Alimentary Pharmacology & Therapeutics

Efficacy of esomeprazole for resolution of symptoms of heartburn and acid regurgitation in continuous users of non-steroidal anti-inflammatory drugs

C. J. HAWKEY*, R. H. JONES†, N. D. YEOMANS‡, J. M. SCHEIMAN§, N. J. TALLEY¶, J. L. GOLDSTEIN**, H. AHLBOM†† & J. NÆSDAL††

*Institute of Clinical Research Trials Unit, University Hospital, Nottingham; †GKT Department of General Practice and Primary Care, King's College London, London, UK; ‡University of Western Sydney Medical School, Sydney, Australia; §Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; ¶Mayo Clinic College of Medicine, Rochester, MN; **Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA; ††AstraZeneca R&D, Mölndal, Sweden

Correspondence to:
Prof C. Hawkey, Institute of Clinical Research Trials Unit, University Hospital, Derby Road, Nottingham, NG7 2UH, UK.
E-mail: cj.hawkey@nottingham.ac.uk

Publication data
Submitted 19 July 2006
First decision 28 July 2006
Resubmitted 19 October 2006
Resubmitted 21 November 2006
Accepted 21 November 2006

SUMMARY

Background
The use of non-steroidal anti-inflammatory drugs (NSAIDs) is often associated with upper gastrointestinal symptoms such as heartburn and acid regurgitation.

Aim
To assess the efficacy of esomeprazole 20 and 40 mg for resolution of heartburn and acid regurgitation in continuous NSAIDs.

Methods
A *post hoc* analysis of five clinical trials was performed. Two identically designed, placebo-controlled, 4-week studies (NASA1, SPACE1) enrolled non-ulcer, NSAIDs-treated patients with upper abdominal pain, discomfort or burning. PLUTO and VENUS were identically designed, placebo-controlled, 6-month studies that enrolled patients at risk of NSAIDs-induced ulcers. Study 285 was an 8-week comparative study with ranitidine (300 mg/day) in patients with NSAIDs-induced gastric ulcers. Resolution of investigator-assessed heartburn and acid regurgitation was defined as symptom severity of 'none' in the last 7 days.

Results
In NASA1/SPACE1, heartburn resolved in 61% and 62% of patients taking esomeprazole 20 and 40 mg, respectively (vs. 36% on placebo, $P < 0.001$), and acid regurgitation resolved in 65% and 67% (vs. 48%, $P < 0.001$). Resolution of both symptoms was greater with esomeprazole than with placebo in PLUTO/VENUS ($P \leq 0.001$), and than with ranitidine in study 285 ($P < 0.05$ for esomeprazole 20 mg).

Conclusion
Heartburn and regurgitation are common in patients taking NSAIDs and esomeprazole is efficacious for resolution of these symptoms.

doi:10.1111/j.1365-2036.2006.03210.x

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed to treat arthritic disorders and to manage pain and inflammation in a variety of other conditions.[1, 2] Although NSAIDs are effective in the treatment of inflammatory conditions, their use has been shown to increase the incidence of gastric mucosal damage and upper gastrointestinal (GI) symptoms.[3–6] Cyclooxygenase (COX)-2-selective NSAIDs were developed for their ability to circumvent the effects on the GI mucosa and ulcer development,[6] but the benefit of COX-2 inhibitors over non-selective NSAIDs appears to be less substantial in relation to upper GI symptoms.[7–10]

Upper GI symptoms that may occur during NSAID therapy include dyspepsia, heartburn, acid regurgitation and nausea. In an attempt to minimize the effects of such symptoms among NSAID users, physicians may opt to reduce the dose,[11] and thus risk recurrence of the underlying inflammatory condition. Another clinically appropriate option would be effective prevention or treatment of upper GI symptoms to facilitate well-tolerated administration of NSAID therapy at the most appropriate dose.

Although NSAID-induced upper GI injury may, in part, be pH dependent,[12] the mechanisms underlying concomitant upper GI symptoms are not as well understood. Symptoms may potentially be caused by microscopic injury or exacerbation of underlying conditions, such as gastro-oesophageal reflux disease (GERD).[13] However, as acid-suppressive therapy with a proton pump inhibitor (PPI) has been shown to improve upper GI symptoms in chronic NSAID users with or without gastroduodenal lesions,[14–16] it is possible that symptoms are related to gastric acidity.

