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Lack of Pharmacokinetic Interaction between Esomeprazole and the Nonsteroidal Anti-Inflammatory Drugs Naproxen and Rofecoxib in Healthy Subjects

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Abstract

Background: We investigated the potential interactions between esomeprazole and a non-selective nonsteroidal anti-inflammatory drug (NSAID; naproxen) or a cyclo-oxygenase (COX)-2-selective NSAID (rofecoxib) in healthy subjects.

Methods: Two studies of identical randomised, open, three-way crossover design were conducted. Subjects (n = 32 for both studies) were to receive 1 week's treatment with esomeprazole 40mg once daily (studies A and B), naproxen 250mg twice daily (study A), rofecoxib 12.5mg once daily (study B), and esomeprazole in combination with naproxen (study A) or rofecoxib (study B). Study periods were separated by a 2-week washout period.

Results: On day 7 of dosing, the ratios (and 95% CIs) for the area under the plasma concentration-time curve during the dosing interval (AUC_τ) and observed maximum plasma concentration (C_{max}) of esomeprazole and NSAID combination/NSAID alone were 0.98 (0.94, 1.01) and 1.00 (0.97, 1.04), respectively, for study A, and 1.15 (1.06, 1.24) and 1.14 (1.02, 1.28), respectively, for study B. The ratios (and 95% CIs) for AUC_τ and C_{max} of esomeprazole and NSAID combination/esomeprazole alone were 0.96 (0.89, 1.03) and 0.92 (0.85, 1.00), respectively, for study A, and 1.05 (0.96, 1.15) and 1.05 (0.94, 1.18), respectively, for study B. All treatments were well tolerated during the study period.

Conclusion: Naproxen and rofecoxib do not interact with esomeprazole, and esomeprazole does not affect the pharmacokinetics of naproxen or rofecoxib. These findings indicate that esomeprazole can be used in combination with NSAIDs without the risk of a pharmacokinetic interaction.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and a wide variety of other acute and chronic painful musculoskeletal disorders, and can, in most countries, be used as standard analgesics and bought without a prescription. There were over 111 million NSAID prescriptions in the US for the year ending August 2000, with one-third of the total number of prescriptions being for cyclo-oxygenase (COX)-2-selective NSAIDs.[1] The use of NSAIDs is expected to increase further in the future, especially if they become more widely used for the prevention of colorectal cancer and Alzheimer's disease. The use of low-dose aspirin for cardiovascular protection is also expected to increase.

All NSAIDs are, however, associated with a substantial number of adverse events, with non-selective NSAIDs accounting for 20% and 25% of all reported adverse drug events in the UK and US, respectively.[2,3] NSAID-associated upper gastrointestinal (GI) tract adverse effects range from dyspeptic symptoms to peptic ulceration and ulcer complications.[4] Some 15–40% of NSAID users report upper GI symptoms[5] and 10–30% of long-term NSAID users will develop a peptic ulcer, predominantly in the stomach.[6,7] NSAID use increases the risk of peptic ulcer complications by 3- to 5-fold, and 15–35% of all peptic ulcer complications are reported to be caused by NSAID use.[4]

It has been estimated that there are over 100 000 hospital admissions per year and 16 500 deaths per year due to NSAID-induced GI complications in the US.[8]

The anti-inflammatory properties of NSAIDs are mediated through the inhibition of the COX-2 enzyme, whereas GI adverse effects occur as a result of their action on COX-1. COX-2-selective NSAIDs, such as celecoxib and rofecoxib, preferentially inhibit COX-2. One conclusion of the VIGOR (Vioxx GI Outcomes Research) study, which compared naproxen with rofecoxib in patients with RA, was that treatment with rofecoxib was associated with significantly fewer upper GI events than treatment with naproxen.[9] Celecoxib was compared with ibuprofen and diclofenac in a similar study. The annual rates of upper GI complications were lower for celecoxib compared with ibuprofen and diclofenac, but the difference did not reach statistical significance, and the combination of celecoxib and low-dose (≤325 mg/day) aspirin negated the GI advantage of celecoxib.[10] It is also worth noting that in this trial, the doses of celecoxib used were 2–4 times the maximum recommended doses for the treatment of RA and OA.

