AstraZeneca

SH-NEH-0002

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Nexium™

ACTIVE INGREDIENT: Esomeprazole

Trial title (number): A four-way cross-over multpel-dose open-label pharmacokinetic drug inteaction study with esomeparzole 20 mg b.i.d., metronidazole 500 mg b.i.d., clarithromycin 250 mg b.i.d. and their combination b.i.d. in healthy non-smoking male and female subjects.

Developmental phase: Clinical pharmacology
First subject recruited:06 January 2001
Last subject completed:10 May 2001
Approval date:24 April 2002

OBJECTIVES

Primary objective

To investigate pharmacokinetic interactions between 20 mg esomeprazole b.i.d., 500 mg metronidazole b.i.d., and 250 mg clarithromycin b.i.d. and their metabolites after repeated administration in healthy male and female subjects

Secondary objective

To evaluate the safety of esomeprazole alone and in combination with metronidazole and clarithromycin

METHODS

STUDY DESIGN

Four-way, crossover, multiple-dose, open-label pharmacokinetic drug interaction study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

The study was performed in healthy subjects.

TEST PRODUCTS, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Esomeprazole 20 mg MUPS™ tablets (lot #: SH-NEH-0002-01) taken orally b.i.d.
Metronidazole 500 mg capsules (Flagyl®) (lot #: SH-NEH-0002-01) taken orally b.i.d.
Clarithromycin 250 mg tablets (Bremón®) (lot #: SH-NEH-0002-01) taken orally b.i.d.

DURATION OF TREATMENT

A cross-over study consisting of four treatment periods, each one being seven consecutivedays in duration, separated by a 14 to 28 day wash-out period

MAIN MEASUREMENTS AND VARIABLES:

- PHARMACOKINETIC

The main pharmacokinetic variables were: AUC_{τ}, C_{max}, $t_{1/2}$, and t_{max} of esomeprazole, its sulphone, and 5-hydroxy metabolites; metronidazole and hydroxymetronidazole; and clarithromycin and metabolite 14-hydroxyclarithromycin.

- SAFETY

All subjects underwent a full clinical examination, including medical history, height, weight, physical examination, pregnancy test (for female subjects), vital signs (blood pressure and heart rate), ECG, laboratory tests, H.p. status test, and drug screen within 14 days prior to the start of the first study period. All subjects underwent an examination that included a physical examination, laboratory tests, pregnancy test (for female subjects), and vital signs at the completion of the study. Additional laboratory tests were performed on Day 7 of each period. Adverse events were documented, summarised, and followed up until resolution (whenever possible) during the whole study

STATISTICAL METHODS

Separate analyses were carried out on the raw (non-transformed)$t_{1/2}$, t_{max} and$\lambda_z$data and on the logarithmically (natural) transformed AUC_{τ}, C_{max}, and $t_{1/2}$(shown in Appendix 16.2.5 and not reported in the body of the report) data for each of the three parent drugs and the four measured metabolites. A mixed model ANOVA with fixed effects for sequence, period and treatment and a random effect for subjects within sequence was applied. Volume of distribution, clearance and C_{min} were not analysed because oral formulations of the three drugs studied were used.

SUBJECTS	
	Total
No. planned	24
No. enrolled	36
No. randomised and treated	35
Males/Females (randomised subjects)	22 / 13
Mean age (range) (randomised subjects)	30 (21-48)
No. analysed for pharmacokinetics	27
No. analysed for safety	35
No. completed	27

RESULTS

SUMMARY

PHARMACOKINETIC RESULTS

Ratios of estimated geometric means, 90% confidence intervals (CI) and p-values of AUC_{τ}, C_{max} and $t_{1/2}$ for esomeprazole, metronidazole, clarithromycin and triple combination are presented in Table 1. Please note, comments for each analyte refer to the geometric meansof their pharmacokinetic parameters for AUC and C_{max}. The $t_{1/2}$ parameter was untransformed.