We aimed to assess the efficacy of esomeprazole therapy for treatment of heartburn and acid regurgitation in continuous users of NSAIDs, including COX-2-selective agents. This *post hoc* analysis comprised five large, randomized, double-blind, multicentre clinical trials.[16–18] Two of the studies (NASA1/SPACE1) evaluated esomeprazole for relief of upper abdominal pain, discomfort or burning in non-ulcer populations who did not have *a prior* history of GERD or dyspepsia.[16] Another two studies (PLUTO/VENUS) investigated esomeprazole for the prevention of NSAID-associated peptic ulcer in at-risk patients.[17] Study 285 assessed healing of NSAID-associated gastric ulcers with esomeprazole.[18]

PATIENTS AND METHODS

Patients on continuous NSAID therapy, including COX-2-selective agents, were enrolled into various randomized, double-blind multicentre studies (Figure 1). Patients entering these studies were *Helicobacter pylori*-negative and were expected to require stable, continuous NSAID therapy for the duration of the trials. All studies were approved by independent ethics committees and were performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Studies in non-ulcer patients with baseline pain, discomfort or burning in the upper abdomen (NASA1/SPACE1)

Two identical placebo-controlled studies [NASA1 (ClinicalTrials.gov Identifier: NCT00241540, study code: SH-NEN-0001) and SPACE1 (ClinicalTrials.gov Identifier: NCT00241527, study code: SH-NEN-0003)] enrolled patients with pain, discomfort or burning in the upper abdomen who had been taking stable, continuous NSAID treatment for ≥4 weeks prior to baseline endoscopy and whose treatment was expected to continue for ≥7 months (i.e. the duration of these and the subsequent maintenance studies). Treatment could include COX-2-selective agents, non-selective NSAIDs, high-dose aspirin (>325 mg/day), or a combination of any of these.[16] Continuous NSAID treatment was defined as medication use on ≥5 days in any given week for at least 4 weeks prior to screening. Patients who reported pain, discomfort or burning of at least moderate severity [score of ≥3 on a 7-point scale,[19] where 0 = none and 6 = very severe] on at least 3 days of the screening week prior to the study were randomized to treatment with esomeprazole 20 or 40 mg once daily or matching placebo. Patients were excluded if they had a history of dyspepsia or GERD not associated with NSAID use (based on patient recall), as were those with current or previous gastroduodenal ulcer or erosive oesophagitis. The primary objective of these studies was to assess the efficacy of esomeprazole for the relief of pain, burning or discomfort in the upper abdomen; these results are reported elsewhere.[16]

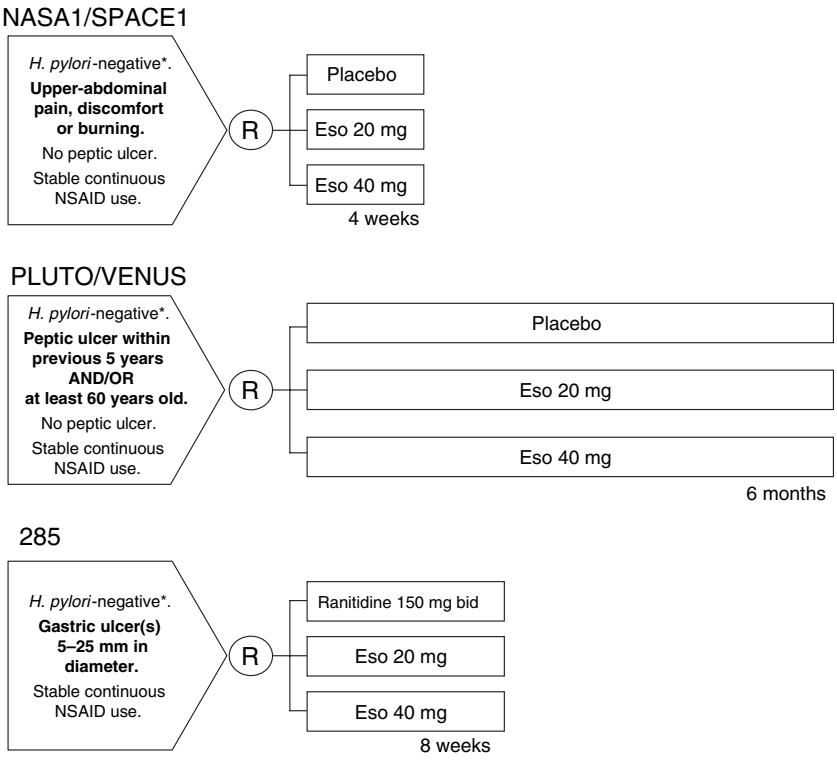

Figure 1. Study designs of the NASA1/SPACE1, PLUTO/VENUS, and 285 studies. * Patients initially diagnosed *Helicobacter pylori*-negative at baseline, who were then found to be *H. pylori*-positive by histological analysis, were included in the studies. b.d., twice daily; Eso, esomeprazole; NSAID, non-steroidal anti-inflammatory drug; R, randomization.