Unfavourable cardiovascular risk data has led to an urgent re-evaluation of the use of the COX-2-selective class of NSAIDs in clinical practice, culminating in the market suspension of the COX-2-selective agents rofecoxib and valdecoxib.[11,12] The US FDA has requested that manufacturers of all marketed prescription NSAIDs revise product labeling to include a boxed warning highlighting the potential for increased risk of cardiovascular events, and is encouraging physicians to limit the use of COX-2-selective agents to the lowest practical dose for the most urgent cases.[13] All COX-2-selective agents available in Europe contain cardiovascular warnings, and prescribers are advised to carefully regard the warnings in patients with a history of cardiovascular disease.[14] Celecoxib is still available in the US, and celecoxib and various other COX-2-selective agents are still available in Europe.[13,14] Additionally, during the first quarter of 2005, an FDA advisory panel recommended that rofecoxib should again be made available to patients, and that black-box warnings be placed on the labels of all COX-2-selective agents.[15,16] Canadian health authorities may also be moving towards approving the return of rofecoxib to the market.[17] Consequently, it does seem likely that, in the future, a range of COX-2-selective

agents may still have a role to play in the effective management of certain patients with low cardiovascular risk.

The proton pump inhibitor (PPI) omeprazole has been shown to be superior to ranitidine and misoprostol for both the healing and the prevention of NSAID-associated ulcers and dyspeptic symptoms during continued NSAID treatment.[18,19] The degree of gastric damage caused by NSAIDs is highly dependent on intragastric pH.[18,20] Esomeprazole, which confers a longer time with intragastric pH >4 than all other PPIs,[21] is expected to be effective for the prevention of NSAID-associated ulcers.

As esomeprazole is expected to be widely used in the healing and prevention of gastric and duodenal ulcers, and to control upper GI symptoms in patients needing continuous NSAID treatment to relieve inflammation and pain, it is important to rule out any drug-drug interactions between esomeprazole and NSAIDs, including non-selective and selective agents. In order to test for pharmacokinetic interactions between esomeprazole and naproxen, a popular non-selective NSAID, and between esomeprazole and rofecoxib, a previously popular COX-2-selective NSAID that may still be a beneficial drug in carefully selected patients, we conducted two identically designed studies in healthy subjects.

Materials and Methods

Subjects

Healthy subjects were included if they: were 20–50 years old; had a body mass index of 19–27 kg/m^2; weighed 50–95kg; showed normal physical findings and laboratory values; had not used esomeprazole for the previous 8 weeks, any prescribed medication for the previous 2 weeks, or over-the-counter drugs (including herbal remedies, vitamins and minerals) in the week preceding the first dose of study drug; were not using anabolic steroids; were not of childbearing potential or lactating; had no history of cardiac, renal, hepatic, neurological or significant gastrointestinal diseases; had not donated blood in the 12 weeks prior to the first dose of study drug or during the study; did not smoke or consume any other sort of nicotine (or equivalent); and were not using concomitant medications (except nasal spray for nasal congestion, or paracetamol).

The studies (study codes: SH-Nen-0016 and SH-Nen-0017) were conducted in accordance with the Declaration of Helsinki and were approved by the ethics committee of the University of Uppsala and by the Swedish Medical Products Agency. Written informed consent was received from all subjects prior to participation. The studies were performed at Quintiles AB, Uppsala, Sweden.

All subjects underwent a full clinical examination, physical examination and electrocardiogram (ECG) at pre-entry. A laboratory screen for haematology and serum biochemistry was performed prior to enrolment, on day 7 of each treatment period, and 5–7 days after the last study day.

