24 hours after the capsule dose and 10, 20, 30, 45 minutes and 1, 1.5, 2, 3 and 4 hours after the suspension dose. The plasma was stored at -70 degrees C until analyzed.

Urine was collected quantitatively over the 24-hour period following dosing in a 2 liter plastic bottle containing 60 ml 1M Na_2CO_3. The urine was then weighed and a 50 ml sample was stored at -20 degrees C until analyzed.

Bioanalytical Methodology

The plasma and urine samples were analyzed for omeprazole and hydroxy-omeprazole, respectively, at the Department of Analytical Chemistry at AB Hassle using HPLC methods as in previous studies. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 50-100 nmole/L with a RSD of 10-15%, the limit of determination of hydroxy-omeprazole in urine was 200 nmole/L), linear (omeprazole in plasma was 50 nmole/L-100 micromole/L, hydroxy-omeprazole in urine was 200 nmole/L-50 micromole/L) and reproducible. The intra-day CV's of the standard curves were 6.6% for 100 nmole/L and 0.5% for 4,100 nmole/L for omeprazole in plasma and 1.2% for 10 micromole/L and 1.5% for 100 micromole/L for hydroxy-omeprazole in urine. The mean intra-day CV of single concentration standard sets were 1.7% (range 0.6-3.4%) for omeprazole in plasma and 2.0% (range 1.9-2.1%) for hydroxy-omeprazole in urine. The mean CV of inter-day quality control samples were 3.5% (range 95-112% of recovered spike) for omeprazole in plasma and 2.8% (range 89.5-93.5% of recovered spike) for hydroxy-omeprazole in urine.

Pharmacokinetic Analytical Methodology

The AUC was calculated from zero time to Cp-last by the trapezoidal rule. In the experiment with the suspension, the area from 240 minutes to infinity was calculated as Cp-last divided by the terminal slope of the plasma concentration curve. The slope and terminal half-life was calculated by log-linear regression of the plasma concentrations measured between 60 and 240 minutes after drug administration. Comparison between BOG II and BOG III with respect to AUC, Cp-max and Tmax was made by Wilcoxon's matched-pairs signed-ranks test. Differences were regarded as statistically significant if p was less than or equal to 0.05. The coefficient of correlation between AUC for omeprazole and the 24 hour urinary excretion of hydroxy-omeprazole was calculated and statistically evaluated using Student's t-test.

Results

For the suspension, the terminal half-lives ranged between 29 and 80 minutes with a mean of 45 minutes. There was considerable variability in the data, with 7 out of 12 subjects having a higher AUC value with BOG III than with BOG II. The mean urinary excretion of hydroxy-omeprazole was 21.5, 14.6 and 14 micromol/24 hour after dosing with suspension, BOG II and BOG III, respectively. The following table summarizes the Cp-max, Tmax and AUC after the three experiments:

Formulation	Cp_{max} (µmol/l)	T_{max} (min)	AUC (µmol h/l)		
	Mean±SEM	Median	Mean±SEM	Range	% of suspension
Buffered suspension	5.59±0.623	20	6.14±1.41	1.82-18.2	-
ECG II	1.09±0.330	120	4.21±1.05	1.24-13.8	67.4
ECG III	2.37±0.408	90	4.43±1.03	0.915-13.1	71.1

Sponsor's Conclusions

1. There were no statistically significant differences between the ECG formulations regarding AUC and Tmax.

2. Cp-max was significantly higher after administration of ECG III compared to ECG II.

3. There was no statistically significant correlation between the urinary excretion of hydroxy-omeprazole and plasma AUC, irrespective of the formulation ($r=0.15$, $p>0.1$)

4. The mean AUC with the suspension was in agreement with those found in previous studies (4.38-6.41 micromol*h/l). The mean AUC with ECG II was also similar to that found in an earlier study (4.3 micromol*h/L). However, the mean relative bioavailability was higher in that study compared to the present one (86 and 67%, respectively).

5. Minor deviations outside the reference range of some laboratory values were observed, however, they were considered to be of no clinical significance.

COMMENTS

1. The sponsor stated that the AUC with formulation ECG II was similar to that found in an earlier study (report I-211). Since reference to this earlier study is supportive to the present study, the sponsor should explain why that study (report I-211) was not included with the submission.

2. In the study report subjects are referred to by their initials, however, there is no cross-reference provided between subject initials and subject numbers. This makes almost impossible any accurate attempt to correlate laboratory values outside the reference range with outlier pharmacokinetic parameters. For example, subject BS had increased total and conjugated S-bilirubin and subject 2 had urinary excretion of hydroxy-omeprazole 83%, 2% and 26% of the mean after solution, ECG II and ECG III respectively. If subject BS is subject 2, then an examination of abnormal bilirubin level relationship to altered metabolism or urinary excretion may be warranted.

3. The sponsor stated that the Cp-max differences between BCG II and BCG III may have been due to chance rather than to a "true" difference between formulations since the true peak may have been missed owing to the relatively long interval between the sampling occasions. This reasoning may also be applied to the comparison of AUC's, where the sponsor concluded that there were no statistically significant differences in AUC between BCG II and BCG III, and a different sampling interval may have resulted in significantly different AUC's.

4. Dissolution information (in summary format) for the capsule dosage forms used in this study was provided in the Summary section of the Human Pharmacokinetics and Bioavailability Data section. The BCG II dosage form (not encapsulated) had a mean acid resistance of 87% and 88% dissolved in 10 min and the BCG III dosage form had a mean acid resistance of 96% and 85% dissolved in 15 min.

5. The sponsor utilized a nonparametric statistical test to examine the significance of differences but provided no justification or explanation for their choice of test.

6. The results of ANOVA test with comparison of means by Duncan's Multiple Range Test indicated that the means of AUC's of the BCG II and BCG III formulations are not significantly different. However, the two formulations can not be declared equivalent because the lower 90% CI (% of reference mean with BCG II as reference) was 85.4% and the upper 90% CI was 122.2%. Results of ratio analysis indicated that 16% (2 of 12) fell outside the 75-125 range.

7. The results of ANOVA test with comparison of means by Duncan's Multiple Range Test indicated that the means of Cp-max's of the BCG II and BCG III formulations were not significantly different. However, the two formulations can not be declared equivalent because the lower 90% CI (% of reference mean with BCG II as reference) was 87% and the upper 90% CI was 158.2%. Results of ratio analysis indicated that 50% fall outside the 75-125 range.

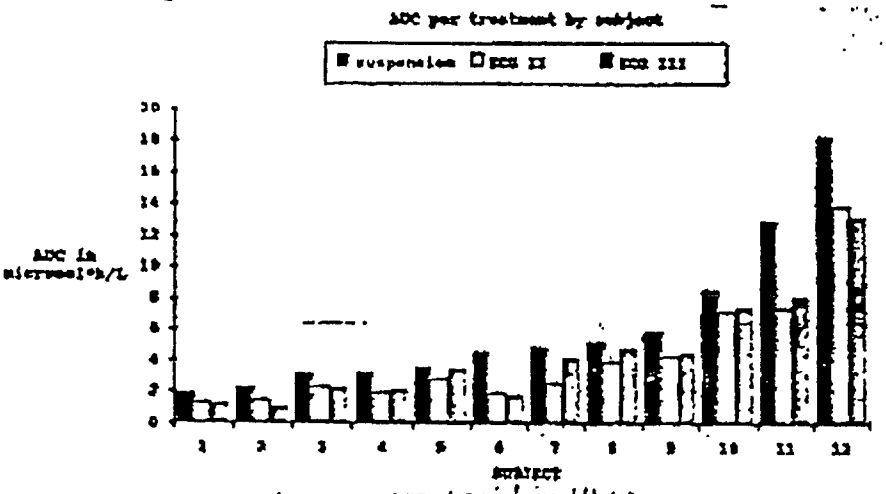
8. The results of ANOVA test with comparison of means by Duncan's Multiple Range Test indicated that the means of Tmax's of the BCG II and BCG III formulations were significantly different. The lower 90% CI (% of reference mean with BCG II as reference) was 58.1% and the upper 90% CI was 92.1%. Results of ratio analysis indicated that 58% (7 of 12) fell outside the 75-125 range.

9. The sponsor did not present an analysis of the differences in urinary excretion of hydroxy-omeprazole. The results of ANOVA test with comparison of means by Duncan's Multiple Range Test indicated that the means of urinary excretion of hydroxy-omeprazole of the BCG II and BCG III formulations were not significantly different. However, the two formulations can not be declared equivalent because the lower 90% CI (% of reference mean with BCG II as reference) was 66.3% and the upper 90% CI was 126.5%. Results of ratio analysis indicated that 75% (9 of 12) fell outside the 75-125 range.

10. ANOVA testing also indicated significant differences between the different sequences of dosage form administration. The sequence of

suspension-ECG II-ECG III had nearly twice the mean AUC and Cp-max of the next highest sequence. The sequence of ECG II-ECG III-suspension had mean urinary excretion of hydroxy-omeprazole nearly 1/3 of the next highest sequence. This potential sequence effect may warrant further investigation.

11. As in previous studies, multimodal disposition characteristics may be evident. As shown in the chart below, intra-subject variability was fairly low, however, only 1-3 subjects contributed to the relatively large inter-subject variability. This finding may be highly contributory to the significant sequence effect.



12. The mean relative bioavailabilities (F) with ECG II and ECG III compared to the buffered suspension were not significantly different (p=0.37) when compared by paired T-test.

13. Re-analysis of the data with exclusion of subject 10 (judged to be a potential outlier) did not result in any significant change from the statistical conclusions of Comments 6-9 above.

14. A conclusion of bioequivalence (as concluded by the sponsor) between formulations ECG II and ECG III may not be valid. Even though, statistical tests showed that the means of AUC, Cp-max and urinary excretion were not significantly different, a declaration of bioequivalence cannot be made. Subsequently, the pivotal clinical studies in which ECG II was used (I-260, I-403 and I-406) must be evaluated in that light. However, since on average, the ECG III dosage form resulted in slightly higher AUC and Cp-max, the lack of bioequivalence may not have a major impact on the results of clinical studies.

XV. Study 12. (Study Code I-316)

Title:

Bioavailability of Omeprazole. Comparison Between the Enteric-Coated Formulation Used in Phase III Clinical Studies and the Intended Market

Formulation (N.B. See Summary Comment No. 10 for clarification of actual market formulation.)

Objective

To compare the bioavailability under fasting conditions of omeprazole from two formulations of enteric-coated (EC) granules (market and phase III formulations, respectively).

Drug Dosage Forms Used

Hard gelatin capsules containing 20 mg omeprazole as EC granules.

Phase III formulation	Batch No. H 431-7-7
Market formulation	Batch No. H 431-9-1

Clinical Investigator and Study Site

Per Lundborg, MD

Dept of Clinical Pharmacology
AB Hässle
S-431 83 MÖLNDAL
Sweden

Study Protocol

Twenty healthy male subjects with a median age of 25 years (range 22-29 years), median weight of 78 kg (range 68-87 kg) and median height of 184 cm (range 175-194 cm) were enrolled in and completed the study. All inclusion and exclusion criteria were met except for the inclusion criteria of weight being 66-86 kg (subject 11 was 87 kg). Each subject participated in a two-period crossover experiment with a single dose of 20 mg omeprazole given alternatively in the [illegible] two dosage forms. The experimental order was randomized using complete randomized block design and the experiments were carried out double-blind at intervals of at least seven days. After an overnight fast (about 10 hours), one capsule was administered with a glass of water (150 ml). Subjects stayed at the laboratory for 12 hours. They were allowed to sit and walk around but not to lie down for periods longer than 10 minutes. Standardized meals were served 2.5, 6 and 10 hours after dosing.

Specimens Collected

Blood samples (5 ml) were collected (in heparinized tubes) from a forearm vein via a plastic cannula prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after dosing. The plasma was separated and stored at -20 degrees C until analysis.

Bioanalytical Methodology

Plasma samples were analyzed for omeprazole at the Department of Bioanalytical Chemistry at AB Hässle, using HPLC as in previous studies. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 20-50 nmole/L with a RSD of 10-15%), linear

(20 nmols/L-100 micromols/L) and reproducible. The intra-day CV's of the standard curves ranged from 0.0-5.4% and 0.1-0.8%. The mean intra-day CV of single concentration standard sets was 1.3% (range 0.3-2.9%) and the mean CV of inter-day quality control samples was 3.0% (range 94-106% of recovered spike).

Pharmacokinetic Analytical Methodology

The AUC was calculated from the time of dosing to Cp-last by the trapezoidal rule. AUC was assumed to be lognormally distributed and 90% confidence limits for the expected values of the logarithms of AUC were constructed. These were then transformed to 90% confidence intervals in the original scale. Cp-max and Tmax were not statistically evaluated since the time intervals between blood samples were too long to allow for any accurate estimation of these variables.