Studies in patients at increased risk of gastric ulcers (PLUTO/VENUS)

Two identical placebo-controlled studies [PLUTO (study code: SH-NEN-0013) and VENUS (study code: SH-NEN-0014)] assessed the efficacy of esomeprazole 20 or 40 mg once daily for preventing gastric ulcers in at-risk patients (≥60 years old and/or a history of gastric or duodenal ulcers in the past 5 years) taking continuous NSAID therapy.[17] NSAID therapy must have been stable during the 4 weeks before baseline endoscopy, and was to remain stable throughout the study. Patients had no gastric or duodenal ulcers or evidence of oesophagitis detectable by endoscopy at baseline. Patients with evidence of oesophagitis, oesophageal stricture or Barrett's oesophagus were excluded.

Study in patients with gastric ulcers (Study 285)

Study 285 (study code: SH-NEN-0005) assessed the efficacy of esomeprazole 20 or 40 mg once daily vs. ranitidine 150 mg b.d. for healing NSAID-associated gastric ulcers.[18] Patients were required to be taking daily NSAID treatment (defined as ≥5 days/week) at a stable prescribed dose for a minimum of 4 weeks before baseline endoscopy. NSAID treatments could include COX-2-selective agents, multiple NSAIDs, or aspirin at doses of ≥80 mg/day. Patients were to have at least one NSAID-related gastric ulcer ≥5-mm diameter, but no gastric or duodenal ulcer >25-mm diameter, at baseline. Patients were excluded if they had current or historical evidence (within 3 months) of malabsorption, oesophageal stricture, oesophagitis or Barrett's oesophagus.

Assessments

This *post hoc* analysis assessed the efficacy of esomeprazole for the relief of NSAID-associated heartburn and acid regurgitation in these five studies. In all studies, heartburn was defined as 'a burning feeling, rising from the stomach or lower part of the chest towards the neck' and acid regurgitation was defined as 'flow of sour or bitter fluid into the mouth'. Investigators assessed the severity of patients' heartburn and acid regurgitation symptoms during the past 7 days using a 4-grade scale (where 0 = none, 1 = mild, 2 = moderate and 3 = severe) validated for the assessment of heartburn severity in symptomatic GERD patients.[20] Responsiveness of the 4-point scale was previously evaluated using the Overall Treatment Effect

questionnaire as an anchor. The scale correlated well with the GI Symptom Rating Scale, both for investigator- and for diary-assessed heartburn severity, and demonstrated good construct validity, responsiveness and reliability.[20]

The timing of investigator assessments was prospectively defined in each individual study. Assessments were made at 2 and 4 weeks in the NASA1 and SPACE1 studies, at months 1, 3 and 6 in the PLUTO and VENUS studies, and at 4 and 8 weeks in study 285. Resolution of heartburn and acid regurgitation was defined as a severity score of 'none' in the week preceding assessment. Only patients with heartburn or acid regurgitation at baseline were included in this analysis. Patients from the PLUTO, VENUS and 285 studies were included in this analysis regardless of whether they had also experienced heartburn or acid regurgitation when not taking NSAIDs. Patients were excluded from the NASA1 and SPACE1 studies if they had a history of GERD when not taking NSAIDs. To assess the effect of COX-2-selective NSAIDs on heartburn and acid regurgitation in the NASA1 and SPACE1 studies, patients were included in the COX-2-selective subpopulations only if they were using a COX-2-selective agent with no other NSAID or aspirin.

Statistical analysis

In patients eligible for analysis (i.e. with heartburn or acid regurgitation at baseline), differences between treatment groups in each study were analysed by using Fisher's exact test. Number needed to treat to avoid persistent heartburn or acid regurgitation during NSAID therapy was calculated as the inverse of absolute risk reduction for the different populations (non-ulcer patients who are taking NSAIDs and who have upper abdominal pain, burning or discomfort, patients at risk of developing NSAID-associated ulcers, and patients with NSAID-associated gastric ulcers). The 95% CI were also calculated.