Study Design

The two studies were conducted according to a randomised, open, three-way crossover design. Each of the three treatment periods lasted for 7 days, which was sufficient to achieve steady state. The subjects received either oral doses of an esomeprazole 40mg capsule once daily (studies A and B), a naproxen 250mg tablet twice daily (study A), a rofecoxib 12.5mg tablet once daily (study B), or esomeprazole in combination with naproxen (study A) or rofecoxib (study B). Each treatment period was separated by a washout period of at least 14 days. Blood samples for determination of esomeprazole, naproxen and rofecoxib were taken for 24 hours post-dose on the last day of each treatment period. Alcohol was not allowed from 2 days before pre-entry, during each treatment period, and be-

tween the last study day and the follow-up visit. Drugs available on prescription were not allowed during the last 2 weeks preceding the studies and during the studies.

On the investigational days, the subjects arrived at the study centre in the morning, having fasted since the previous evening, for administration of the study drug and collection of repeated blood samples. On these days, standardised meals were served 4 (lunch), 6 (light meal), 10 (dinner) and 13 (light meal) hours after drug administration.

Study Drugs

In study A, the subjects received an esomeprazole 40mg capsule (Nexium®, AstraZeneca Tablet Production, Sweden)[1] once daily, a naproxen 250mg tablet (Naprosyn®, Roche, Switzerland) twice daily, or a combination of the two drugs orally for 7 days. In study B, the subjects received an esomeprazole capsule (Nexium®) once daily, a rofecoxib 12.5mg tablet (Vioxx®, MSD, Germany) once daily, or a combination of the two drugs orally for 7 days.

Blood Sampling and Bioanalytical Methods

Blood samples for assay of esomeprazole, naproxen and rofecoxib were taken at pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 20 and 24 hours following drug administration on day 7. The blood samples were drawn from an indwelling cannula in a forearm vein and collected in heparinised tubes, centrifuged and the plasma transferred, frozen and stored until analysis.

The plasma concentration of esomeprazole was analysed using normal phase liquid chromatography with ultraviolet detection.[22] The limit of quantification (LOQ) for this method is 25 nmol/L with a coefficient of variation (CV) of <20%. The plasma concentration of naproxen was determined using liquid chromatography and fluorescence detection. The flow rate was 0.5 mL/min and the injection volume was 20–40µL. The retention time was 3.0 minutes and absolute recovery in the concentration range of 0.5–500 µmol/L was between 89% and 100%. The LOQ was 0.5 µmol/L (CV ≤20%). Intra- and interassay repeatability were 4–5% and 4–6%, respectively. Rofecoxib plasma concentration was also determined using liquid chromatography and fluorescence detection. The flow rate was 1.2 mL/min and the injection volume was 150µL. The retention time was 4.5 minutes and the absolute recovery in the concentration range of 3.0–200 nmol/L was between 90% and 91%. The LOQ was 1.5 nmol/L (CV ≤20%). Both intra- and interassay repeatability were 6–7%. The plasma samples were analysed for esomeprazole, naproxen and rofecoxib at Quintiles AB, Uppsala, Sweden.

Pharmacokinetic and Statistical Analyses

Pharmacokinetic parameters of esomeprazole, naproxen and rofecoxib were estimated by non-compartmental analysis using WinNonlin computer software. The area under the plasma concentration versus time curve during the dosing interval (AUC_τ) was calculated according to a log-linear trapezoidal method. For naproxen, the AUC_τ was calculated up to 12 hours post-dose, while for esomeprazole and rofecoxib the AUC_τ was calculated up to 24 hours post-dose. The elimination rate constant (λ) was determined by log-linear regression analysis of the terminal slope of at least the last three plasma concentration versus time points. The terminal plasma elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda$. The observed maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were also recorded.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

The pharmacokinetic parameters were analysed using a mixed-model analysis of variance (ANOVA) with fixed effects for sequence, period and treatment (the drug alone or in combination) and a random effect for subjects within sequences. The pharmacokinetic parameters were log-transformed prior to the analysis. Estimates and 95% confidence limits of the log-transformed parameters were antilogarithmised, and the results are presented as geometric means and ratios with 95% confidence intervals (CIs). The median was presented for t_{max}.

Results

Thirty-two healthy subjects (13 males and 19 females) with a mean age of 24 years and a mean bodyweight of 69kg participated in the esomeprazole and naproxen study (study A). Thirty-one subjects completed the treatment comparison of esomeprazole alone and in combination with naproxen, while 30 subjects completed the treatment comparison of naproxen alone and in combination with esomeprazole.