Results

		Market form	Phase III form
Cp-max (micromol/L)	median range	0.43	0.46
Tmax (h)	median range	1.5	1.5

			GC granules market formulation	GC granules phase III formulation
AUC (µmol/l)	Geometric	mean	[illegible] (A)	[illegible] (B)
	90% conf. for geometric mean	interval	[illegible]-[illegible]	[illegible]-[illegible]
	Range			
	[illegible]		1.007	
	90% conf. for [illegible]	interval	[illegible]-1.21	
[illegible]*	Geometric	mean	[illegible] (A)	[illegible] (B)
	90% conf. for geometric mean	interval	[illegible]-[illegible]	[illegible]-[illegible]
	[illegible]		[illegible]	
	90% conf. for [illegible]	interval	[illegible]-1.13	

* [illegible] without patient 19

One subject (No. 10) showed an extreme variation in AUC values between the two formulations and the AUC data were analyzed with and without that subject.

Sponsor's Conclusions

1. There was no difference in bioavailability of omeprazole when given either as EC granules market formulation or as EC granules phase III formulation. Thus the two formulations can be regarded as bioequivalent.

Comments

1. Dissolution information (in summary format) for the capsule dosage forms used in this study was provided in the Summary section of the Human Pharmacokinetics and Bioavailability Data section. The EOG III dosage form had a mean acid resistance of 91% and 90% dissolved in 30 min and the market formulation (LOSEC) had a mean acid resistance of 93% and 90% dissolved in 30 min.

2. The limit of determination for omeprazole in plasma was reported as being 20-50 nmole/L. Numerous plasma concentrations below 50 nmole/L were reported in the table of individual plasma concentrations. The calculations of AUC based on the numerous plasma concentrations at or below the limit of determination of the assay, introduces some uncertainty in the reported AUC values which were then used for a determination of bioequivalence.

3. The results of ANOVA test of untransformed AUC values indicated that the means of AUC's of the EOG III and market formulations were not significantly different due to formulation effect. However, the two formulations can not be declared bioequivalent because the lower 90% CI (% of reference mean with EOG III as reference) was 89% and the upper 90% CI was 134%. Results of ratio analysis indicated that 40% fell outside the 75-125 range. Analysis of the data with the exclusion of subject 10 (a clear outlier as justified by the sponsor) indicated that the two formulations could be declared bioequivalent. However, ratio analysis indicated that 37% still fell outside the 75-125 range. Analysis of the AUC data after log transformation resulted in similar results.

4. Analysis of Cp-max and Tmax values resulted in similar results as in the previous comment.

5. A conclusion of bioequivalence (as concluded by the sponsor) between formulations EOG III and LOSEC (market formulation) may not be valid. Subsequently, the pivotal clinical studies in which EOG III was used must be evaluated in that light since it appears that the market formulation was not utilized in any pivotal clinical studies. However, since on average, the market formulation dosage form resulted in slightly higher AUC and Cp-max, the lack of bioequivalence may not have a major impact on the results of clinical studies.

Purged

purged

XVII. Study 14. (Study Code I-270/281)

Title:

Pharmacokinetic study of omeprazole in elderly healthy subjects

Objective

The aim of these investigations was to study the pharmacokinetics of omeprazole and its metabolites in elderly healthy subjects.

Drug Dosage Forms Used

a. Buffered oral solution - 40 mg omeprazole (radioactivity of 20 microCi in study I-270), 8% PEG 400, 8 mmol $NaHCO_3$ in a total volume of 50 ml. Batch Nos. H 404-4-2 and H 404-6-1.
b. IV solution - 20 mg omeprazole (radioactivity of 20 microCi in study I-270) and 40% PEG 400 in 10 ml of a sterile sodium bicarbonate solution. Batch Nos. H 395-4-2 and H 395-3-3.
The sodium bicarbonate solutions used had Batch Nos. H 322-2-16, H 322-2-19, H 397-4-1 and H 397-4-5.

Clinical Investigator and Study Site

Sten Landahl, MD
Department of Geriatric and Longterm care Medicine
Clinic IV
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Sweden

Study Protocol

This study, a randomized, open cross-over, was a combination of two separate studies with similar protocols, the only difference was the use of tagged omeprazole in study I-270. Fifteen elderly healthy subjects (9 in study I-270 and 6 in study I-281) were enrolled but only fourteen completed the study. The 14 completing the study (6 male and 8 female) had a median age of 76 years (range 75-79), median weight of 71 kg (range 58-88) and a median height of 163 cm (range 151-190). All inclusion and exclusion criteria appeared to have been met.

Alcohol and all medication, including OTC drugs, were not allowed for 2 days prior to and during each experiment. After at least a 10 hour fast, subjects were administered either the IV (via a cannula in a forearm vein) or the oral preparation together with several 50 ml portions of sodium bicarbonate. While the subjects remained in the laboratory, standardized meals were served. All subjects remained recumbent for the first 3 hours of each experiment. There was a 7 day washout period between treatments.

Specimens Collected

I-270: Blood samples (8 ml) were collected in heparinized tubes prior to and 5, 7, 11, 15, 20, 25, 30, 40 minutes and 1, 1.5, 2, 4, 6, 8, 12 and 24 hours after the start of IV infusion. The 7 minute sample was omitted when omeprazole was given orally. After at least 5 minute cooling and centrifugation for 10 minutes, the plasma was transferred to plastic tubes and stored at -20 degrees C until analysis.
Urine was collected (in plastic bottles containing 1M $NaHCO_3$ as buffer to pH>7) in the following intervals: 0-3, 3-6, 6-9, 9-12, 12-24, 24-48, 48-72 and 72-96 hours. The volumes were recorded and 50 ml aliquots were stored frozen for subsequent analysis.

I-281: Blood samples (5 ml) were collected similar to study I-270 except for the omission of the 12 and 24 hour sample and the inclusion of a 10 hour sample.

Bioanalytical Methodology

In study I-270, the concentrations in plasma of omeprazole, the hydroxy-, sulphone and sulphide metabolite were determined by an HPLC method similar to ones used in previous studies (analytical site was not specified). The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole, hydroxy-omeprazole and omeprazole sulphone in plasma was 50 nmole/L with a relative standard deviation of less than 10-15% and for hydroxy-omeprazole in urine was 200 nmole/L), linear (plasma method was 50 nmole/L-100 micromole/L and urine method was 200 nmole/L-120 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole, hydroxy-omeprazole and omeprazole sulphone in plasma and hydroxy-omeprazole in urine were 1.6 and 4.5%, 2.5 and 4.4%, 3.8 and 5.5% and 1.6 and 1.7% respectively. The mean intra-day CV of single concentration standard sets was 2% (range 0.5-4.2%) and the mean CV of inter-day quality control samples was 3.1% (range 98-107% of recovered spike) for omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 4.6% (range 3.1-6.9%) and the mean CV of inter-day quality control samples was 3.5% (range 93.5-107% of recovered spike) for hydroxy-omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 3.4% (range 2.0-6.5%) and the mean CV of inter-day quality control samples was 4.9% (range 95.5-113% of recovered spike) for omeprazole sulphone in plasma. The mean intra-day CV of single concentration standard sets was 2.6% (range 1.2-5.7%) and the mean CV of inter-day quality control samples was 2% (range 96.5-102% of recovered spike) for hydroxy-omeprazole in urine. Assay validation for the detection of the sulphide metabolite in plasma was not included with the report.
Total radioactivity was determined in 0.5 ml of plasma or urine after

addition of 10 ml of a liquid scintillator and counting in a Beckman LS 3800 with correction for quenching made by external standardization.

In study I-281, the concentrations in plasma of omeprazole were determined by an HPLC method similar to ones used in previous studies (analytical site was not specified). The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 15-20 nmole/L with a relative standard deviation of less than 10-15%), linear (15 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves were 0.0-5.4% and 0.1-0.8%. The mean intra-day CV of single concentration standard sets was 2.8% (range 1.1-4.3%) and the mean CV of inter-day quality control samples was 5.3% (range 95-106.5% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Analytical Methodology

The pharmacokinetics of omeprazole following IV administration were evaluated according to a 2-compartment model and by modal independent methods. The coefficients (A, B) and exponents (alpha, beta) were derived in each individual by non-linear regression analysis using ESPIT (Ver 4.1) on a Digital VAX 11/780 computer. The total area under the plasma concentration-time curve was calculated according to:

$$AUC_{iv} = A/alpha + B/beta$$

The total plasma clearance was calculated as:

$$CL = dose_{iv}/AUC_{iv}$$

The volume of distribution in the central compartment and the apparent volume of distribution at equilibrium were calculated as:

$$V_c = dose_{iv}/(A + B) \text{ and } V_{beta} = CL/beta$$

The t1/2 of omeprazole and of hydroxy-omeprazole following the oral dose were calculated by linear regression analysis of the log plasma concentration curve between 1 hour and the last determinable plasma concentration (except in subjects I-270-3, -5 and -10 where 1.5 hours to Cp-last was used). For the sulphone, from 2 hours to Cp-last was used except for subjects I-270-3, -5 and -10 where 6 hours to Cp-last was used.

For the oral dose, the AUC of omeprazole, hydroxy-omeprazole, the sulphone and the total pool of metabolites were determined by the trapezoidal rule and extrapolation to infinity by dividing the Cp-last by beta.

Systemic availability of the oral dose was calculated as:

$$F = (AUC_{oral}/AUC_{iv})(dose_{iv}/dose_{oral})$$

The t1/2 of urinary excreted metabolites was calculated by linear regression analysis of the individual log excretion rate-time curves from 18-84 hours.

Results

1. Subject I-270-8 was withdrawn from the study when she developed psoriasis-like dermal changes which started three days after the first omeprazole administration (40 mg orally). No connection between the dermal changes and omeprazole administration was found.

2. No determinable plasma concentrations of the sulphide metabolite were found and the sulphone and sulphide were below determinable concentrations in the urine.

3.

Table 3. Individual disposition characteristics of omeprazole calculated from plasma levels following a single i.v. administration (20 mg) to 14 elderly healthy subjects.

Subject No.	b (min⁻¹)	c (μg/ml)	AUC_0 (h)	AUC_∞ (h)	$t_{1/2}$ (h)	$t_{1/2}$ (h)	CL_T (ml/min)	MRT (min)
I-270								
8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
I-281								
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

4.

Table 3. Individual absorption and disposition characteristics of omeprazole calculated from plasma levels following a single oral administration (40 mg) to 14 elderly healthy subjects.

Subject No.		t_{max} (h)	C_{max} (μmol·l⁻¹)	$t_{½}$ (h)	AUC (μmol·l⁻¹·h)	F
[illegible]	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
[illegible]	Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SDM	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	Median	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
[illegible]	Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SDM	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	Median	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* [illegible] calculated between [illegible] and [illegible]

5.

Table 4. Individual kinetic parameters of hydroxyomeprazole calculated from plasma levels following single i.v. and oral administrations of 20 and 40 mg omeprazole, respectively, to eight elderly healthy subjects.

Subject No.	i.v. dose				oral dose			
	t_{max} (h)	C_{max} (μmol·l⁻¹)	$t_{½}$ (h)	AUC (μmol·l⁻¹·h)	t_{max} (h)	C_{max} (μmol·l⁻¹)	$t_{½}$ (h)	AUC (μmol·l⁻¹·h)
1								
2								
3								
4								
5								
6								
7								
8								
Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SDM	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Median	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* [illegible] calculated from [illegible] and [illegible]

6.

Table 5. Individual kinetic parameters of the sulphone calculated from plasma levels following single i.v. and oral administrations of 20 and 40 mg omeprazole, respectively, to eight elderly healthy subjects.

Subject No.	i.v. dose				oral dose			
	t_{max} (h)	C_{max} (mg·l⁻¹)	$t_{½}$ (h)	AUC (mg·l⁻¹·h)	t_{max} (h)	C_{max} (mg·l⁻¹)	$t_{½}$ (h)	AUC (mg·l⁻¹·h)
1								
2								
3								
4								
5								
6								
7								
8								
Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Median	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* [illegible]

7.

Table 6. Individual kinetic parameters of the total pool of radioactive metabolites following single i.v. and oral administrations of 20 and 40 mg omeprazole, respectively, to eight elderly healthy subjects.

Subject No.	i.v. dose				oral dose			
	t_{max} (h)	C_{max} (mg·l⁻¹)	AUC (mg·l⁻¹·h) 0-36 h	AUC (mg·l⁻¹·h) 0-48	t_{max} (h)	C_{max} (mg·l⁻¹)	AUC (mg·l⁻¹·h) 0-36 h	AUC (mg·l⁻¹·h) 0-48
1								
2								
3								
4								
5								
6								
7								
8								
Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Median	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

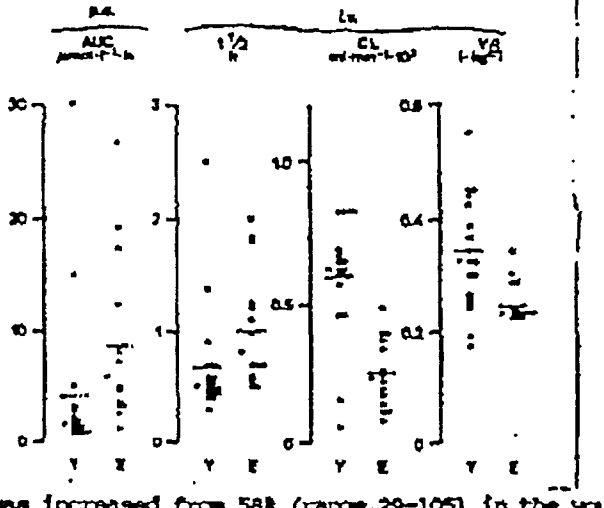
8. Unchanged omeprazole was not found in the urine.