RESULTS

Baseline demographic and clinical characteristics of the study populations are shown in Table 1. The prevalence of heartburn and acid regurgitation was highest in the NASA1/SPACE1 population, with 87% of patients reporting some degree of heartburn, as assessed by the investigator, and 77% having acid regurgitation. In each study, the prevalence of heartburn and acid regurgitation was similar between treatment groups. The mean age was higher in the PLUTO/VENUS study population, while the use of COX-2-selective agents was lowest in study 285. For all studies, resolution rates refer only to patients who had the symptom at baseline.

Non-ulcer patients with baseline pain, discomfort or burning in the upper abdomen (NASA1/SPACE1)

In these studies, both doses of esomeprazole (20 or 40 mg once daily) were significantly more effective than placebo for resolution of heartburn and acid regurgitation after 4 weeks of treatment (Figure 2).

Table 1. Baseline demographic and clinical characteristics of patients in the NASA1/SPACE1, PLUTO/VENUS, and 285 studies (overall populations)

Characteristic	NASA1/SPACE1 ($n = 1149$)	PLUTO/VENUS ($n = 1378$)	Study 285 ($n = 399$)
Sex,% women	75	71	71
Mean age (year)	55	65	58
Type of chronic condition, %:			
Rheumatoid arthritis	21	19	11
Osteoarthritis	42	65	58
Other	37	16	31
Heartburn at baseline, %	87	50	69
Acid regurgitation at baseline, %	77	40	50
Helicobacter pylori-positive (histology), %	11	11	19
COX-2-selective NSAID use, %	34	29	19

NSAID, non-steroidal anti-inflammatory drug.

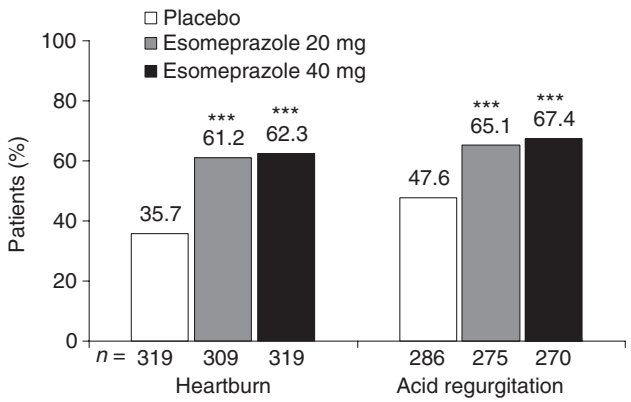

Figure 2. Patients in the NASA1/SPACE1 population achieving resolution of heartburn or acid regurgitation after 4 weeks of treatment, as a proportion of those having either symptom at baseline. *** $P < 0.001$ vs. placebo.

Moreover, esomeprazole was significantly more effective than placebo for resolution of heartburn and acid regurgitation in users of non-selective and COX-2-selective NSAIDs (Table 2).

Patients at increased risk of ulcers (PLUTO/VENUS)

Among continuous NSAID users at increased risk of peptic ulcer development, esomeprazole at either dose (20 or 40 mg once daily) was significantly more effective than placebo for resolution of heartburn and acid regurgitation after 6 months of treatment (Figure 3).

Patients with gastric ulcers (Study 285)

Among patients with NSAID-associated gastric ulcer who, at baseline, also had heartburn or acid regurgitation, esomeprazole 20 and 40 mg once daily was more effective than ranitidine 150 mg b.d. for symptom resolution after 8 weeks of treatment (Figure 4).

Numbers needed to treat

The numbers needed to treat with esomeprazole to prevent persistent heartburn and acid regurgitation among continuous NSAID users are shown in Table 3, alongside the absolute risk reductions. These values indicated that, in the population of non-ulcer patients with epigastric pain, discomfort or burning in the upper abdomen at baseline, no more than six patients (range: 3–11 patients based on the 95% CI for the absolute risk reduction) would need to be treated with esomeprazole to avoid 1 case of persistent heartburn or acid regurgitation during NSAID therapy that would otherwise occur if symptoms were treated with placebo. In the population at risk for ulcer development, the corresponding number of patients was 5 (range: 3–12). Additionally, no more than seven patients (range: 3–188) would need to be treated with esomeprazole to avoid 1 case of persistent heartburn or acid

Table 2. Patients in the NASA1/SPACE1 population achieving resolution of heartburn or acid regurgitation, by non-steroidal anti-inflammatory drugs (NSAID) type (patients having symptom at baseline).