For esomeprazole, there was more than a two-fold higher AUC_{τ} during the triple combination compared to monotherapy (4682 and 2125 ng·hr/mL, respectively). For C_{max}, there was a 59% increase during the triple combination compared to monotherapy (1447 and 908 ng/mL, respectively). The $t_{1/2}$ increased by 56% during the triple combination compared to monotherapy (1.89 and 1.21 hours, respectively).

The AUC_{τ} values for the sulphone and hydroxy metabolites of esomeprazole were 4106 and 128 ng·hr/mL, respectively, in the triple combination. The corresponding values in the monotherapy were 3388 and 120 ng·hr/mL, respectively.

The $AUC_{\tau}$and $t_{1/2}$ for metronidazole during the triple combination (136102 ng·hr/mL, respectively) were similar to those observed in the treatment with metronidazole alone (132775 ng·hr/mL and 9.68 hours, respectively) The C_{max} was also similar and was 18410 ng/mL in the triple combination compared to the monotherapy (17214 ng/mL).

The $AUC_{\tau}$for the hydroxy metabolite of metronidazole in the triple combination (60684ng·hr/mL) was similar to that in the monotherapy (61604 ng·hr/mL).

The AUC_{τ}, and $t_{1/2}$ for clarithromycin were not significantly changed during triple combination treatment (8267 ng·hr/mL, and 4.38 hours, respectively) as compared to monotherapy (8734

ng·hr/mL, and 3.81 hours, respectively). The C_{max} decreased slightly when given in the triple combination (1084 ng/mL) compared to monotherapy (1278 ng/mL) respectively.

The AUC_{τ} for the 14-hydroxyclarithromycin was slightly higher in the triple combination (8362 ng·hr/mL) compared to that in monotherapy (7301 ng·hr/mL).

Table 1.

Ratios, limits for 90% CI and p-values for tests of equal geometric means of AUC_{τ}(ng), C_{max}(ng/mL) and $t_{1/2}$(h) following repeated oral administration of 20 mg esomeprazole b.i.d. (A), 500 mg metronidazole b.i.d. (B), 250 mg clarithromycin b.i.d. (C) or a triple combination (20 mg esomeprazole b.i.d., 500 mg metronidazole b.i.d. and 250mg clarithromycin b.i.d.) (D) to healthy subjects are presented (n=27).

Ratio of estimated geometric mean		90% confidence interval lower	upper	p-value†
AUC_{τ}				
Esomeprazole (D/A)	2.2038	2.0078	2.4188	<0.0001
Metronidazole (D/B)	1.0251	0.9873	1.0643	0.2700
Clarithromycin (D/C)	0.9466	0.8539	1.0493	0.3705
C_{max}				
Esomeprazole (D/A)	1.5938	1.4240	1.7838	<0.0001
Metronidazole (D/B)	1.0695	1.0404	1.0993	0.0004
Clarithromycin (D/C)	0.8482	0.7552	0.9527	0.0234
$t_{1/2}$ *				
Esomeprazole (D/A)	1.5569			<0.0001
Metronidazole (D/B)	0.9703			0.8065
Clarithromycin (D/C)	1.1494			0.1006

* $t_{1/2}$ untransformed

† taken from the ANOVA tables, based on a comparison between the indicated treatments

SAFETY RESULTS

A total of 66 adverse events (AEs) were reported for the 35 randomised subjects during the entire study (including washout periods). Most adverse events were reported during metronidazole monotherapy. Headache, diarrhoea, dizziness, abdominal pain, nausea, and taste perversion were the most common adverse events. No SAEs, AEs of severe intensity or Other Significant AEs were reported. One AE (ear infection) leading to discontinuation was reported. Repeated oral doses of esomeprazole, alone or in combination with metronidazole and clarithromycin, were generally well tolerated in this study.

Reference:

None at this time

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Nexium™ (esomeprazole), Healthcare Professionals should view their specific country information.