9. The mean cumulative excretions (of total radioactivity), as per cent of given dose, were 68 (range [redacted]) and 68 (range [redacted]) following the IV and oral doses, respectively. The excretion rate declined in a bi-exponential fashion with a mean t1/2 of the terminal phase of 13.3 h (range [redacted]) and 13.1 h (range [redacted]) following IV and oral administration respectively.

10. The mean cumulative excretions (of hydroxy-omeprazole), as per cent of given dose, over the 24 h collection period were 8.2 (range [redacted]) and 9.9 (range [redacted]) following the IV and oral doses, respectively.

11. A comparison of pharmacokinetic parameters was made between this study and studies I-208 and I-225 (with 18 young healthy subjects). The comparisons of the pooled data is depicted in the figure below:

Figure 7. Pharmacokinetic parameters of omeprazole in the elderly (E) compared to those in young healthy subjects (Y). Horizontal bars indicate mean values and asterisks indicate median values.



12. The mean F was increased from 58% (range 29-105) in the young to 76% (range 33-104) in the elderly, suggesting that the first pass elimination of the drug is decreased in the elderly.

13. The t1/2 of hydroxy-omeprazole and the sulphone metabolite were prolonged by 50% when compared to those in the young healthy, following both IV and oral dosing. The AUC values for hydroxy-omeprazole and the sulphone, following oral dosing were increased 2.5- and 3-fold, respectively, compared to those in the young.

14. The amount of total radioactivity excreted in the urine, as per cent of given dose, was decreased by approximately 10% in the elderly compared to that of young subjects, indicating a somewhat impaired urinary

excretion capacity in the elderly.

Sponsor's Conclusions

1. Omeprazole was completely metabolized since no unchanged drug was recovered in the urine.

2. Inspection of the individual data from study I-270 indicates that 3 subjects (I-270-3, -5 and -10) can be classified as "slow metabolisers" of omeprazole. These subjects differed from the others with respect to F, t1/2, CL and AUC of omeprazole and some parameters of the metabolites.

3. The results of this study compared to similar data in young subjects suggest that pre-systemic and systemic elimination of omeprazole are reduced in the elderly. The average metabolic capacity of the elderly for omeprazole and two of its identified metabolites is decreased compared to young healthy individuals.

Comments

1. The sponsor's pooling of studies I-270 and I-281 may not be warranted. Even though the same investigator conducted the study at the same site with nearly an identical protocol, there was more than two years span of time between the two studies.

2. The sponsor's method for performing a study on the comparison between young and elderly subjects is not the preferred method to meet their objectives. Data were pooled from two previous studies (I-208 and I-225) which had utilized young healthy male subjects receiving, in some cases, different doses of omeprazole. The data were pooled and used as the basis of comparison to show the differences in pharmacokinetic parameters in elderly males and females.

3. The results and subsequent conclusions of this study are indicative of differences in the pharmacokinetics of omeprazole between young and elderly healthy subjects. However, it must be realized that this study utilized an intravenous and an oral solution as the dosage forms upon which to form a comparison between young and old subjects. There is no assurance that the differences observed in this study would be less, greater or the same if the actual market formulation were used. This is based on the fact that rate of input appears to have an impact on bioavailability. Furthermore, since no statistical evaluations appeared to have been performed with the data, it can not be assumed that the differences are statistically significant.

4. A model dependent method was used to calculate the pharmacokinetic parameters after IV dosing making them only as reliable as the estimates of A, B, alpha and beta. In study I-225 there was large variability associated with the aforementioned estimates (%CV's ranged from 26-114). The reliability (goodness-of-fit) of modeling was omitted from the study report.

5. The validation report of the assay included intra-day CV's of the standard curves used for the analysis of plasma and urine samples. The information provided appeared to show that only two points were used in

the standard curves which would render all samples assayed with such a standard curve suspect to gross inaccuracies.

6. The sponsor should explain why the experiments on one subject in study I-270 were performed 3 months after the rest of the subjects in that study and why a similar delay in completing the study occurred in study I-281.

7. There appears to be a discrepancy, or at the least an item warranting some explanation, in the plasma level data (IV dose) of subject I-270-1. The first measured time point had a value of 2810 nmol/L of omeprazole and a total radioactivity equivalent of 8080 nmol/L. This resulted in a total metabolite equivalent of 5270 nmol/L which was nearly an order of magnitude greater than the other subjects.

8. Serum bilirubin levels were decreased in 12 of 14 subjects. A medical officer should evaluate if this laboratory finding may be of significance.

XVIII. Study 15. (Study Code I-336)

Title:

Comparison between the effects of intravenous and oral omeprazole on pentagastrin-stimulated gastric acid secretion in duodenal ulcer patients in remission

Objective

To study the effects of repeated once-daily administration of oral and IV omeprazole on pentagastrin-stimulated gastric acid secretion in duodenal ulcer patients in remission. (NOTE: The pharmacodynamic aspects of this study will not be detailed in this review.)

Drug Dosage Forms Used

a. Hard gelatin capsules containing 20 mg enteric coated granules of omeprazole. Batch No. H 431-7-14

b. The intravenous formulation consisted of an ampul with lyophilized omeprazole sodium (42.6 mg) and EDTA (1.5 mg). Immediately before use, the lyophilized drug was mixed in a commercially available infusion bag containing 100 ml of 0.9% NaCl. The final solution contained 0.4 mg omeprazole/ml, and was infused over 30 minutes, 25 ml for the 10 mg dose and 100 ml for the 40 mg dose. Batch No. H705-1-3

Clinical Investigator and Study Site

Tore Lind, MD

Sahlgrenska Hospital
Department of Surgery II
S-413 45 GOTEBORG
Sweden

Study Protocol

Eight patients (7 male and 1 female) with a median age of 69 years (range 47-77), median weight of 77.5 kg (range 60.5-97.5) and a median height of 181 cm (range 161-187) were enrolled in and completed the study. All patients had a history of active duodenal ulcer disease within the previous 24 months, but were otherwise regarded as healthy. This study was conducted as an open cross-over trial. Each patient was randomly assigned and participated in two study periods, either 5 or 6 days, that were separated by at least 16 days of washout. In one study period 20 mg omeprazole was given orally once daily for 5 days followed by an IV dose of 10 mg on the sixth day. In the other study period 40 mg omeprazole was given intravenously once daily for 5 days. Gastric secretion tests including pentagastrin stimulation was performed starting 5.5 hours after administration of the first and fifth dose of 40 mg IV and 20 mg oral omeprazole and also 5.5 hours after the 10 mg IV dose. Control experiments were also performed.
The patients were requested to refrain from taking any alcohol during the two days prior to and during the control experiment and each study period. None of the patients received any antisecretory drug during the week prior to and during the study.
Study day 1: After at least a 10 hour fast, patients were given either 20 mg orally or 40 mg IV of omeprazole. A standardized breakfast and a standardized liquid "meal" were given 0.5 and 3.5 hours respectively after dosing.
Study days 2-4: Patients either came to the laboratory in the morning for the daily dose of 40 mg IV omeprazole or took the daily dose of 20 mg omeprazole orally at home.
Study day 5: Same as day 1.
Study day 6 (only after 5 days of oral dosing): The same as day 1 except the dose was 10 mg omeprazole IV.

Specimens Collected

Blood samples (5 ml) for the analysis of omeprazole in plasma were collected in heparinized tubes at the following times after dosing:
oral: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6 and 7 hours
IV: 10, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 240, 300, 360 and 420 minutes. After cooling the sample and centrifugation for 10 minutes, the plasma was transferred to plastic tubes and stored at -20 degrees C. until analysis.

Bioanalytical Methodology

The samples were analyzed for omeprazole at the Department of Bioanalytical Chemistry at [redacted] using similar HPLC methods as in previous studies. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 20-25 nmole/L with a relative standard deviation of less than 10-15%), linear (20 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves were 0.5-7.8% and 0.5-10.0%. The mean intra-day CV of single concentration standard sets was 1.6% (range 0.6-4.0%) and the mean CV of inter-day quality control samples was 3.7% (range 95.5-109.5% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Analytical Methodology

T1/2 of IV omeprazole was determined from the individual regression lines of the log plasma concentration curve during the elimination phase. The AUC was calculated using the trapezoidal rule and in the case of IV dosing, the area was extrapolated to infinity (Cp-last X (t1/2/0.693)). Bioavailability and clearance were calculated as:

$$F = (AUC_{oral}/2 \times AUC_{10\ mg\ iv})$$

and

$$CL = dose/AUC$$

Wilcoxon matched pairs signed rank test was used in the statistical evaluation with a p-value of less than or equal to 0.05 being significant.

Results

Table III. Area under the plasma omeprazole concentration-time curve (AUC, umol·h/l) and bioavailability (F, %).

	AUC					F	
Pat	20 mg po		10 mg iv	40 mg iv		20 mg po	
No	day 1	day 5	day 6	day .	day 5	day 1	day 5
1							
2							
3							
4							
5							
* 6							
7							
8							
Geom mean	0.81	1 35	1.33	4.74	7.60	34	38
95% conf							
lower/upper	0.43/1 52	0.77/3.11	0.96/1.82	3.35/4.79	4.90/11.8	27/53	26/53

* excluded from analysis

The increase in AUC (between day 1 and day 5) after 5 days of oral dosing was significant (p=0.0117) as was the increase in AUC (between day 1 and day 5) after 5 days of IV dosing (p=0.0117).

Table IV. Clearance of omeprazole (ml/min).

Pat No	10 mg iv day 5	40 mg iv day 1	40 mg iv day 5
1			
2			
3			
4			
5			
6			
7			
8			
Geom mean	361	407	253
95% conf int	493/267	564/294	383/168

* excluded from analysis

Table V. Terminal half-life of omeprazole (h) following iv-administration.

Pat No	10 mg iv day 5	40 mg iv day 1	40 mg iv day 5
1			
2			
3			
4			
5			
6			
7			
8			
Geom mean	0.71	0.76	0.94
95% conf lower/upper	0.47/1.06	0.56/1.04	0.60/1.48

* excluded from analysis

The decrease in systemic clearance (between day 1 and day 5) after 5 days of IV dosing was significant (p=0.0117) as was the increase in terminal half-life (p=0.028).

Sponsor's Conclusions

1. During repeated once-daily oral dosing administration of 20 mg omeprazole the level of acid inhibition markedly increases.

2. The degree of acid suppression after both oral and IV administration was in this study somewhat higher than that seen in young normals.

3. An IV-dose of 40 mg produced on day 1 a similar degree of acid inhibition as that seen after 5 days of oral treatment. However, a 10 mg IV dose could essentially maintain the degree of acid suppression reached after 5-days of oral treatment.

4. The omeprazole AUC was similar after 10 mg IV to that after the fifth 20 mg oral dose.

5. There is an increased omeprazole AUC during repeated once daily administration of omeprazole enteric coated granules. This is due to a decreased presystemic clearance from decreased acid exposure of the oral dose and/or decreased first pass metabolism.

6. There is decreased systemic clearance during repeated IV administration of 40 mg. This could be due to a change from linear to non-linear kinetics of subsequent IV doses because of an inhibition of omeprazole's own metabolism.

7. The lack of significant difference in clearance between 10 mg IV, given at the end of the oral treatment period, and the first 40 mg IV dose suggest that the systemic clearance was unchanged during oral treatment and that the increase in F is a true change in the amount systemically available after oral dosing.

Comments

1. Dissolution data for the oral dosage form used in this study was not provided with the study report.

2. The tabulated summary data indicated that subject 1 was excluded from analysis, however, the table of individual plasma concentrations indicated that subject 2 was not included in the statistical evaluation. There was no explanation provided as to why subject 1 (or was it subject 2) was excluded from the analysis.

3. The individual plasma concentration data after oral dosing indicated an interesting phenomena which may warrant further investigation. Subjects 3 and 4 had omeprazole levels at 7 hours of 193 and 166 nmole/L respectively after the first oral dose. Both subjects had substantially lower levels several hours before the 7 hour level, with subject 3 having a level of 220 nmole/L before the levels dropped and subject 4 having a level of 301 nmole/L before the levels dropped. This occurred more markedly in subject 5 after the fifth day of oral dosing. Her 7 hour level was 182 nmole/L, which happened to be her Cmax, and none of her other levels were above 96 nmole/L. This may be indicative of biliary re-cycling or a change in absorption pattern of previously unabsorbed omeprazole.

4. The sponsor is encouraged to further investigate the strong relationship which appears to be evident between plasma concentrations of omeprazole (as ADC) and per cent inhibition of peak acid output. An established pharmacokinetic-pharmacodynamic relationship would solidify dosage recommendations and be extremely supportive to an intravenous dosage form NDA submission.