Symptom	NSAID type	Treatment (mg)	Patients with symptom resolution at week 4 (%)	*P*-value
Heartburn	COX-2-selective	Placebo	39/114 (34)	–
		Esomeprazole 20	66/102 (65)	<0.001
		Esomeprazole 40	79/112 (71)	<0.001
	Non-selective	Placebo	75/205 (37)	–
		Esomeprazole 20	123/207 (60)	<0.001
		Esomeprazole 40	116/201 (58)	<0.001
Acid regurgitation	COX-2-selective	Placebo	43/93 (46)	–
		Esomeprazole 20	57/88 (65)	<0.05
		Esomeprazole 40	69/95 (73)	<0.001
	Non-selective	Placebo	93/193 (48)	–
		Esomeprazole 20	122/187 (65)	0.001
		Esomeprazole 40	113/175 (65)	<0.005

COX-2, cyclooxygenase-2

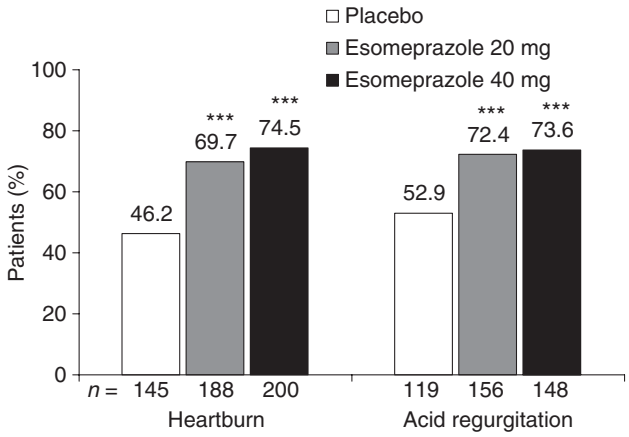

Figure 3. Patients in the PLUTO/VENUS population achieving resolution of heartburn or acid regurgitation after 6 months of treatment, as a proportion of those having either symptom at baseline. *** $P \leq 0.001$ vs. placebo.

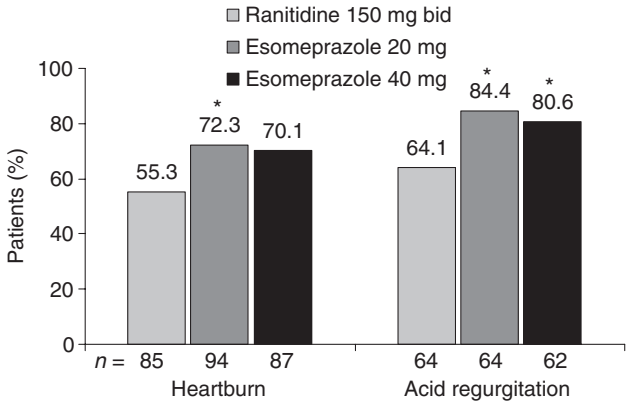

Figure 4. Patients in the 285 study achieving resolution of heartburn or acid regurgitation after 8 weeks of treatment, as a proportion of those having either symptom at baseline. * $P < 0.05$ vs. ranitidine 150 mg b.d.

regurgitation that would otherwise occur if patients with gastric ulcers were treated with ranitidine.

DISCUSSION

A substantial proportion of patients receiving continuous NSAID therapy experienced symptoms of heartburn and acid regurgitation in the three study populations analysed, which is consistent with previous observations.[7, 21] The results of the current analysis show that esomeprazole is effective for the resolution of such symptoms in these patient subgroups, who represent a spectrum of NSAID-associated disorders: continuous NSAID users without endoscopically evident mucosal damage in the oesophagus but with symptoms of pain, discomfort or burning in the upper abdomen; continuous NSAID users at risk of peptic ulcer development; and patients with current NSAID-associated gastric ulcers.

Heartburn and acid regurgitation were most common in the combined NASA1/SPACE1 study population, occurring in 77–87% of patients. The NASA1/SPACE1 population was free of peptic ulcers and oesophagitis and had no history of heartburn or acid regurgitation when not receiving NSAIDs, thereby suggesting that these symptoms were occurring as a consequence of NSAID therapy. The PLUTO/VENUS population comprised patients at risk of ulcer development, many of whom were ≥60 years old. This population is likely to be broadly representative of a general population of patients on NSAID therapy, most of whom are elderly.[22] These patients were, on average, 10 years older than those in the NASA1/SPACE1 population but had less heartburn and acid regurgitation. Although this may reflect different entry criteria, it is possible that the decreased oesophageal pain sensitivity in more elderly patients that has been postulated previously[23] played a role.

