AstraZeneca

25N54

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Nexium

ACTIVE INGREDIENT: Esomeprazole

Trial title (number): To assess the diagnostic accuracy of the proton pump inhibitor test in a primary care population as well as its additional value over reflux history, using the symptom association probability outcome during 24-h oesophageal pH recording as reference test for gastro-oesophageal reflux disease.

Developmental phase: IV
First subject recruited: 02 January 2003
Database Lock: 17 January 2006
Approval date: 19 March 2002

OBJECTIVES

The aim of this study was to determine the diagnostic accuracy of the PPI test in a primary care population using the SAP outcome as reference test. In addition we wished to evaluate the additional value of the PPI test over a reflux history in the diagnosis of GORD.

METHODS

Patients

Patients with symptoms suggestive of GORD (i.e heartburn, regurgitation, acid taste, burning sensation in the epigastric region, epigastric pain and chest pain) were recruited from primary care practices and by local advertisement. The general practitioner (in case of primary care recruitment) or the research nurse (in case of recruitment by advertisement) judged whether the patient had symptoms suggestive of reflux disease. Patients had to have these symptoms for at least twice a week for the past 3 months or longer to be included. Subjects were not included when they had undergone gastro-intestinal surgery or when they needed endoscopic evaluation because of alarm symptoms (weight loss, dysphagia or hematemesis). Also those who had used PPIs longer than 30 days in the past 3 months or used H_2-antagonists or prokinetic drugs during the last month, were excluded. Pregnant and lactating women were not allowed to participate in the study and phenytoine and diazepam were prohibited because of possible drug interaction. Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Study protocol

On day one of the study, at baseline, symptoms suggestive of GORD were scored. Subsequently, 7 days later the patient underwent a 24-hour oesophageal pH monitoring. After the recording the patient used 40 mg of esomeprazole daily for two weeks. During these two weeks the patient had to answer daily whether his or her reflux symptoms were adequately suppressed (yes/no). The response to this question was used to judge whether the PPI test was positive or negative. Patients and general practitioners were kept blind for the result of the 24-hour pH monitoring until after the study.

24-hour pH monitoring

Prior to the 24-hour pH recording the LOS was manometrically identified using a 10-channel silicone rubber catheter with a reversed sleeve sensor (DentSleeve International Ltd, Mississauga, Ontario, Canada) which was perfused at a rate of 0.2 mL/min with degassed water, using hydraulic flow restrictors (DentSleeve International Ltd, Mississauga, Ontario, Canada). The pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland). After removal of the manometric catheter, a glass pH catheter with in-built reference electrode (Ingold, Urdorf, Switzerland) was transnasally placed 5 cm above the LOS. The pH catheter was calibrated with 3.2 and 7.4 pH buffers solutions. The pH catheter was then attached to a digital datalogger (MMS, Enschede, the Netherlands) which used a sampling frequency of 2 Hz.
All patients were instructed to record their symptoms by pressing the event marker button on the datalogger and at the same time specifying the symptom in a diary card. In the diary card also the times of consumption of meals and beverages and the recumbent time were noted. Patients were instructed to restrict their intake to 3 meals and 3 drinks during the 24 hours at standardised times. Meals and drinks had to be consumed within 15 and 30 minutes respectively. Patients were encouraged to maintain their normal daily activities during the 24-hour pH study.
After the 24-hour recording period the data from the datalogger was transferred to a personal computer.

Data analysis

The 24-hour pH recording data were analysed automatically (MMS, Enschede, the Netherlands), excluding all eating and drinking periods. The SAP was calculated according to Weusten et al. and was considered positive if it exceeded 95% (17). The SI was defined as the number of reflux-associated symptom episodes divided by the total number of symptom episodes multiplied by 100%. The threshold for a positive SI was set at 50% (16). The SSI was defined as the number of symptom-associated reflux episodes divided by the total number of reflux episodes times 100%. Values above 10% were considered to be positive (15). The sensitivity, specificity and predictive values were calculated using a 2 by 2 contingency table. For each of the 13 PPI test days, comparisons were made between the symptomatic response and with each of the three symptom-reflux association indices; SAP, SI and SSI. The presence of a reflux symptom (i.e. positive result) was compared to the SAP outcome.
The sensitivity of the PPI test or the presence of a reflux symptom was defined as the fraction of all individuals with the disease in whom a positive result was obtained, specificity was calculated as the fraction of those without the disease who yielded a negative test result. Predictive values indicated the chance of whether the test result was really true. Likelihood ratios, which express the discriminating power of the test, were calculated by dividing the sensitivity by 1 minus specificity.