XIX. Study 16. (Study Code I-265) NOTE: This study was published in CPT Vol. 40, No.3, pp. 344-351, September, 1986.

Title:

Pharmacokinetic study of [^{14}C]-omeprazole in patients with impaired renal function

Objective

The aim of this investigation was to study the pharmacokinetics of [^{14}C]-omeprazole and its metabolites in patients with impaired renal function.

Drug Dosage Form Used

The oral solution used in this study (Batch No. E 404-4-1) was similar to that used in study 14 (study code I-270/281) with a concentration of 40 mg omeprazole and a radioactivity of 20 microCi in a total volume of 50 ml.

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The IV solution used (Batch No. H 395-4-1) was also similar to that used in study 14 with the final solution to be infused containing 20 mg omeprazole and a radioactivity of 20 microci in a total volume of 10 ml.

Clinical Investigator and Study Site

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Sweden

Study Protocol

This study was performed as an open cross-over with each patient participating in 2 experiments (IV and oral) in random order with at least a 9 day washout between experiments. Twelve patients (8 male and 4 female) with chronic renal insufficiency (creatinine clearance between 10-62 ml/min/1.73 m^2, normal range 70-160), with a median age of 60 years (range 33-70), median weight of 72 kg (range 49-95) and a median height of 174 cm (range 151-192) were enrolled in and completed the study. After at least a 10 hour fast, the IV or the oral dose was administered along with several aliquots of a sodium bicarbonate solution. All patients remained recumbent for the first 3 hours of each experiment and remained in the laboratory for about 12 hours, during which time 4 standardized meals were served.

Specimens Collected

Blood samples (8 ml) for assay of omeprazole, identified major metabolites and total radioactivity were collected in heparinized tubes prior to and 5, 11, 20, 30 and 40 minutes and 1, 1.5, 2, 4, 6, 8, 12 and 24 hours after dosing. The samples were handled as in previous studies.
Urine was collected 24 hours prior to the first experiment for determination of creatinine clearance, which was repeated prior to the second experiment. During the experiment, collection intervals were 0-3, 3-6, 6-9, 9-12, 12-24, 24-48, 48-72 and 72-96 hours. The urine was buffered to pH>7 during collection, the volumes recorded and a 50 ml aliquot frozen for later analysis.

Bioanalytical Methodology

The concentrations in plasma of omeprazole, the hydroxy-, sulphone and sulphide metabolites were determined by an HPLC method similar to ones used in previous studies (analytical site was not specified). The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole, hydroxy-omeprazole and omeprazole sulphone in plasma was 50 nmole/L with a relative standard deviation of less than 10-15% and for hydroxy-omeprazole in urine was 100 nmole/L), linear (plasma method was 50 nmole/L-100 micromole/L and urine method was 200 nmole/L-120 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole, hydroxy-omeprazole and omeprazole sulphone in plasma and hydroxy-omeprazole in urine were 1.6 and 4.5%, 2.5 and 4.4%, 1.8 and 5.5%

and 1.6 and 1.7% respectively. The mean intra-day CV of single concentration standard sets was 1.8% (range 0.5-4.9%) and the mean CV of inter-day quality control samples was 1.9% (range 98-104.5% of recovered spike) for omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 3.9% (range 1.7-6.4%) and the mean CV of inter-day quality control samples was 4.0% (range 98.5-115% of recovered spike) for hydroxy-omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 3.1% (range 1.6-10.0%) and the mean CV of inter-day quality control samples was 3.1% (range 95-106% of recovered spike) for omeprazole sulphone in plasma. The mean intra-day CV of single concentration standard sets was 4.5% (range 3.0-10.5%) for hydroxy-omeprazole in urine. Assay validation for the detection of the sulphide metabolite in plasma was not included with the report. Total radioactivity was determined in 0.5 ml of plasma or urine after addition of 10 ml of a liquid scintillator and counting in a Beckman LS 3800 with correction for quenching made by external standardization.

The binding of omeprazole to plasma proteins was determined by ultrafiltration. Five ml of plasma from each individual patient was equilibrated to 37 degrees C in a 10 ml test tube. A phosphate buffer (25 microl, ph>7.35) containing a mixture of ^{3}H-omeprazole (radiochem. purity 98%) and unlabelled omeprazole to give a final concentration of 2 micromol/ml, was added to the plasma. The specific radioactivity of ^{3}H-omeprazole was 25.2 GBq/mmol. One ml of plasma was transferred to each of 3 Amicon MPS-V ultrafiltration devices equipped with YMT membranes. The samples were centrifuged at 37 degrees C for 20 min, yielding approximately 100 microl of ultrafiltrate. The membrane binding was negligible. The resultant drug concentrations in plasma and ultrafiltrate were determined by liquid scintillation counting.

Pharmacokinetic Methodology

The analytical methods were very similar to those employed in study 14. Correlations between creatinine clearance and various calculated parameters of interest were determined by linear regression analysis with a p-value less than or equal to 0.05 being statistically significant.

Results

1. No determinable plasma concentrations of the sulphide were found.

2. The mean plasma protein binding of omeprazole in the 12 patients was 94.8% (range 93.7-96.3).

3. Individual and mean disposition characteristics of omeprazole calculated from plasma levels following a single IV 20 mg dose

Patient No	A ($\mu mol \cdot l^{-1}$)	B ($\mu mol \cdot l^{-1}$)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	V_C ($l \cdot kg^{-1}$)	V_β ($l \cdot kg^{-1}$)	CL ($ml \cdot min^{-1}$)	AUC ($\mu mol \cdot l^{-1} \cdot h$)
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	3.70	1.83	0.12	0.57	0.173	0.549	543	1.99
SEM	1.01	0.138	0.031	0.059	0.0137	0.0175	62.7	0.233

* Calculated as a one-compartment model.

4. Individual and mean absorption and disposition characteristics of omeprazole calculated from plasma levels after a single 40mg oral dose

Patient No	t_{max} (h)	C_{max} ($\mu mol \cdot l^{-1}$)	$t_{1/2}$ (h)	AUC ($\mu mol \cdot l^{-1} \cdot h$)	F
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	1.34	3.39	0.60	3.01	0.70
SEM	0.039	0.439	0.078	0.630	0.093

a) F.area over at 4 h excluded from the calculation of $t_{1/2}$.
b) $t_{1/2}$ calculated from 0.25 h and onwards.

5. Individual and mean kinetic parameters of hydroxy-omeprazole calculated from plasma levels after single 20 mg IV and 40mg oral doses

Patient No.	IV dose				oral dose			
	t_{max} (h)	C_{max} (mmol·l⁻¹)	$t_{1/2}$ (h)	AUC (mmol·l⁻¹·h)	t_{max} (h)	C_{max} (mmol·l⁻¹)	$t_{1/2}$ (h)	AUC (mmol·l⁻¹·h)
1								
2								
3								
4								
5								
6								
10								
11								
12								
Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

6. Individual and mean kinetic parameters of the sulphone metabolite calculated from plasma levels after single 20 mg IV and 40mg oral doses

Patient No.	IV dose				oral dose			
	t_{max} (h)	C_{max} (mmol·l⁻¹)	$t_{1/2}$ (h)	AUC (mmol·l⁻¹·h)	t_{max} (h)	C_{max} (mmol·l⁻¹)	$t_{1/2}$ (h)	AUC (mmol·l⁻¹·h)
1								
2								
3								
4								
5								
6								
10								
11								
12								
Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

7. Individual and mean kinetic parameters of the total pool of radioactive metabolites (total radioactivity conc. minus omeprazole conc.) after single 20 mg IV and 40mg oral doses

Patient No.	IV dose				oral dose			
	t_{max} (h)*	C_{max} (mmol·l⁻¹)	$t_{1/2}$ (h)	AUC (mmol·l⁻¹·h)	t_{max} (h)*	C_{max} (mmol·l⁻¹)	$t_{1/2}$ (h)	AUC (mmol·l⁻¹·h)
				0-12h 0-96h				0-12h 0-96h
1								
2								
3								
4								
5								
6								
10								
11								
12								
Mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* [illegible] for calculation of relative AUC is based on the p.o. dose.

8. Individual and mean cumulative excretions of radioactivity over 96 h as per cent of given dose after 20 mg IV and 40 mg oral doses

	Cumulative excretion (per cent)													
Pat. No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
i.v.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
p.o.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

9. The individual excretion rates of total radioactivity in urine plotted against the midpoint of the collection interval declined in a biexponential fashion following both routes of administration, with a mean t1/2 of the terminal phase corresponding to 19.5 (range [redacted]) and 16.0 (range [redacted]) h following IV and oral doses respectively.

10. Individual and mean cumulative excretions of hydroxy-omeprazole over 24 h, as per cent of given dose, after 20mg IV and 40 mg oral doses

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]												[illegible]	[illegible]
[illegible]												[illegible]	[illegible]

11. The accumulated 96-hour urinary excretion of radioactive metabolites was significantly related to creatinine clearance (IV: r=0.83; p<0.001, oral: r=0.84; p<0.001).

12. There was a correlation between the reciprocal of creatinine clearance and the AUC of the total pool of metabolites for the IV dose (r=0.82; p<0.01).

13. There was a negative correlation between creatinine clearance and clearance of omeprazole (r=-0.61; p<0.05, see Appendix II). This may have been due to an induction of the cytochrome P-450 system by the uremic state leading to an increased metabolic clearance.

14. There was a correlation between creatinine clearance and amount of hydroxy-omeprazole excreted over 24 h (IV: r=0.84; p<0.001, oral: r=0.89; p<0.001).

Sponsor's Conclusions

1. The disposition characteristics of omeprazole were unaltered in patients with chronic renal insufficiency compared to those of healthy subjects. The pharmacokinetic constants for intact omeprazole were within the range of those reported previously in young healthy subjects. The mean values of the derived pharmacokinetic parameters of the sulphone metabolite were almost identical to those of young healthy individuals. However, the capacity for urinary excretion of the metabolites was decreased in these patients.

2. The plasma levels of the total pool of radioactive metabolites were higher, 2-3 times, in patients with renal insufficiency than in young healthy subjects.

3. Omeprazole was completely metabolized since practically no unchanged drug was detected in urine.

4. The protein binding in renally impaired patients was not significantly different from six healthy subjects. The binding was not significantly correlated to the plasma concentration of albumin or of alpha$_1$-acid glycoprotein. The free fraction of omeprazole will probably increase, however, as the albumin fraction falls below the normal range.

5. The renal excretion of radioactivity was virtually complete 4 days

after dosing, which suggests that the metabolites are eliminated by alternative routes or retained for a sustained period of time in the body.

Comments

1. The sponsor's method (across study comparison) for evaluating the differences in pharmacokinetics of omeprazole between renally impaired patients and healthy subjects is not the preferred method to meet their objectives.

2. The results and subsequent sponsor's conclusions of this study suggest that the disposition characteristics of omeprazole are unaltered in renally impaired patients. However, the disposition of the hydroxy-metabolite appears to be different (mean AUC of 40 mg dose nearly tripled) and this may be further accentuated upon multiple dosing (for which no information was provided). Furthermore, it must be realized that this study utilized an intravenous and an oral solution as the dosage forms upon which to form a comparison between healthy and renally impaired patients. There is no assurance that similar results would occur if the actual market formulation were used. This is based on the fact that rate of input appears to have an impact on bioavailability. Additionally, no statistical evaluations were reported on the comparisons of pharmacokinetic parameters.

3. The assay validation report appeared to show that only two points were used in the standard curves which would render all samples assayed with such a standard curve suspect to gross inaccuracies. Furthermore, the limit of determination of hydroxy-omeprazole in urine was reported as 100 nmole/L but in the CPT reprint article the limit of determination was reported as 200 nmole/L. The sponsor should clarify the disparity.

XX. Study 17. (Study Code I-264) Abstract #600 At III World Conference on Clinical Pharmacology and Therapeutics, 1986

Title:

Pharmacokinetic study of [^{14}C]-omeprazole in patients with impaired hepatic function

Objective

The aim of this study was to study the pharmacokinetics of [^{14}C]-omeprazole and its metabolites in patients with impaired hepatic function

Drug Dosage Forms Used

The dosage forms and batch numbers were nearly identical to the ones used in study 16 (Study Code I-265).

Clinical Investigator and Study Site

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Study Protocol

This study was performed as an open cross-over study. Each patient participated in two experiments, one with an IV and one with an oral dose. The experiments were performed in random order with at least a 9 day washout between them. Eight patients with chronic liver disease were included in the study. The patients were grouped as being A, B or C according to Childs definitions of liver disease with A, B and C roughly corresponding to mild, moderate and severe liver failure, respectively. All patients except for numbers 10 and 11 were alcohol-cirrhotics, while patients 2 and 3 also had portosystemic shunts. The study protocol originally identified subject inclusion criteria with laboratory values of P-simplastin A less than or equal to 50% and/or bilirubin greater than or equal to 30 mmol/L. However, an amendment to the protocol indicated that this inclusion criteria was dropped because of the difficulty in recruiting patients for the study. This may account for the greater than 2 year span of time to complete a study with only eight subjects. Patient demographic data is below:

Patient No	Sex M/F	Age (years)	Weight (kg)	Degree of Liver Failure (A, B or C)	Creatinine (grams/day)	P-Simplastin A (ref. 80-120 mmol·l⁻¹)[1]	P-Bilirubin (ref. 3.4-21.0 mmol·l⁻¹)[1]	P-Albumin (ref. 35-50 g/l)[1]
2	M	48	78	A	10	88	34**	47*
3	F	61	63	B	0	107*	35	34*
5	M	50	84	C	5	92	14	37*
6	M	63	56	B	10	136**	14	41
8	F	40	59	B	10	88	34**	34*
9	M	50	110*	B	0	97	38**	36*
10	F	62	67	A	5	93	14	47*
11	F	76	73	A	0	84	5	34

1) Mean of pre- and post-treatment values
* Below normal
** Above normal

The drug administration of this study was nearly identical to study 16.