Use of COX-2-selective agents is associated with a lower risk of GI events and drug-related discontinuations compared with non-selective NSAIDs.[6, 9] Indeed, fewer patients with gastric ulcers in study 285 used COX-2-selective agents compared with the non-ulcer patients in NASA1/SPACE1 and PLUTO/VENUS (19% vs. 34% and 29%, respectively). However, results from our studies are consistent with previous observations that, while the comparative risk of ulcers is less in patients using COX-2 inhibitors than in patients receiving non-selective NSAIDs, the two classes are less differentiated in terms of upper GI symptoms.[7, 8, 10] In the pooled NASA1/SPACE1 patient population, the relatively high proportion of patients using COX-2-selective agents, and the high proportions of patients with heartburn and acid regurgitation at baseline, facilitated meaningful comparisons by NSAID type. In this analysis, a similar proportion of placebo recipients experienced persistent symptoms of heartburn and acid regurgitation regardless of whether they were using COX-2-selective agents or non-selective NSAIDs, as has been reported for the endpoints of pain, burning or discomfort centred in the upper abdomen.[16]

Table 3. Absolute risk reduction and number needed to treat to avoid patients having persistent heartburn or acid regurgitation after 4 weeks (NASA1/SPACE1), 8 weeks (285) or 6 months' (PLUTO/VENUS) treatment with esomeprazole relative to placebo or ranitidine 150 mg b.d.

Study population (comparator)	Gastro-oesophageal reflux disease symptom	Treatment (mg)	Absolute risk reduction (95% CI)	Number needed to treat (range)
NASA1/SPACE1 (placebo)	Heartburn	Esomeprazole 20	0.25 (0.18–0.33)	4 (3–6)
		Esomeprazole 40	0.26 (0.19–0.34)	4 (3–5)
	Acid regurgitation	Esomeprazole 20	0.18 (0.09–0.26)	6 (4–11)
		Esomeprazole 40	0.20 (0.12–0.28)	5 (4–8)
PLUTO/VENUS (placebo)	Heartburn	Esomeprazole 20	0.23 (0.13–0.34)	4 (3–8)
		Esomeprazole 40	0.28 (0.18–0.38)	4 (3–6)
	Acid regurgitation	Esomeprazole 20	0.2 (0.08–0.31)	5 (3–12)
		Esomeprazole 40	0.2 (0.09–0.32)	5 (3–11)
285 (ranitidine)	Heartburn	Esomeprazole 20	0.17 (0.03–0.31)	6 (3–32)
		Esomeprazole 40	0.15 (0.01–0.29)	7 (3–188)
	Acid regurgitation	Esomeprazole 20	0.2 (0.06–0.35)	5 (3–18)
		Esomeprazole 40	0.17 (0.01–0.32)	6 (3–79)

It is of note that this analysis only included patients with symptoms of heartburn and acid regurgitation at baseline. As these patients were a subgroup of the entire patient populations randomized in the respective studies, the population for analysis may be influenced by systematic bias. This analysis included all patients with heartburn and acid regurgitation at baseline, regardless of whether their symptoms were exclusively NSAID-associated or not. In an effort to exclude patients with heartburn and acid regurgitation not associated with NSAIDs, patients with a history of GERD when not taking NSAIDs (based on patient recall) were excluded from the NASA1/SPACE1 studies. However, this was not an exclusion criterion for the PLUTO/VENUS and 285 studies. Therefore, while symptoms of heartburn and acid regurgitation in the NASA1/SPACE1 populations are unlikely to be directly attributable to GERD, this may have been a confounding factor in the PLUTO/VENUS and 285 studies, meaning that some patients in these studies may have had NSAID-independent GERD. In addition, given the high prevalence of GERD in the general population, it is also possible that some patients' symptoms may have been due to the presence of occult GERD. By the same token, however, it can pragmatically be argued that our data do represent patients with NSAID-associated GERD. Another potential limitation is that symptom history when not taking NSAIDs was based exclusively on patient recall. It is possible that this may have been inaccurate in patients who had been taking NSAID medication for a long period of time.