Thirty-two healthy subjects (15 males and 17 females) with a mean age of 26 years and a mean weight of 69kg participated in the esomeprazole and rofecoxib study (study B). Twenty-eight subjects completed the treatment comparison of esomeprazole alone and in combination with rofecoxib, while 30 subjects completed the treatment comparison of rofecoxib alone and in combination with esomeprazole.

All those who withdrew before the end of the study did so for personal reasons. There were no safety issues.

Esomeprazole and Naproxen

Median t_{max} values following administration of esomeprazole, naproxen and the combination are presented in table I. Estimates of the pharmacokinetic parameters with 95% CIs for esomeprazole and naproxen and the ratios with 95% CIs of the parameters are presented in table II and table III, respectively. The mean plasma concentration-time cuves are shown in figure 1 and figure 2.

Both esomeprazole and naproxen were rapidly absorbed, and the median t_{max} was approximately 1.5 hours for both drugs, both during monotherapy and during combination therapy (table I and figures 1 and 2). No changes were observed in AUC_τ, C_{max} and $t_{1/2}$ for esomeprazole after co-administration with naproxen compared with esomeprazole monotherapy (see table II). The ratios (combination/esomeprazole alone) for AUC_τ, C_{max} and $t_{1/2}$ were 0.96, 0.92 and 1.02, respectively, as shown in table III. For naproxen, the AUC_τ, C_{max} and $t_{1/2}$ after co-administration with eso-

Table I. Median time to the observed maximum plasma concentration (t_{max}) with minimum and maximum values following monotherapy with esomeprazole 40mg once daily, naproxen 250mg twice daily, rofecoxib 12.5mg once daily and a combination of esomeprazole with naproxen or rofecoxib for 7 days in healthy male and female subjects

Treatment	Median (h)	Minimum (h)	Maximum (h)
Study A			
Esomeprazole alone (n = 31)	1.50	1.00	2.75
Naproxen alone (n = 31)	1.50	0.75	4.00
Esomeprazole with naproxen (n = 31)	1.75	1.00	4.00
Naproxen with esomeprazole (n = 30)	1.50	0.50	4.50
Study B			
Esomeprazole alone (n = 28)	1.50	1.00	3.50
Rofecoxib alone (n = 30)	2.88	1.75	4.50
Esomeprazole with rofecoxib (n = 28)	1.50	0.75	3.50
Rofecoxib with esomeprazole (n = 30)	3.00	1.25	4.50

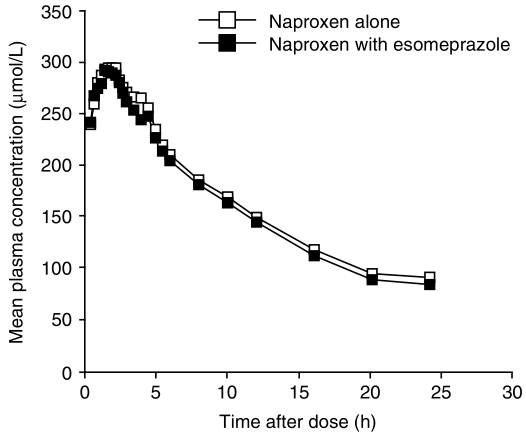

Fig. 2. Mean plasma concentration of naproxen following repeated oral administration of a naproxen 250mg tablet twice daily alone and in combination with an esomeprazole 40mg capsule once daily for 7 days in healthy male and female subjects (n = 30).