Specimens Collected

Blood samples (8 ml) for assay of omeprazole, identified major metabolites and total radioactivity were collected in heparinized tubes prior to and 5, 8, 11, 15, 20, 25, 30, 40 and 50 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours after dosing. The samples were handled as in previous studies.
Urine collection intervals were 0-1, 1-2, 2-4, 4-6, 6-9, 9-12, 12-24, 24-48, 48-72 and 72-96 hours. The urine was buffered to pH>7 during collection, the volumes recorded and a 50 ml aliquot frozen for later

analysis.

Bioanalytical Methodology

The concentrations in plasma of omeprazole, the hydroxy-, sulphone and sulphide metabolites were determined by an HPLC method similar to ones used in previous studies (analytical site was not specified). The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole, hydroxy-omeprazole and omeprazole sulphone in plasma was 50-100 nmole/L with a relative standard deviation of less than 10-15% and for hydroxy-omeprazole in urine was 150-200 nmole/L), linear (plasma method was 50 nmole/L-100 micromole/L and urine method was 200 nmole/L-120 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole, hydroxy-omeprazole and omeprazole sulphone in plasma and hydroxy-omeprazole in urine were 1.6 and 4.5%, 2.5 and 4.4%, 3.8 and 5.5% and 1.6 and 1.7% respectively. The mean intra-day CV of single concentration standard sets was 1.9% (range 0.5-4.7%) and the mean CV of inter-day quality control samples was 2.9% (range 97.5-107% of recovered spike) for omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 3.7% (range 1.4-8.0%) and the mean CV of inter-day quality control samples was 10.4% (range 80.5-120.5% of recovered spike) for hydroxy-omeprazole in plasma. The mean intra-day CV of single concentration standard sets was 3.2% (range 1.5-5.8%) and the mean CV of inter-day quality control samples was 3.9% (range 98.5-110% of recovered spike) for omeprazole sulphone in plasma. The mean intra-day CV of single concentration standard sets was 3.0% (range 1.5-5.0%) and the mean CV of inter-day quality control samples was 2.1% (range 98-104.5% of recovered spike) for hydroxy-omeprazole in urine. Assay validation for the detection of the sulphide metabolite in plasma was not included with the report.
Total radioactivity was determined in 0.5 ml of plasma or urine after addition of 10 ml of a liquid scintillator and counting in a Beckman LS 3800 with correction for quenching made by external standardization.

Pharmacokinetic Methodology

The analytical methods were very similar to those employed in study 16 except for the exclusion of the kinetic parameters of the distribution phase because of some uncertainty as to the values of the vary first plasma concentrations and 5 patients exhibiting biexponential decline and 3 patients exhibiting monoexponential decline after IV dosing.
Correlations between values of pharmacokinetic parameters of omeprazole (AUC and CL) and liver function were determined by linear regression analysis and a p-value of less than 0.05 was accepted as statistically significant.

Results

1. Three patients dropped out of the study following the entrance physical examination which accounts for the non-sequential numbering of the subjects.

2. 24 hours after IV dosing, no patients had measurable concentrations of omeprazole, however, after oral dosing, 4 patients still had measurable levels.

Individual and mean pharmacokinetic parameters of omeprazole calculated from plasma levels after 20 mg IV dose

Patient No	$t_{½}$ (h)	V_d ($l \cdot kg^{-1}$)	CL ($ml \cdot min^{-1}$)	AUC ($\mu mol \cdot l^{-1} \cdot h$)
1				
3				
5				
6				
8				
9				
10				
11				
Mean	2.75	0.210	65.0	19.3
SDM	0.199	0.0075	5.19	1.61

Individual and mean pharmacokinetic parameters of omeprazole calculated from plasma levels after 40 mg oral dose

Patient No	t_{max} (h)	C_{max} ($\mu mol \cdot l^{-1}$)	$t_{½}$ (h)	AUC ($\mu mol \cdot l^{-1} \cdot h$)	F
1					
3					
5					
6					
8					
9					
10					
11					
Mean	0.37	0.02	2.94	79.2	0.98
SDM	0.032	0.007	* 0.196	2.22	0.047

3. One patient had no measurable levels of hydroxy-omeprazole and another patient had only one measurable level (70 nmole/L) after IV dosing.

Individual and mean kinetic parameters of hydroxy-omeprazole calculated from plasma levels after single 20 mg IV and 40 mg oral dosing

Patient No.	i.v. dose				oral dose			
	t_{max} (h)	C_{max} ($\mu mol \cdot l^{-1}$)	$t_{½}$ (h)	AUC ($\mu mol \cdot l^{-1} \cdot h$)	t_{max} (h)	C_{max} ($\mu mol \cdot l^{-1}$)	$t_{½}$ (h)	AUC ($\mu mol \cdot l^{-1} \cdot h$)
2								
3								
5								
6								
8								
9								
10								
11								
Mean	1.64	0.16	3.4	1.15	0.79	0.33	4.4	3.07
SDM	0.341	0.025	0.40	0.091	0.226	0.056	0.46	0.322

* = only one determinable plasma concentration
** = no determinable plasma concentration

4. The sulphone was still detected in plasma in all patients 24 hours after both the IV and oral administration.

Individual and mean kinetic parameters of the sulphone calculated from plasma levels after single 20 mg IV and 40 mg oral doses

Patient No.	i.v. dose					oral dose				
	t_{max} (h)	C_{max} (µmol·l⁻¹·h⁻¹)	$t_{½}$ (h)	AUC (µmol·l⁻¹·h⁻¹·h) 0-24h	AUC (µmol·l⁻¹·h⁻¹·h) 0-∞	t_{max} (h)	C_{max} (µmol·l⁻¹·h⁻¹)	$t_{½}$ (h)	AUC (µmol·l⁻¹·h⁻¹·h) 0-24h	AUC (µmol·l⁻¹·h⁻¹·h) 0-∞
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
mean	1.4	0.44	14	10.4	14	4.6	2.35	17	21.1	29
SD	0.48	0.062	2.1	0.76	1.8	0.84	0.217	1.6	1.55	1.8

5. No measurable levels of the sulphide were found.

6. Individual and mean kinetic parameters of the total pool of radioactive metabolites after single 20 mg IV and 40 mg oral doses

Patient No.	i.v. dose					oral dose				
	t_{max} (h)	C_{max} (µmol·l⁻¹·h⁻¹)	$t_{½}$ (h)	AUC (µmol·l⁻¹·h⁻¹·h) 0-24h	AUC (µmol·l⁻¹·h⁻¹·h) 0-∞	t_{max} (h)	C_{max} (µmol·l⁻¹·h⁻¹)	$t_{½}$ (h)	AUC (µmol·l⁻¹·h⁻¹·h) 0-24h	AUC (µmol·l⁻¹·h⁻¹·h) 0-∞
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
mean	2.2	1.36	18.9	26		3.5	3.97	36.3	53	
SD	0.79	0.306	1.99	1.4		0.48	0.317	3.31	3.4	

a) calculation of residual area is based on $t_{½}$ from 12h and onwards
b) calculation of residual area is based on $t_{½}$ from the i.v. dose
c) calculation of residual area is based on $t_{½}$ from 8h and onwards

7. No unchanged omeprazole was found in the urine and the sulphone and sulphide were below determinable concentrations.

8. The mean cumulative excretions, as per cent of given dose, over the 96 hour collection period were 76 (range 66-84) and 76 (range 68-92) after the IV and oral doses, respectively. The plot of the mean excretion rates against the midpoint of the collection interval showed a mean t1/2 of the terminal phase corresponding to 11.6 (range [redacted]) and 11.7 (range [redacted] h after IV and oral dosing, respectively.

9. The mean cumulative excretions, as per cent of given dose, over the 24 hour collection period were 8.3 (range [redacted]) and 7.7 (range 3.6-11) after the IV and oral doses respectively.

10. The mean F was increased from 0.58 in young healthy subjects to 0.94 in cirrhotic patients. Mean Cmax and AUC values of omeprazole were also increased compared to the young healthy subjects both after oral and IV dosing. There was a substantial (nine fold) reduction in drug clearance in cirrhotic patients as well as a 40% decrease in Vbeta.

11. There was no apparent correlation between liver function values (S-Bilirubin and P-Simplastin A) and values of the pharmacokinetic parameters of interest (AUC and CL). There was less inter-individual variability in pharmacokinetic parameters in cirrhotic patients.

12. The mean Tmax of the sulphone was substantially prolonged, compared to the value for young healthy individuals.

13. The mean AUC of the total pool of metabolites after oral dosing was increased almost three fold as compared to young healthy. In young healthy, the sulphone accounted for only 10% of the total pool of metabolites while it constituted more than 50% in cirrhotic patients.

14. The amount of total radioactivity excreted in the urine, as per cent of given dose, by cirrhotics was the same as that of young healthy individuals.

Sponsor's Conclusions

1. The rate of elimination from plasma of omeprazole and two of its metabolites is substantially decreased in patients with liver cirrhosis.

2. The dose of omeprazole should be reviewed and perhaps reduced in patients with impaired liver function.

Comments

1. The sponsor's method (across study comparison) for evaluating the differences in pharmacokinetics of omeprazole between hepatically impaired patients and healthy subjects is not the preferred method to meet their objectives. No statistical evaluations were reported on the comparisons of pharmacokinetic parameters.

2. The assay validation report appeared to show that only two points were used in the standard curves which would render all samples assayed with such a standard curve suspect to gross inaccuracies.

3. Comparisons of the disposition of the total pool of metabolites based on AUC(0-infinity) are highly suspect because the values were extrapolated to levels of questionable reliability. After IV dosing, the AUC(0-inf.) was increased by 55% (range 20-134) and after oral dosing by 50% (range 20-144) over the AUC(0-Cp_{last}).

4. The large F found in cirrhotics is indicative that first pass metabolism has much greater influence on increasing the bioavailability of omeprazole than acid degradation. The F, based on hydroxy- and sulphone metabolites were nearly the same as based on the parent drug.

5. The nearly 50% greater Cmax and AUC of the total pool of metabolites as

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compared to sulphone and hydroxy-omeprazole, indicates that a large pool of metabolites is unaccounted for.

6. The sponsor should explain why the urinary excretion of hydroxy-omeprazole wasn't followed for 96 hours.

7. Comparison of Tmax values of the sulphone metabolite to those in young healthy subjects may not be valid due to the difficulty in interpreting a true Tmax. The individual plasma concentration data had so many "hills and valleys" that the Tmax as reported by the sponsor may not be very reliable.

XXI. Study 18. (Study Code I-252)

Title:

Bioavailability of omeprazole given as a single dose of enteric-coated granules in connection with food intake

Objective

To determine the bioavailability of omeprazole from a formulation of enteric coated granules (EOG III) given as a single dose 15 minutes before and less than or equal to 2 minutes before breakfast and, furthermore, to determine the correlation between the AUC for omeprazole and the 24-h urinary excretion of hydroxy-omeprazole.

Drug Dosage Forms Used

1. Hard gelatin capsules containing 30 mg enteric coated granules of omeprazole (Control number HC 8333). On Summary Table of Investigations the formulation No. was H 415-6-1.
2. Buffered (with sodium bicarbonate) suspension containing 60 mg of omeprazole in 50 ml (Batch No. H 410-1-5 as per Summary Table of Investigations).

Clinical Investigator and Study Site

Dunnar Ekenved, Phd
Asgar Heggelund, MD
Per Lundberg, MD
Ake Pilbrant, Phd

AB Hassle
S-431 83 MOLNDAL
Sweden

Study Protocol

Twelve male subjects, mean age of 26 years (range 22-35), mean weight of 77 kg (range 68-85) and mean height of 182 cm (range 173-190) participated in this three-way cross-over randomized study. Each subject received a single oral dose of 60 mg omeprazole, as a buffered suspension under [illegible] EOG III, 15 minutes or less than or equal to 2

treatments. The suspension was administered with several aliquots of sodium bicarbonate solution prior to, with and after dosing. The capsules were given with 150 ml of water.

Specimens Collected

Blood samples were collected prior to and 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes post-dosing of the suspension and prior to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12-24 hours after the capsule dosing. Urine was quantitatively collected over the 24-hour period following drug administration in all experiments.