The associative mechanisms of NSAID use and upper GI symptomatology are not fully understood. NSAIDs have multiple effects on GI biology that may act in concert to compromise mucosal defence and potentiate acid-related symptoms. For example, reduction in prostaglandin levels resulting from COX inhibition by NSAIDs compromises the barrier that protects the gastric mucosa from acid damage;[24, 25] the extent to which analogous effects occur in the oesophagus, however, is not clear. NSAIDs have been observed to cause increased gastric acidity,[26, 27] which could contribute to the upper GI symptoms that may occur with such therapy. Altered motility could also potentially be responsible, but the effects of NSAIDs on gastro-oesophageal sphincter function and gastric emptying have been little studied and results are inconsistent.[28, 29] Thus, direct and indirect mucosal injury may be implicated in the development of some symptoms, and it is possible that the increased gastric acidity associated with NSAIDs results in increased oesophageal acid exposure and associated symptoms of heartburn and acid regurgitation. The finding that NSAID-associated symptoms of heartburn and acid regurgitation were resolved with esomeprazole therapy indicates that these symptoms are likely to be acid-related.

A dose–response relationship was not observed between esomeprazole 20 and 40 mg in terms of resolution rates for the entire NSAID population. Although a slight dose–response relationship was observed for the COX-2 subpopulation, this was not significant.

Thus, the maximum efficacy appears to have been achieved with the 20-mg dose of esomeprazole.

In conclusion, in three patient populations representing the spectrum of continuous NSAID users, esomeprazole provided resolution of heartburn and acid regurgitation. Therefore, our results add to the evidence supporting the use of esomeprazole therapy for relief of these symptoms in patients receiving continuous NSAID therapy, including COX-2-selective agents.

ACKNOWLEDGEMENTS

Authors' declaration of personal interests: C. J. Hawkey has served as a speaker, a consultant or an Advisory Board member for AstraZeneca, GSK, Merck, Novartis, Pfizer, Takeda and has received research funding from the same organisations.

R. H. Jones has served as a speaker, a consultant or an Advisory Board member for AstraZeneca, Altana and Reckitt Benckiser.

N. D. Yeomans has served as a speaker, a consultant or an Advisory Board member for AstraZeneca.

J. M. Scheiman has served as a consultant to AstraZeneca, Merck, McNeil, Novartis, Takeda Pharmaceuticals, Pfizer, GI company Posen, Bayer, GSK, AstraZeneca, PLx Pharma, Nicox, and TAP Pharmaceuticals. He has served as a speaker for AstraZeneca and Santarus and has received research funding from AstraZeneca.

N. J. Talley served as a consultant for Altana, EBMed, Giaconda, Medscape, ProEd Communications, Solvay, Strategic Consultants International, Takeda Pharmaceuticals Inc, TAP Pharmaceutical Products Inc, Therapeutic Gastrointestinal Group, and Theravance. He has received research funding from TAP Pharmaceuticals, Merck, Novartis, Axcan, Boehringer-Ingelheim, Forest and GlaxoSmithKline.

J. L. Goldstein has served as a speaker, a consultant or an Advisory Board member for Pfizer, AstraZeneca, TAP Pharmaceuticals, Takeda, Pozen, GlaxoSmithKline, Novartis, Amgen and Sucampo and has received research funding and/or educational grants from the same organisations.

H. Ahlbom is an employee of AstraZeneca

J. Naesdal is an employee of AstraZeneca

Declaration of funding interests: The study was funded in full by AstraZeneca. Writing support was provided by Claire Burn, Joanne Dalton and Steve Winter from Baltus Kluwer Health and funded by AstraZeneca.

REFERENCES

1 McCarthy D. Nonsteroidal anti-inflammatory drug-related gastrointestinal toxicity: definitions and epidemiology. *Am J Med* 1998; **105**: 3S–9S.

2 Cullen DJ, Seager JM, Holmes S, *et al*. Pharmacoepidemiology of non-steroidal anti-inflammatory drug use in Nottingham general practices. *Aliment Pharmacol Ther* 2000; **14**: 177–85.

3 Voutilainen M, Sipponen P, Mecklin JP, Juhola M, Farkkila M. Gastroesophageal reflux disease: prevalence, clinical, endoscopic and histopathological findings in 1128 consecutive patients referred for endoscopy due to dyspeptic and reflux symptoms. *Digestion* 2000; **61**: 6–13.

4 Wolfe F, Hawley DJ. The comparative risk and predictors of adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. *J Rheumatol* 2000; **27**: 1668–73.

5 Kotzan J, Wade W, Yu HH. Assessing NSAID prescription use as a predisposing factor for gastroesophageal reflux disease in a Medicaid population. *Pharm Res* 2001; **18**: 1367–72.

6 Laine L. The gastrointestinal effects of nonselective NSAIDs and COX-2-selective inhibitors. *Semin Arthritis Rheum* 2002; **32** (3 Suppl. 1): 25–32.