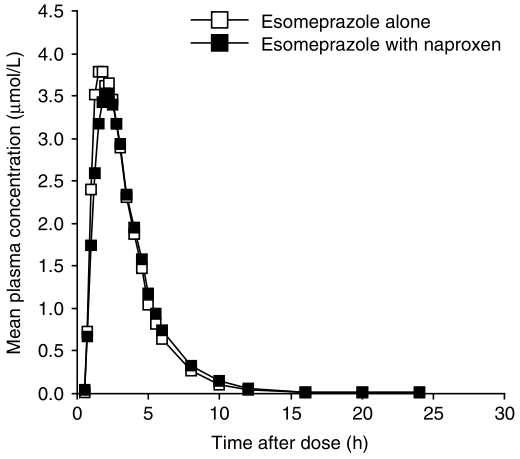

Fig. 1. Mean plasma concentration of esomeprazole following repeated oral administration of an esomeprazole 40mg capsule once daily alone and in combination with a naproxen 250mg tablet twice daily for 7 days in healthy male and female subjects (n = 31).

meprazole were similar to those after treatment with naproxen alone (see table II). The ratios (combination/naproxen alone) for AUC_τ, C_{max} and $t_{1/2}$ were 0.98, 1.00 and 0.96, respectively, as shown in table III.

Table II. Geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_τ), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$) of esomeprazole and naproxen following repeated oral administration of an esomeprazole 40mg capsule once daily (A), a naproxen 250mg tablet twice daily (B), or a combination of an esomeprazole 40mg capsule once daily and a naproxen 250mg tablet twice daily (C), for 7 days in healthy male and female subjects

Treatment	Geometric mean	95% CI
Esomeprazole (n = 31)		
AUCτ (μmol • h/L)		
Esomeprazole with naproxen (C)	12.22	10.61, 14.07
Esomeprazole alone (A)	12.75	11.07, 14.69
Cmax (μmol/L)		
Esomeprazole with naproxen (C)	4.52	4.06, 5.03
Esomeprazole alone (A)	4.90	4.40, 5.45
t½ (h)		
Esomeprazole with naproxen (C)	1.39	1.29, 1.50
Esomeprazole alone (A)	1.36	1.26, 1.46
Naproxen (n = 30)		
AUCτ (μmol • h/L)		
Naproxen with esomeprazole (C)	2530.7	2420.4, 2646.1
Naproxen alone (B)	2594.2	2481.0, 2712.5
Cmax (μmol/L)		
Naproxen with esomeprazole (C)	327.24	313.28, 341.82
Naproxen alone (B)	326.16	312.25, 340.69
t½ (h)		
Naproxen with esomeprazole (C)	12.90	12.41, 13.41
Naproxen alone (B)	13.47	12.96, 14.01

Table III. Ratios of the geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_τ), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$) of esomeprazole and naproxen. Values relate to a combination of an esomeprazole 40mg capsule once daily and a naproxen 250mg tablet twice daily, divided by those following administration of an esomeprazole 40mg capsule once daily (n = 31) or a naproxen 250mg tablet twice daily (n = 30) for 7 days in healthy male and female subjects.

Treatment	Estimate	95% CI
Esomeprazole (n = 31)		
AUC_τ (C/A)	0.96	0.89, 1.03
C_{max} (C/A)	0.92	0.85, 1.00
$t_{1/2}$ (C/A)	1.02	0.98, 1.07
Naproxen (n = 30)		
AUC_τ (C/B)	0.98	0.94, 1.01
C_{max} (C/B)	1.00	0.97, 1.04
$t_{1/2}$ (C/B)	0.96	0.93, 0.99

A = esomeprazole, **B** = naproxen; **C** = esomeprazole/naproxen combination.

Esomeprazole and Rofecoxib

Median t_{max} values following esomeprazole, rofecoxib and the combination are presented in table I. Estimates of the pharmacokinetic parameters with 95% CIs for esomeprazole and rofecoxib are presented in table IV. The ratios of the pharmacokinetic parameters with 95% CIs are presented in table V. The mean plasma concentration-time curves are shown in figure 3 and figure 4.

Esomeprazole was rapidly absorbed with a t_{max} of 1.5 hours, while the median t_{max} for rofecoxib was approximately 3 hours, both with rofecoxib alone and in combination with esomeprazole (table I). The AUC_τ, C_{max} and $t_{1/2}$ for esomeprazole were not affected by rofecoxib (table IV). The ratios (combination/esomeprazole alone) for AUC_τ, C_{max} and $t_{1/2}$ were 1.05, 1.05 and 0.99, respectively, as shown in table V. For rofecoxib, there was a slight increase in AUC_τ and C_{max} after co-administration with esomeprazole compared with rofecoxib monotherapy (table IV). The ratios (combination/rofecoxib alone) for AUC_τ, C_{max} and $t_{1/2}$ were 1.15, 1.14 and 1.06, respectively, as shown in table V.