Bioanalytical Methodology

The concentrations in plasma of omeprazole were determined by an HPLC method similar to ones used in previous studies (analytical site was not specified). The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 50-100 nmole/L with a relative standard deviation of less than 10-15%), linear (50 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole in plasma were 0.5 and 6.6%. The mean intra-day CV of single concentration standard sets was 1.5% (range 0.3-3.0%) and the mean CV of inter-day quality control samples was 2.4% (range 99.5-109.5% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Methodology

The pharmacokinetic parameters AUC, Cmax, Tmax and relative bioavailability were used to compare treatment effects.

Results

1. The values (mean ± SEM) of the pharmacokinetic variables are tabulated below:

	Buffered suspension	EOG III 15 min before breakfast	EOG III ≤ 2 min before breakfast
AUC (micromol*h/L)	4.28 ± 0.549		2.77 ± 0.417
(subject 7 excluded)	4.34 ± 0.598	2.94 ± 0.49	2.81 ± 0.46
Cp_{max} (micromol/L)	5.58 ± 0.571		1.58 ± 0.429
(subject 7 excluded)	5.47 ± 0.613	1.38 ± 0.298	1.55 ± 0.469
Tmax (hours)	0.22 ± 0.03		2.4 ± 0.6
(subject 7 excluded)	0.23 ± 0.03	2.0 ± 0.42	2.5 ± 0.66
T1/2 (minutes)	38.3 ± 2.3		
(subject 7 excluded)	38.6 ± 2.47		
urinary excretion of OH-omeprazole (micromol/24 h)	20.6 ± 1.9		15.4 ± 1.3
(subject 7 excluded)	20.7 ± 2	16.1 ± 1.7	14.7 ± 1.3

2. There were no significant differences observed between ECG III given 15 minutes and ≤ 2 minutes before breakfast, regarding Cp_{max}, Tmax or AUC.

3. The mean relative bioavailability for ECG III given 15 minutes and ≤ 2 minutes before breakfast, respectively, were 65.5 and 66.6 per cent of the buffered suspension.

4. There was no correlation between urinary excretion of hydroxy-omeprazole and AUC ($r = 0.004$; $p > 0.1$).

Sponsor's Conclusion

Omeprazole can be taken before breakfast, with no restrictions on the time interval between the dose intake and the breakfast.

Comments

1. The detailed report of this study (with a complete description of the type of breakfast) was omitted from the submission, only the study synopsis was provided. Omitted items were similar to those omitted from study (study code .

2. The batch number provided in the study report did not match the batch numbers as listed in the Summary Table of Investigations. It is assumed that batch No. HC 8333 is identical to batch No. H 415-6-1 as listed in the aforementioned table. Dissolution information (in summary format) for the capsule dosage form (batch No. H 415-6-1) was provided in the Summary section of the Human Pharmacokinetics and Bioavailability Data section. The 30 mg ECG III had a mean acid resistance of 96% and 85% dissolved in 15 min.

3. The assay validation report appeared to show that only two points were used in the standard curves which would render all samples assayed with such a standard curve suspect to gross inaccuracies. Furthermore, there was no assay validation provided for the analysis of hydroxy-omeprazole in urine.

4. Re-analysis of the data by this reviewer confirmed the sponsor's conclusion of no significant differences between the two administrations of ECG III, however, it was impossible to analyze for sequence or period effects due to the omission of the randomization scheme from the study report.

5. The design of this study was not the most appropriate to examine a possible food interaction with omeprazole bioavailability. A more appropriate comparison of potential food effect is to dose 30 minutes before breakfast and 5 minutes after. This would have simulated a more realistic clinical situation in which a patient remembers to take his dose after finishing breakfast. Furthermore, a more definitive approach would be to dose concurrently with breakfast and to dose in a fasting state (i.e., no food for 10 hours before and 4 hours after the dose).

XXII. Study 19. (Study Code I-298) Abstract #207 at III World Conference on Clinical Pharmacology and Therapeutics, 1986

Title:

Bioavailability of omeprazole on the first and last day of a one week's

treatment with omeprazole given in conjunction with food

Objective

This trial was performed to study the bioavailability of omeprazole on the first and last days of seven days' treatment with omeprazole given as EC granules to healthy subjects either before or immediately after breakfast.

Drug Dosage Forms Used

1. Hard gelatin capsules containing 20 mg of omeprazole as EC granules (Batch No. H 431-7-7).
2. The intravenous formulation was similar to that used in study 6 (study code I-303) and study 7 (study code I-321) (Batch No. H 529-3-1 and solvent Batch No. H 530-2-2)

Clinical Investigator and Study Site

Per Lundborg, MD, Dept. of Clinical Pharmacology, AB Hassle, S-431 83 MOLNDAL, Sweden

Study Protocol

The study was conducted as an open cross-over trial in 12 healthy, male subjects with a median age of 24 years (range 22-37), median weight of 74 kg (range 68-86) and median height of 179 cm (range 172-184). Inclusion and exclusion criteria appeared to have been met. The study consisted of three periods. In the first study period, subjects were given omeprazole as a single 20 mg IV dose (infused over 5 minutes) after at least a 10 hour fast. The subjects stayed at the laboratory for 4 hours and were given a standardized lunch 2.5 hours after dosing. In the other 2 study periods, the ECG III formulation was given (after at least a 10 hour fast), once daily, for seven days either before or immediately after breakfast, in random order. The standardized breakfast consisted of 2 slices of white bread, 30 g cheese, 15 g butter, 1.5 dl coffee or tea, 1.5 dl orange juice, 1.5 dl milk and 20 g cornflakes, with a total content of 22 g protein, 29 g fat, 72 g carbohydrate and 2500 kJ. On study days 1 and 7, the subjects stayed at the laboratory for 12 and 24 hours, when the drug was given before and after breakfast, respectively. They were allowed to sit and walk but not to lie down for more than 10 minute periods during the first 12 hours. Standardized meals were served during the stay. On study days 2 to 6, subjects took one capsule together with a glass of water either before or immediately after breakfast at home. Study periods were separated by at least 14 days during which time subjects were given iron supplements to compensate for the large amount of blood drawn.

Specimens Collected

Blood samples (5 ml) were collected in heparinized tubes at the following times:
IV: prior to dose, end of infusion (0 time), 5, 10, 20, 30, 45 minutes and 1, 1.5, 2, 2.5, 3 and 4 hours after dosing.
Oral (days 1 and 7): prior to, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8,

9, 10, 11 and 12 hours after dosing when dosed before breakfast and additionally at 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 hours when dosed after breakfast.

Bioanalytical Methodology

The concentrations in plasma of omeprazole were determined by an HPLC method similar to one used in previous studies at the Department of Bioanalytical Chemistry at AB Hässle. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 15-25 nmole/L with a relative standard deviation of less than 10-15%), linear (15 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole in plasma were 0.0-3.4% and 0.1-0.8%. The mean intra-day CV of single concentration standard sets was 2.1% (range 0.4-4.3%) and the mean CV of inter-day quality control samples was 6.5% (range 85-115.5% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Methodology

AUC was calculated by trapezoidal rule. The residual AUC for the IV dose was calculated by standard methods as was elimination half-life. Bioavailability of the different dosing regimes of the capsule was calculated as:

$$\text{Bioavailability} = AUC_{(EC\ granules)}/AUC_{(IV)}$$

The variable, AUC, was assumed to be lognormally distributed, however, the variable, F, was considered to be normally distributed. 90% confidence limits for the expected values of the logarithms of AUC were constructed and these were then transformed to 90% confidence intervals in the original scale. The two modes of oral dosing were compared in terms of confidence intervals for the ratio between the geometric means of AUC (the antilog of the mean of the logarithms of the individual ratios between AUC after and before breakfast) and confidence intervals for the ratio between arithmetic means for F.

Results

1. One subject (No. 8), by mistake was given the dose after breakfast on day 7 when it should have been given before breakfast. Since this was not discovered until the end of the experimental day, this subject underwent an additional study period with the correct dosing seven weeks later. The plasma samples from the incorrect period were excluded from the analysis.

2. The AUC values after IV dosing showed a 10-fold variation between subjects, ranging from 1.34 to 13.92 micromol*h/L with a geometric mean of 2.38 micromol*h/L (90% C.I.: 1.74-3.26). The median t1/2 was 0.58 hour (range [redacted]).

3. The tabulated results of the oral dosing (AUC, F, T-time of first detectable concentration) are below:

		day 1:after breakfast	day 1:before breakfast	day 7:after breakfast	day 7:before breakfast
	Geometric mean	0.913 (A)	0.882 (B)	1.449 (A)	1.121 (B)
	95% conf. interval for geometric mean	0.722-1.092	0.696-1.105	0.994-1.445	0.871-1.085
AUC (umol/l)	R(=A/B)	1.03		0.92	
	95% conf. interval for R	0.79-1.36		0.72-1.18	

		day 1:after breakfast	day 1:before breakfast	day 7:after breakfast	day 7:before breakfast
	Geometric mean	0.913 (A)	0.882 (B)	1.405 (A)	1.121 (B)
	95% conf. interval for geometric mean	0.576-1.437	0.555-1.400	0.899-2.351	0.705-1.797
AUC (umol/l)	Ratio				
	R(=A/B)	1.01		0.92	
	95% conf. interval for R	0.83-1.29		0.75-1.13	
T (h)	median	1.75	0.50	1.50	0.50
	Range	1.0-5.0	0.5-1.0	0.5-2.5	0.5-1.0

		day 1:after breakfast	day 1:before breakfast	day 7:after breakfast	day 7:before breakfast
	Arithmetic mean	0.41 (A)	0.40 (B)	0.87 (A)	0.72 (B)
	95% conf. interval for arithmetic mean	0.31-0.51	0.30-0.51	0.45-0.89	0.49-0.94
F	R (=A/B)	1.13		0.99	
	95% conf. interval for R	0.90-1.44		0.76-1.31	

		day 1:after breakfast	day 1:before breakfast	day 7:after breakfast	day 7:before breakfast
	Arithmetic mean	0.41 (A)	0.40 (B)	0.87 (A)	0.73 (B)
	95% conf. interval for arithmetic mean	0.33-0.49	0.32-0.48	0.49-0.95	0.52-0.93
F	Ratio				
	R(=A/B)	1.13		0.95	
	95% conf. interval for R	0.93-1.40		0.79-1.19	

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Sponsor's Conclusions

1. The AUC of omeprazole increases during once-daily dosing with EC granules, irrespective of whether the drug is administered before or after breakfast.

2. The administration of omeprazole after, instead of before breakfast does not affect the total amount of drug absorbed but appears to prolong the time to absorption of the drug.

Comments

1. Dissolution information was not included with the study report, however, the formulation used in this study was the same as in study 12 (study code I-316) for which dissolution information has been provided.

2. As in a previous study, the "0" time blood level after IV dosing is not the accepted timing of blood samples. When infusion begins is considered to be the "0" time and in the present study the end of infusion would be considered a 5 minute sample.

3. The sponsor's consideration of AUC to be log-normally distributed and subsequent statistical analysis may be very valid. However, justification for their consideration should have been provided.

4. This reviewer's analysis of the non-log transformed AUC data using ANOVA with Duncan's Multiple Range Test indicated that the means of day 7 before or after breakfast were not significantly different. However, the test did indicate that a significant difference could not be found between the means of day 7 after breakfast and day 1 before or after breakfast.

5. The sponsor did not perform any statistical evaluation on the time to first detectable plasma concentration since the time intervals between blood samples were too long to allow for any accurate estimation of the variable. Analysis by this reviewer indicated that the means of this parameter were not statistically different (Duncan's Multiple Range Test) between day 1 (2.3 h) and day 7 (1.7 h) after breakfast or between day 1 (1 h) and day 7 (0.7 h) before breakfast. However, they were statistically different between day 1 after breakfast and day 1 before breakfast and between day 7 after breakfast and day 7 before breakfast. This confirms the sponsor's conclusion that dosing after breakfast prolongs the time to absorption of the drug.

6. Blood sampling should have been carried out for a longer period of time after IV dosing and after the experiment of dosing before breakfast because some of the subjects' plasma concentrations had not returned to zero. The failure of proper sampling may have contributed to the finding of bioavailability greater than 1.0 in three subjects (those 3 subjects did not have zero plasma concentrations when sampling was stopped).

7. There were some plasma concentrations reported which were below the limit of determination of the assay.

8. The plasma concentration-time profiles after oral dosing indicated a very erratic (e.g., multiple peaks) absorption pattern in many of the subjects. This finding makes any truly meaningful interpretations of the

data very difficult.

g. Eight of 12 subjects had reduced serum bilirubin values post-treatment. A medical officer may want to examine this finding further for potential clinical significance.

XXIII. Study 20. (Study Code I-213)

Title:

The influence of antacids on the bioavailability of omeprazole given as enteric-coated granules

Objective

The aim of the present investigation was to study the influence of a liquid Al/Mg antacid (Novaluzid), with a high acid binding capacity, on the bioavailability of omeprazole when administered orally as enteric coated granules.

Drug Dosage Forms Used

Hard gelatin capsules containing 30 mg omeprazole as enteric-coated granules (Batch Nos. H 415-2-3 and H 415-2-4).
Novaluzid (Al/Mg antacid suspension) manufactured by AB Hässle (Batch No. H 117-12-1) containing in each 10 ml aluminum hydroxide corresponding to 21.8 mmol of Al and magnesium hydroxide and carbonate corresponding to 9.9 mmol of Mg, with an in vitro acid-binding capacity of 85 mmol.