Statistical analysis

The p values were determined with ANOVA tests and Bonferroni post hoc tests and statistically significant differences were judged to be present when $p<0.05$. Results are presented as mean with a 95% confidence interval (CI).

RESULTS

Ninety patients with reflux symptoms were included of which 74 were analysable (see figure 1). The 74 subjects had a median age of 51 year (41- 62). Sixty-two percent were male, twenty-one percent smoked and 74% used alcoholic beverages.
The symptoms of the 74 patients at baseline are shown in table 1. Heartburn was the most frequently reported symptom (82% of the patients). Four patients had used a PPI and four patients an H_2-antagonist in the past. Thirty-nine patients used antacids before this study. Three patients had undergone eradication therapy for H. pylori and one patient had a history of gastric ulcers.

Table 1
Prevalence of symptoms at baseline.

Symptom	(%)
Heartburn	82
Regurgitation	75
Burning sensation in epigastric region	70
Acid taste	48
Chest pain	46
Epigastric pain	44

The SAP, SI and SSI calculations indicated a positive symptom-reflux association in 70%, 62% and 45% of the patients respectively. The 24-hour pH monitoring data are shown in table 2.

Table 2
Results of 24-hour pH measurement

		Median	Percentiles	
			25^{th}	75^{th}
Time with pH<4 upright	(%)	9.6	4.4	15.6
Time with pH<4 supine	(%)	2.9	0.2	9.3
Time with pH<4 total	(%)	7.7	4.9	11.4
Number of reflux episodes upright	(n)	47.5	27.8	72.0
Number of reflux episodes supine	(n)	3.5	1.0	11.0
Number of reflux episodes total	(n)	53.0	33.8	78.5
Number of symptom episodes	(n)	9.0	4.8	13.3
Number of reflux-related episodes	(n)	5.0	2.0	9.3

The sensitivities of the PPI test obtained with the SAP (0.91, CI 0.78-0.96) and the SI (0.90, CI 0.77-0.96) as reference standard were statistically higher than those obtained with the SSI as standard (0.83, CI 0.65-0.93) (SAP vs SSI, SI vs SSI $p<0.01$, see figure 2A). The specificities of the PPI test calculated with SAP (0.26, CI 0.10-0.49) and SI (0.21, CI 0.09-0.42) as reference standard differed significantly from the specificity obtained by the SSI (0.11, CI 0.04-0.26) (SAP vs SSI, SI vs SSI $p<0.01$, see figure 2B).
The sensitivity and specificity of the found reflux suggestive symptoms are shown in table 3. The presence of all reflux suggestive symptoms gave a sensitivity of 0.59 (CI 0.45-0.72) and a specificity of 0.43 (CI 0.23-0.65) with the SAP as reference test.

Table 3
Sensitivity and specificity of the symptoms scored at baseline calculated with SAP as reference standard.

Reflux symptoms	Sensitivity	95%CI		Specificity	95%CI	
Heartburn	87%	0.74	0.94	27%	0.12	0.50
Regurgitation	82%	0.69	0.91	41%	0.21	0.63
Burning sensation in epigastric region	73%	0.59	0.84	38%	0.19	0.61
Acid taste	45%	0.31	0.60	45%	0.60	0.67
Chest pain	42%	0.29	0.57	45%	0.25	0.67
Epigastric pain	40%	0.27	0.55	48%	0.26	0.70