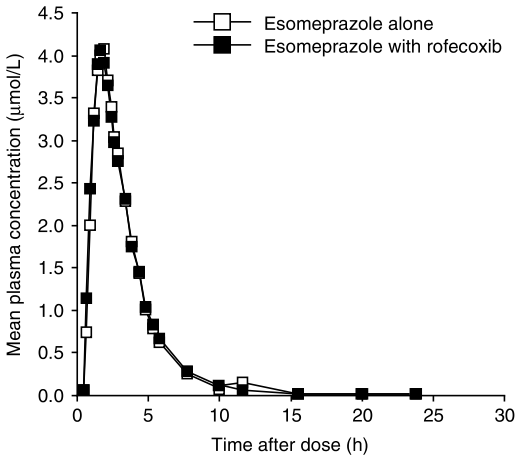

Fig. 3. Mean plasma concentration of esomeprazole following repeated oral administration of an esomeprazole 40mg capsule once daily alone and in combination with a rofecoxib 12.5mg tablet once daily for 7 days in healthy male and female subjects (n = 28).

Discussion

Esomeprazole is expected to be widely used in the management of upper GI symptoms, and to heal and prevent gastric and duodenal ulcers associated with continued NSAID use. Therefore, esomeprazole will commonly be used in combination with NSAIDs. Although it seems likely that in most

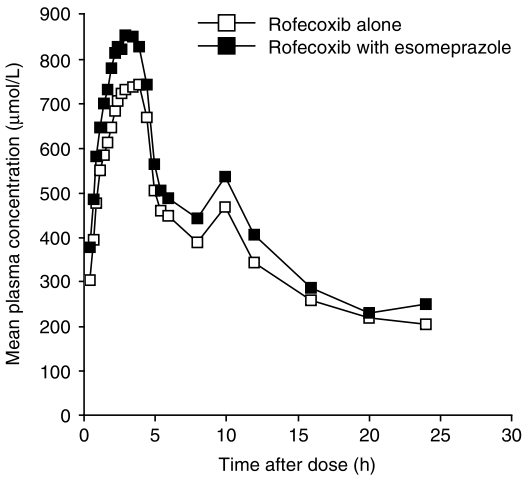

Fig. 4. Mean plasma concentration of rofecoxib following repeated oral administration of a rofecoxib 12.5mg tablet once daily alone and in combination with an esomeprazole 40mg capsule once daily for 7 days in healthy male and female subjects (n = 30).

Table IV. Geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_τ), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$) of esomeprazole and rofecoxib following repeated oral administration of an esomeprazole 40mg capsule once daily (A), a rofecoxib 12.5mg tablet once daily (B), or a combination of an esomeprazole 40mg capsule once daily and a rofecoxib 12.5mg tablet once daily (C) for 7 days in healthy male and female subjects

Treatment	Geometric mean	95% CI
Esomeprazole (n = 28)		
AUCτ (μmol • h/L)		
Esomeprazole with rofecoxib (C)	12.57	10.47, 15.10
Esomeprazole alone (A)	11.99	9.98, 14.40
Cmax (μmol/L)		
Esomeprazole with rofecoxib (C)	4.88	4.18, 5.70
Esomeprazole alone (A)	4.63	3.96, 5.41
t½ (h)		
Esomeprazole with rofecoxib (C)	1.39	1.25, 1.56
Esomeprazole alone (A)	1.41	1.26, 1.57
Rofecoxib (n = 30)		
AUCτ (μmol • h/L)		
Rofecoxib with esomeprazole (C)	9.61	8.37, 11.04
Rofecoxib alone (B)	8.36	7.28, 9.61
Cmax (μmol/L)		
Rofecoxib with esomeprazole (C)	0.89	0.78, 1.01
Rofecoxib alone (B)	0.78	0.68, 0.88
t½ (h)		
Rofecoxib with esomeprazole (C)	12.91	11.58, 14.40
Rofecoxib alone (B)	12.17	10.91, 13.58

cases the NSAID in question will be a non-selective agent, use of COX-2-selective agents has not been ruled out, and certain patients may still benefit from these agents. The aim of the present study was to rule out any potential for drug-drug interaction between esomeprazole and naproxen, being a representative non-selective NSAID, and rofecoxib, as an example of a COX-2-selective NSAID.