Clinical Investigator and Study Site

Per Lundberg, MD

Research Laboratories
AB Hässle
Molndal, Sweden

Study Protocol

This investigation was conducted as a two-way cross-over, randomized study in six healthy male subjects with a mean age of 24 years (range 20-26), mean weight of 78 kg (range 71-86) and a mean height of 183 cm (range 175-188). Inclusion and exclusion criteria appeared to have been met. Each subject took part in two experiments, one in which 60 mg (2 capsules) omeprazole was given alone and one in which an antacid was given with the omeprazole dose (after at least a 10 hour fast, except for antacid dosing). A total of seven 10 ml doses of antacid were given on the day before omeprazole dosing (one dose 1 and 3 hours after each meal and 1 dose at bedtime) and 1 dose was given just prior to omeprazole dosing. During their stay in the laboratory, the subjects received a standardized lunch. The experiments were separated by at least four days.

Specimens Collected

Blood samples (5 ml) were collected in heparinized tubes 10 minutes prior

to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6 and 7 hours after dosing. The samples were cooled for at least 5 minutes and then centrifuged for 10 minutes. The plasma phase was transferred to plastic tubes containing 20 microl of 1 M Na_2CO_3, mixed lightly and stored at -20 degree C.

Bioanalytical Methodology

The concentrations in plasma of omeprazole were determined by an HPLC method similar to ones used in previous studies at the Department of Analytical Chemistry at AB Hassle. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 20 nmole/L with a relative standard deviation of less than 10-15%), linear (30 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole in plasma were 1.1-9.7%. The mean intra-day CV of single concentration standard sets was 0.9% (range 0.3-2.3%) and the mean CV of inter-day quality control samples was 4.9% (range 94-105% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Methodology

AUC (0-420 minutes) was calculated by trapezoidal rule. Comparisons of areas was made by the Wilcoxon's matched-pairs signed-ranks test.

Results

1. Tabulated values (mean ± SEM) of AUC, Cmax and Tmax (median).

	without antacids	with antacids
AUC (micromol*h/L)	4.03 ± 2.82	4.37 ± 1.67
Cmax (micromol/L)	2.01 ± 0.72	2.19 ± 0.68
Tmax (min)	120	60

2. There was no statistically significant differences in any of the parameters.

3. The within subject variations between experiments were small (%C.V. = 16.2) but the between subject variations were larger (%C.V. = 102.1).

Sponsor's Conclusion

The results suggest that omeprazole as EOC may be given together with antacids without jeopardizing the bioavailability of omeprazole.

Comments

1. Dissolution information (in summary format) for the capsule dosage forms used in this study were provided in the Summary section of the Human Pharmacokinetics and Bioavailability Data section. The 30 mg EOC II, batch no. H 415-2-3, had a mean acid resistance of 88% and 92% dissolved in 10 min and batch no. H 415-2-4 had a mean acid resistance of 90% and 97% dissolved in 10 min.

2. A U.S. marketed antacid comparable (in formula or acid neutralizing

capability) to the antacid used in this study (Novaluzid) is apparently not available. Therefore, similar results to those obtained in this study may not occur with an antacid marketed in the U.S.

3. The blood samples were not obtained for a sufficient length of time since some subjects' plasma concentrations had not returned to "0" when sampling was terminated.

4. Four out 6 subjects had decreased serum bilirubin levels. This observation was found in a previous study. A medical officer should evaluate whether this laboratory finding has any significance to omeprazole treatment.

5. The sponsor's non-parametric statistical test indicated that there was no difference in pharmacokinetic parameters. However, using the standard parametric approach (as used to test for bioequivalence), antacid treatment had a marked effect on all parameters (AUC, Cmax and Tmax) since all results were outside the 90% C.I. and 75/75-125 ratio analysis.

	90% C.I.	Ratio analysis (within 75 - 125%)
AUC	[0.88-1.29]	50%
Cmax	[0.94-1.24]	50%
Tmax	[0.05-1.49]	0%

6. It appears that administration of an antacid increases the rate and extent of bioavailability of omeprazole (dosed as EOG II) because there is a trend indicating AUC and Cmax are increased and Tmax is decreased.

XXIV. Study 21. (Study Code I-307)

Title:

Interaction between omeprazole and antacids given as single doses in healthy subjects

Objective

This study was designed to study the bioavailability of a single oral dose of 20 mg omeprazole administered with or without a single dose of antacids in healthy subjects.

Drug Dosage Forms Used

Hard gelatin capsules containing 20 mg omeprazole as enteric coated granules (EOG III, Batch No. H 431-7-4).
Commercially available (from Canada) Maalox TC suspension containing $Al(OH)_3$ and $Mg(OH)_2$ with an acid binding capacity of 28.3 mmol/5 ml (no batch number provided).

Clinical Investigator and Study Site
Hank Fasten, MD, PhD
Department of Gastroenterology
Free University Hospital
De Boelelaan 1117
AMSTERDAM
The Netherlands

Study Protocol

12 healthy male subjects with a median age of 22 years (range 20-28), median weight of 74.2 kg (range 68-86) and a median height of 185 cm (range 176-190) participated in this open cross-over, randomized trial with a 2 week wash-out between experiments. All inclusion and exclusion criteria appeared to have been met. After at least a 10 hour fast, subjects were given 20 mg omeprazole alone or immediately after 10 ml of Maalox TC. Subjects were allowed to sit and lk around but not to lie down for more than 10 min periods during the experiment. Standardized meals were served 2.5, 6 and 10 hours after dosing.

Specimens Collected

Blood samples (7 ml) were collected in heparinized tubes prior to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after dosing. Samples were handled as in previous studies.

Bioanalytical Methodology

The concentrations in plasma of omeprazole were determined by an HPLC method similar to ones used in previous studies at the Department of Bioanalytical Chemistry at AB Hassle. The assay validation report was included with the study report and indicated the assay to be specific, sensitive (the limit of determination of omeprazole in plasma was 30-40 nmole/L with a relative standard deviation of less than 10-15%), linear (30 nmole/L-100 micromole/L) and reproducible. The intra-day CV's of the standard curves for omeprazole in plasma were 1.1-9.7%. The mean intra-day CV of single concentration standard sets was 2.1% (range 0.5-3.9%) and the mean CV of inter-day quality control samples was 2.7% (range 89-100.5% of recovered spike) for omeprazole in plasma.

Pharmacokinetic Methodology

AUC was calculated by trapezoidal rule. The variable, AUC, was assumed to be lognormally distributed. 95% confidence limits for the expected mean values of the logarithms were calculated and these were then transformed to 95% confidence intervals for the geometric means of the original values. Any effect of concomitant administration of antacids on the bioavailability of omeprazole was evaluated in terms of the 95% confidence interval for the ratio between the geometric means of AUC with and without antacids (the antilog of the mean of the logarithms of the individual ratios between AUC with and without antacids).

Results

1. The median and range of Cpmax and Tmax are tabulated below

	C_{max} (µmol/l)		T_{max} (h)	
	[illegible]	[illegible]	[illegible]	[illegible]
median	0.410	0.500	1.2	1.2
range				

2. The AUC and statistical evaluations are tabulated below:

	With antacids	Without antacids
Geometric mean	[illegible] (A)	[illegible] (A)
95% conf. interval for geometric mean	0.445-1.430	[illegible]
Range		
[illegible] (A)	0.99	
95% conf. interval for [illegible]	[illegible]	

3. Great inter-individual variations were observed for all pharmacokinetic variables, a finding consistent with observations in previous studies that a great variation exists between individuals in their ability to metabolize omeprazole. One subject (no. 11) had markedly higher values of AUC (almost 10 times the geometric mean) and Cp-max (5 times the median), compared to the rest of the group.

Sponsor's Conclusion

This study shows that the concomitant administration of an antacid suspension with high binding capacity has no influence on the bioavailability of a single oral dose of 20 mg omeprazole.

Comments

1. The tabulated intra-day CV of the standard curve in the Assay Validation Report was identical to the table in study 20 (study code I-213) which was performed more than three years earlier. This would warrant some explanation by the sponsor to assure that intra-day CV's were generated for the standard curves each day that analysis of samples was performed.

2. The sponsor attempted to show that, even though there was great inter-subject variation in Cmax and AUC values, these values remained relatively constant for any given subject with no consistent effect of concomitant administration of antacids. This evaluation was presented in two figures showing log-log plots of Cmax with- versus Cmax without-antacids and AUC with- versus AUC without-antacids and the line of identity indicated an apparent linear relationship. There was no information provided as to the goodness-of-fit so one can only evaluate the results observationally.

3. The summary table of Cmax and Tmax values of all the subjects had an incorrect entry for subject 12. His Cmax should have been entered as [illegible] and not [illegible]. This is just another example of the poor quality and audit procedures of this submission.

4. As in previous studies, this study also exhibited a tendency for decreased serum bilirubin levels post-study. Nine of 12 (75%) of the subjects had this finding.

5. The study report indicated that AUC values were calculated using the

trapezoidal rule. This reviewer's (FDA) re-calculation of AUC's using the trapezoidal rule showed some differences in AUC values from the sponsor's results (difference sponsor vs. FDA ranged from -9.2 to +2.6% for treatment without antacids and from -2.7 to +0.3% for treatment with antacids). Ordinarily, these would not be differences one would be concerned about, however, there shouldn't be any differences in the calculation of a simple parameter such as AUC and as it turned out, different statistical results are obtained using the sponsor's AUC's and FDA's AUC's.

6. Even though ANOVA results indicated that the means of AUC, Cmax and Tmax after the two treatments could not be judged statistically different, the two treatments can not be considered to be bioequivalent. 75/75-125 ratio analysis indicated the following: (sponsor's AUC - 67% within, FDA's AUC - 67% within, Cmax - 42% within and Tmax - 50% within). Using the treatment without antacid as the reference mean, sponsor's AUC, Cmax and Tmax all failed the 90% CI and two one-sided t-test. However, FDA's AUC passed.

7. The results of this study do not appear to coincide with drug release and bioavailability information gathered from another study with antacid. The results of study I-213 indicated that administration of an antacid showed a trend to increase the bioavailability of omeprazole from capsule formulations. However, in this study there was a trend for decreased Cmax and Tmax after antacid treatment. A possible explanation may be that in study I-213, subjects were pre-treated with antacid whereas in this study only one dose of antacid was given.

XXV. Supportive Study 4.

Title:

Development of an oral formulation of omeprazole. Scand J Gastroenterol 1985;20(suppl 108):113-120.

Comment

This journal article was not reviewed since many of the studies cited have been reviewed.

XXVI. Supportive Study 5.

Title:

The Formulation and Evaluation of Enteric-Coated Aspirin. Am J Pharm 1959;131:206-216.

Comment

This journal article was not reviewed.

XXVII. Supportive Study 6.

Title:
Critical Factors Influencing Gastrointestinal Absorption-What is the Role

of Pellets? Acta Pharm Technolog 1982;28:149-157.

Comment

This journal article was not reviewed.

XXVIII. Supportive Study 7.

Title:

Determination of omeprazole and metabolites in plasma and urine. Scand J Gastroenterol 1985;20(suppl 108):71-77.

Comment

This journal article was not reviewed.

XXIX. Supportive Study 8.

Title:

Pharmacokinetics and metabolism of omeprazole in animals and man - an overview. Scand J Gastroenterol 1985;20(suppl 108):79-94.

Comment

This journal article cited many studies which have already been reviewed. However, this article summarized two studies on the effect of omeprazole on oxidative metabolism using the model drugs antipyrine and [^{14}C]aminopyrine which were not included with the Human Pharmacokinetics and Bioavailability Data section of this NDA. The findings of those studies were that omeprazole had no significant effect on the aminopyrine half-life or the metabolic clearance rate of antipyrine, while the half-life of antipyrine was increased by, on average, 10% ($p<0.025$) after the 60 mg omeprazole dose.

XXX. Supportive Study 9.

Title:

Pharmacokinetics and Metabolism of Omeprazole in Man. Scand J Gastroenterol 1986;21(suppl 118):99-104

Comment

1. This journal article cited many studies which have already been reviewed. However, this article included summaries of drug interaction (with diazepam and with phenytoin) studies of omeprazole which were not included with the Human Pharmacokinetics and Bioavailability Data section of this NDA. Diazepam pharmacokinetics were altered (2.5-fold prolongation of the t1/2(beta) and decrease in total plasma clearance) when administered with omeprazole. Additionally, this article referenced the same study of omeprazole effects on aminopyrine and antipyrine as the previous supportive study, however, in this article there was reported a 21% prolongation of aminopyrine half-life in addition to the effect on

antipyrine. The additional studies on omeprazole drug interactions, as stated in the article, will help to provide more information in this area.

2. In view of the fact that omeprazole may have a significant effect on the cytochrome P-450 system, and studies suggestive of such an effect were not submitted in the Human Pharmacokinetics and Bioavailability Section, it is recommended that a pharmacologist evaluate animal studies for possible P-450 or P-448 enzyme interaction.