7 Langman MJ, Jensen DM, Watson DJ, *et al*. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999; **282**: 1929–33.

8 Silverstein FE, Faich G, Goldstein JL, *et al*. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. *JAMA* 2000; **282**: 1247–55.

9 Lisse JE, Perlman M, Johannson G, *et al*. Gastrointestinal tolerability and effectiveness of rofecoxib vs. naproxen in the treatment of osteoarthritis: a randomized, controlled trial. *Ann Inter Med* 2003; **139**: 539–46.

10 Veldhuyzen van Zanten SJO, Bradette M, Chiba N, *et al*. Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. *Can J Gastroenterol* 2005; **19**: 285–303.

11 Singh G, Rosen Ramey D. NSAID induced gastrointestinal complications: the ARAMIS perspective-1997. Arthritis, Rheumatism, and Aging Medical Information System. *J Rheumatol Suppl* 1998; **25** (Suppl. 51): 8–16.

12 Elliot SL, Ferris RJ, Giraud AS, *et al*. Indomethacin damage to rat gastric mucosa is markedly dependent on luminal

pH. *Clin Exp Pharmacol Physiol* 1996; **23**: 432–4.
13 McCarthy DM. Prevention and treatment of gastrointestinal symptoms and complications due to NSAIDs. *Best Pract Clin Gastroenterol* 2001; **15**: 755–73.
14 Ekstrom P, Carling L, Wetterhus S, *et al*. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study. *Scand J Gastroenterol* 1996; **31**: 753–8.
15 Yeomans N, Wilson I, Langstrom G, *et al*. Quality of life in chronic NSAID users: a comparison of the effect of omeprazole and misoprostol. *Scand J Rheumatol* 2001; **30**: 328–34.
16 Hawkey C, Talley NJ, Yeomans ND, *et al*. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiinflammatory drugs, including selective COX-2 inhibitors. *Am J Gastroenterol* 2005; **100**: 1028–36.
17 Scheiman JM, Yeomans ND, Talley NJ, *et al*. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. *Am J Gastroenterol* 2006; **101**: 701–10.
18 Goldstein JL, Johansen JF, Suchower LJ, Brown KA. Healing of gastric ulcers with esomeprazole vs. ranitidine in patients who continued to receive NSAID therapy: a randomized trial. *Am J Gastroenterol* 2005; **100**: 2650–7.
19 Junghard O, Lauritsen K, Talley NJ, *et al*. Validation of seven graded diary cards for severity of dyspeptic symptoms in patients with non-ulcer dyspepsia. *Eur J Surg Suppl* 1998; **583**: 106–11.
20 Junghard O, Wiklund I. Validation of a 4-graded scale for severity of heartburn in symptomatic GERD patients [abstract]. *Gut* 2004; **53** (Suppl. VI): A103.
21 Hirschowitz BI. Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. *Gastroenterologist* 1994; **2**: 207–23.
22 Tenenbaum J. The epidemiology of nonsteroidal anti-inflammatory drugs. *Can J Gastroenterol* 1999; **13**: 119–22.
23 Johnson DA, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastroesophageal reflux disease. *Gastroenterology* 2004; **126**: 660–4.
24 Allen A, Flemstrom G, Garner A, Kivilaakso E. Gastroduodenal mucosal protection. *Physiol Rev* 1993; **73**: 823–57.
25 Rich M, Scheiman JM. Nonsteroidal anti-inflammatory drug gastropathy at the new millennium: mechanisms and prevention. *Semin Arthritis Rheum* 2000; **30**: 167–79.
26 Levine RA, Schwartzel EH. Effect of indomethacin on basal and histamine-stimulated human gastric acid secretion. *Gut* 1984; **25**: 718–22.
27 Savarino V, Mela GS, Zentilin P, *et al*. Effect of one-month treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) on gastric pH of rheumatoid arthritis patients. *Dig Dis Sci* 1998; **43**: 459–63.
28 Kulkarni SG, Parikh SS, Shankhpal PD, *et al*. Gastric emptying of solids in long-term NSAID users: correlation with endoscopic findings and *Helicobacter pylori* status. *Am J Gastroenterol* 1999; **94**: 382–6.
29 Bouras EP, Burton DD, Camilleri M, Stephens DA, Thomforde GM. Effect of cyclooxygenase inhibitors on gastric emptying and small intestinal transit in humans. *Neurogastroenterol Motil* 2004; **16**: 729–35.