Table V. Ratios of the geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_τ), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$). Values relate to a combination of an esomeprazole 40mg capsule once daily and a rofecoxib 12.5mg tablet once daily, divided by those following administration of an esomeprazole 40mg capsule once daily (n = 28) or a rofecoxib 12.5mg tablet once daily (n = 30) in healthy male and female subjects

Treatment	Estimate	95% CI
Esomeprazole (n = 28)		
AUC_τ (C/A)	1.05	0.96, 1.15
C_{max} (C/A)	1.05	0.94, 1.18
$t_{1/2}$ (C/A)	0.99	0.90, 1.08
Rofecoxib (n = 30)		
AUC_τ (C/B)	1.15	1.06, 1.24
C_{max} (C/B)	1.14	1.02, 1.28
$t_{1/2}$ (C/B)	1.06	0.97, 1.16

A = esomeprazole; **B** = rofecoxib; **C** = esomeprazole/rofecoxib combination.

Esomeprazole plasma levels were not affected by naproxen or rofecoxib. The AUC_τ, C_{max} and $t_{1/2}$ for esomeprazole after co-administration with naproxen or rofecoxib were similar to those after esomeprazole alone. The AUC_τ, C_{max} and $t_{1/2}$ of naproxen after co-administration with esomeprazole were similar to those after naproxen alone. There was a marginal increase in AUC_τ and C_{max} for rofecoxib during the combination therapy compared with rofecoxib administered alone. The slight pharmacokinetic changes seen would not be expected to have any clinical relevance. Rofecoxib has double plasma concentration-time profiles when administered alone[23] and in combination with esomeprazole (figure 4). This may be due to redistri-

bution or to an enterohepatic circulation phenomenon. We do not know the reason(s) for the double profile for rofecoxib; however, this is a normal concentration-time profile for rofecoxib.[23]

Pharmacokinetics is one of the factors that may influence the NSAID safety profile. Although the majority of marketed NSAIDs are well absorbed, metabolised extensively, subject to fairly minimal first-pass extraction, and have linear pharmacokinetics, some more subtle differences are apparent.[24] Esomeprazole metabolism is mediated by cytochrome P450 (CYP) isoforms, CYP2C19 and CYP3A4,[25] while the NSAIDs have been shown to be mainly metabolised by another CYP isoform, CYP2C9.[26] On the basis of this knowledge, a drug interaction would not be expected between esomeprazole and the NSAIDs. However, a recently published study has reported that the extent of the role of CYP2C9 in the overall clearance of different NSAIDs is varied, and that CYP3A4 activity can sometimes be involved.[24] We feel that a lack of drug interactions during combination therapy with esomeprazole and all available NSAIDs should not be assumed, but rather evaluated on an individual basis. The results of the present interaction study help to confirm that drug-drug interactions are not an issue between esomeprazole and naproxen or rofecoxib. This study is also in agreement with previous studies involving omeprazole, which showed no drug-drug interactions between omeprazole and three different NSAIDs (naproxen, diclofenac or piroxicam).[27]

Conclusion

Neither naproxen nor rofecoxib have any effect on the pharmacokinetics of esomeprazole, and esomeprazole does not have any effect on the pharmacokinetics of naproxen or rofecoxib. The clinical implications of these findings are that esomeprazole can be used together with naproxen or rofecoxib without pharmacokinetic drug interaction safety concerns for the healing and prevention of gastric and duodenal ulcers in patients needing continuous NSAID treatment to relieve inflammation and pain. Repeated oral administration of esomeprazole alone, as well as in combination with naproxen or rofecoxib, was well tolerated.

Acknowledgements

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