XXXI. Supportive Study 10.

Title:

A Comparison of Numerical Integrating Algorithms by Trapezoidal, Lagrange, and Spline Approximation. J Pharmacokin Biopharm 1978;6:79-98.

Comment

This journal article was not reviewed.

XXXII. Supportive Study 11.

Title:

Pharmacokinetics of (^{14}C)omeprazole in patients with impaired renal function. Clin Pharmacol Ther 1986;40:344-351.

Comment

This journal article is identical to the one in study 16 (study code I-265) and is a duplicate.

XXXIII. Supportive Study 12.

Title:

Antisecretory Effect and Oral Pharmacokinetics of Omeprazole in Patients with Chronic Renal Failure. Eur J Clin Pharmacol 1985;28:637-640.

Comment

This study of 6 patients with advanced chronic renal failure showed that there was no statistically significant differences in the parameters Tmax, Cmax and AUC on a non-dialysis and a dialysis day after dosing with 30 mg omeprazole capsule formulation. Omeprazole was not detectable in samples of dialysis fluid from any subject.

SUMMARY COMMENTS

1. The sponsor should be advised to be more meticulous in preparing the Human Pharmacokinetics and Bioavailability section of future NDA submissions. This submission contained numerous errors and omissions which resulted in an inordinate amount of time by this reviewer in completing a comprehensive review. This reviewer re-analyzed many of the

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studies using the standard and accepted techniques of biopharmaceutical analysis instead of communicating with the sponsor and having them do it, in order to possibly save time in the review process.

2. For future submissions, the sponsor should be advised, that dissolution testing of the intended market product lot, used in bioavailability studies, should include the individual results of 12 dosage units.

3. The sponsor should be advised that in multiple-dose studies establishing the pharmacokinetics at steady state, Cmin values are necessary to characterize possible accumulation. Multiple dose studies in this submission did not provide Cmin values, however, this may have been the result of "0" levels being reached prior to the next dose. Furthermore, multiple-dose studies should be conducted on the upper end of the dosing range.

4. LOSEC capsules are designed to pass through the highly acidic stomach milieu and to dissolve and be absorbed at the higher pH of the small intestine. The delayed-release characteristic of this dosage form imparts a certain amount of inherent variability in absorption patterns which may be expected with LOSEC. The erratic absorption is evident in the plasma concentration-time profiles in several of the studies.

5. Many of the studies have presented data exhibiting large inter-subject variation (with some definite outliers) in the pharmacokinetics of omeprazole which has been attributed mainly to differences in metabolism. Several other drugs, which are also extensively metabolized by the cytochrome P-450 system, have had sub-populations identified who metabolize a given drug at a much different rate than the majority of the population. The sponsor is encouraged to attempt to identify the subset of the population who are apparent different metabolizers of omeprazole.

6. Several studies have alluded to the relationship between the area under the plasma concentration of omeprazole-time curve and percentage reduction of acid secretion. The sponsor is encouraged to develop this relationship further using pharmacokinetic-pharmacodynamic modeling techniques in order to develop a more scientific rationale for proper dose and prevention of possible untoward effects from excessive dose.

7. The data of study 9 (study code I-246), suggested to this reviewer that there may be an increased amount of the sulfone metabolite of omeprazole excreted when dosing occurred in the evening. The sponsor is encouraged to pursue this finding further to explore if this resulted from a change in absorption or in elimination.

8. The sponsor submitted study 11 (study code I-243) to demonstrate bioequivalence of two formulations (ECG II and ECG III) used in clinical trials. The sponsor's conclusion of the two formulations being bioequivalent cannot be supported for the reasons stated in comment nos. 6, 7, 8 and 9 to study 11. Subsequently, the pivotal clinical studies in which ECG II was used must be evaluated in that light.

9. The sponsor submitted study 12 (study code I-316) to demonstrate the bioequivalence of formulation ECG III to LOSEC 20 mg (the intended market image formulation, see following comment). The batch number (and possible

method of manufacture) of ECG III used in this study is different from that used in study 11 (see previous comment). The sponsor's conclusion of the two formulations being bioequivalent cannot be supported for the reasons stated in comment nos. 3 and 4 of study 12.

10. In view of the apparent bio-inequivalence of the intended market image formulation to formulations used in clinical trials and in order to clarify which formulations were used in pivotal studies, the sponsor has submitted a definitive clarification in a letter dated 6 February 1989. The sponsor has identified study nos. 10, [redacted], 19 and 21 (study codes I-278, [redacted], I-298 and I-307, respectively) as pivotal biopharmaceutic studies. Furthermore, they have clarified that the final market formulation will be identical to the ECG III formulation which has batch numbers designated as H431-7- (having an aqueous base subcoat and an organic base outer coat) and not formulation LOSEC 20 mg.

11. The sponsor has adequately demonstrated evidence of the in vivo bioavailability of omeprazole from the intended market formulation (see previous comment). The mean (%CV) values of bioavailability data of the ECG III formulation (with batch no. H431-7-) is summarized in the table below (in addition to the studies identified in the previous comment, other studies in which the aforementioned batch of ECG III, dosed as 20 mg one time or once daily, was used have been included):

Study Code No.	AUC (micromol*h/L)	Cmax (micromol/L)	Tmax (hour)	F (%)
I-338				
(day 1)	0.727(60)	0.624(79)	2.2(88)	36(41)
(day 5)	1.258(95)	0.794(83)	3.1(110)	50(60)
I-278				
(day 1)	0.99(159)	0.607(107)	1(41)	31(74)
(day 8)	1.411(137)	0.79(89)	0.9(39)	43(57)
I-316	0.762(65)	0.516(62)	1.7(49)	
I-336				
(day 1)	1.034(75)	0.856(66)	0.9(26)	39(55)
(day 5)	2.011(70)	1.218(77)	1.5(122)	66(52)
I-298				
(day 1 b/meal)	1.497(158)	0.535(92)	3.1(86)	40(39)
(day 1 a/meal)	1.53(158)	0.583(86)	4.5(63)	41(39)
(day 7 b/meal)	2.285(111)	0.87(88)	2.9(67)	72(53)
(day 7 a/meal)	2.106(116)	0.754(86)	4.1(62)	67(52)
I-307				
(w/antacid)	1.35(148)	0.574(91)	1.2(49)	
(w/o/antacid)	1.41(163)	0.693(112)	1.4(52)	
I-302	1.023(43)	0.75(39)	1.4(44)	52(48)
I-321	0.587(37)	0.405(38)	1.7(37)	30(30)

12.

13. Several studies (study codes I-270/281, I-298, I-213) indicated that serum bilirubin levels were decreased post-study in a majority of the subjects. A medical officer should evaluate if this laboratory finding may be of significance.

14. In study 17 (study code I-264), which was a study of the pharmacokinetics of omeprazole in subjects with impaired hepatic function, the sponsor's conclusion was to perhaps reduce the omeprazole dose in patients with impaired liver function. The submitted proposed Labeling is contrary to that conclusion in recommending no dosage adjustment in patients with hepatic dysfunction. The statement of "The mean F was increased from 0.58 in young healthy subjects to 0.98 in cirrhotic patients. Mean Cmax and AUC values of omeprazole were also increased compared to the young healthy subjects both after oral and IV dosing. There was a substantial (nine fold) reduction in drug clearance in cirrhotic patients as well as a 40% decrease in Vd_{beta}. The mean AUC of the total pool of metabolites after oral dosing was increased almost three fold as compared to young healthy subjects. In young healthy subjects, the sulphone accounted for only 10% of the total pool of metabolites while it constituted more than 50% in cirrhotic patients" should be stated in the pharmacokinetic and metabolism section. The statement in the Labeling "Once daily treatment with 20 mg of omeprazole for 4 weeks was well tolerated in these patients and no accumulation of omeprazole or its metabolites occurred" cannot be verified form the reference I-264 the sponsor cited, because it was a single dose study and not a chronic steady-state dosing.

15. The sponsor's conclusion in study 21 (study code I-307), that concomitant administration of an antacid suspension has no influence on the bioavailability of omeprazole, cannot be supported. Therefore, it is recommended that the Labeling statement "Administration of LOSEC Capsules with food or antacids has no clinically significant affect on the bioavailability of omeprazole." be evaluated by a medical officer to assure that the trend observed in study I-213 and this study are truly not clinically significant. In study I-213, it appeared that administration of an antacid showed a trend to increase the rate and extent of bioavailability of omeprazole EOG II (although not statistically significant). The 90% C.I. for AUC, Cmax and Tmax are 0.88-1.29, 0.94 - 1.24 and 0.05 - 1.49 respectively. However, in study I-307 it appears there is a trend toward lower Cmax and Tmax with antacid. Furthermore, in the Drug Interaction section of the Labeling, the sentence of "No interaction with concomitantly administered antacids has been found." should be omitted.

16. The Labeling indicates that in Pathological Hypersecretory Conditions doses up to 120 mg t.i.d. have been administered. It should be pointed out that pharmacokinetic information supporting such high dosing has not been provided.

17. Studies I-252 and I-292 which looked at the effect of food on omeprazole bioavailability are not definitive since subjects were not administered the dose under true fasting conditions. The sponsor should conduct a proper food effect study which should include a 10 hour fast pre-dosing and a four hour fast post-dosing for the fasted leg, and the meal should be the standard FDA breakfast. The sponsor is advised to submit the study protocol to the Agency for possible comments prior to initiation of the study. In the mean time we suggest that the Labeling include instructions to take the drug with food or without food depending on how clinical studies were carried out.

18. The Labeling alludes to several interaction studies with diazepam, warfarin, phenytoin, theophylline and propranolol. None of these studies have been included in the Human Pharmacokinetics and Bioavailability Data section of this NDA. This information has not been evaluated by the Division of Biopharmaceutics.

19. The dissolution data (see comments to "In-Vitro Dissolution", pages 4-5) were reviewed separately to a submission dated 21 July 1988. The dissolution recommendations which follow are subsequent to that review.

LABELING: (copy of draft attached)

1. The second sentence of the first paragraph of the Pharmacokinetics and Metabolism section should be changed to read as follows: Absorption is...within 0.5 to 3.5 hr.

2. The third sentence of the first paragraph should be changed to read as follows: Peak plasma concentrations of omeprazole are proportional to the dose of LOSEC and, for example, averaged 606.5 nmol/l following LOSEC 20 mg and 1,260 nmol/l following LOSEC 40 mg. However, a non-linear response in peak plasma concentration and area under the plasma concentration-time curve has been observed with doses above 40 mg. (Not to be included in the labeling: References are study code I-278, I-347 and I-225.)

3. The first sentence of the second paragraph should read as follows: The bioavailability of omeprazole increases upon repeated administration ..... becomes manifest and a possible decrease in first pass elimination.

4. Since study I-265 indicated that the plasma levels of the total pool of radioactive metabolites were 2-3 higher times in patients with renal insufficiency than in young healthy subjects, the Labeling related to patients with chronic renal impairment, "No significant accumulation of plasma metabolites is expected, with repeated once daily dosing" should be deleted.

DEFICIENCY:

The sponsor has not provided an acceptable bioequivalence study comparing the formulation of LOSEC used in clinical trials to the intended market

LOSEC [redacted] mg formulation.

RECOMMENDATION:

The Division of Biopharmaceutics has reviewed NDA 19-810, LOSEC (omeprazole) capsules 20 mg and [redacted] mg and has found the submission to be acceptable for the 20 mg strength (formulation ECC III with lot No. H431-7-)

. The sponsor is suggested to conduct a food effect study (which could be conducted during Phase IV) as outlined in Summary comment no. 17.

The dissolution methodology, except for paddle speed, as specified by the sponsor is acceptable. It is recommended that the paddle speed be reduced to 50 rpm for both the acid resistance and the buffer phase portions of the test. Furthermore, it is advised that the final specifications be as follows:

> [redacted] remaining after [redacted] hour acid exposure and NLT [redacted] dissolved in [redacted] minutes.

The above recommendation, summary comments, comments on labeling and deficiency should be forwarded to the firm.

Nicholas M. Fleischer 6/26/89

Nicholas M. Fleischer, R.Ph., M.S.
Pharmacokinetics Evaluation Branch

RD Initialed by Mai-Ying Huang, Ph.D. 5-27-89
PT Initialed by Paul Hopp, Pharm.D. PH 6/26/89

cc: NDA 19-810 (orig), HFD-180(2), HFD-426(Fleischer), HFD-334(Turner), Chron, Drug, Reviewer files, HFD-19(fol)

NMF:mmf:2-28-89/rev3-2-89/rev3-17-89/rev5-25-89/rev6-13-89/rev6-26-89:FC

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November 20, 2002

By Messenger

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petition

Dear Sir or Madam:

Please find enclosed an original and 3 copies of the Petition of Andrx Pharmaceuticals Corp. relating to over the counter Omeprazole Magnesium.

Please file-stamp one of the copies and return it with the messenger who has delivered these papers to you.

Thank you for your attention to this matter.

Sincerely,

Carlos T. Angulo

Carlos T. Angulo

Enclosures