The positive predictive value of the PPI test with the SAP as reference standard (0.75, CI 0.62-0.85) was significantly higher than with SSI (0.43, CI 0.31-0.57) and SI (0.66, CI 0.53-0.77) as reference (SAP vs SSI, SAP vs SI, SSI vs SI $p<0.00$). The negative predictive values of the PPI test obtained with SAP, SI and SSI were 0.54 (CI 0.22-0.81), 0.58 (CI 0.25-0.83) and 0.45 (CI 0.17-0.76) respectively (SSI vs SI $p<0.05$).
The likelihood ratios of the PPI test were highest with SAP as reference standard (1.2, CI 0.9-1.6) compared to SI (1.2, CI 0.9-1.4) and SSI (0.9, CI 0.8-1.1) (SAP vs SSI, SSI vs SI $p<0.01$ SAP vs SI $p<0.05$, see figure 3).

The sensitivity, specificity, positive and negative predictive value did not differ significantly for each test day (see figure 2), neither did the likelihood ratios differ (see figure 3). The likelihood ratios of the reflux symptoms (1.0, CI 0.66-1.46) were similar to PPI test likelihood ratios with reference standard SAP (see figure 4).

Figures plus legends

Figure 1
Flowchart showing the inclusion.

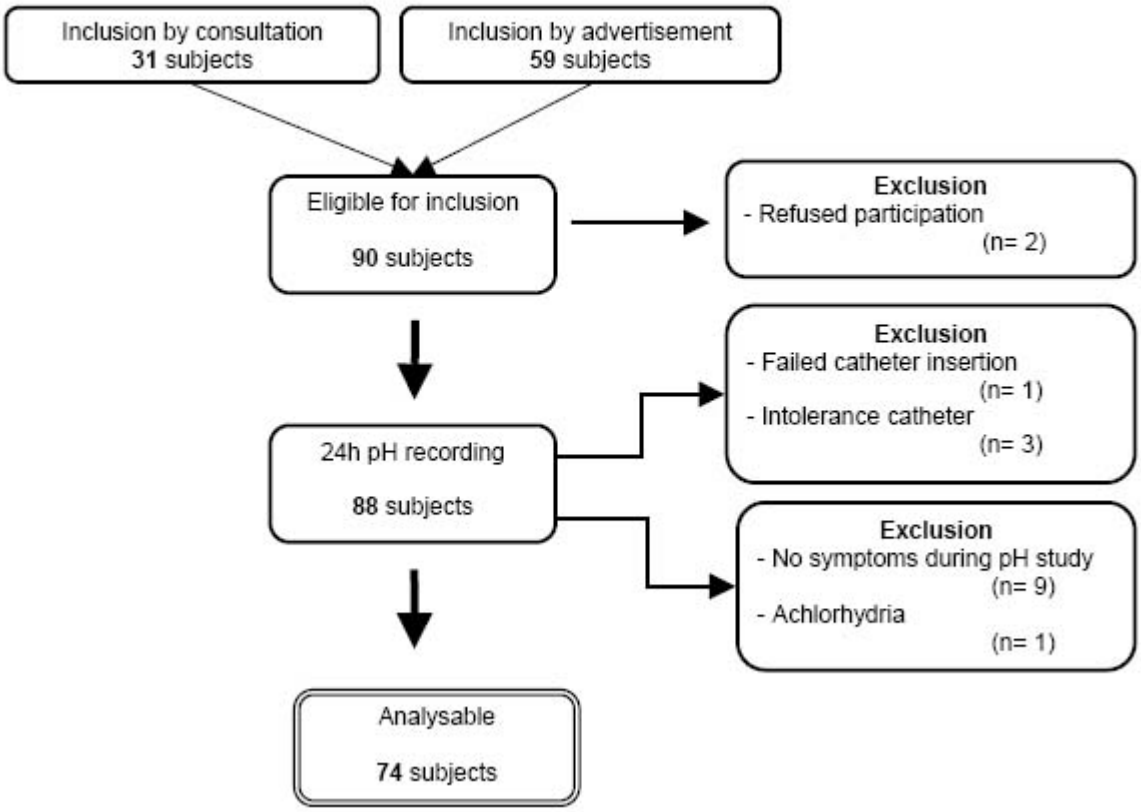
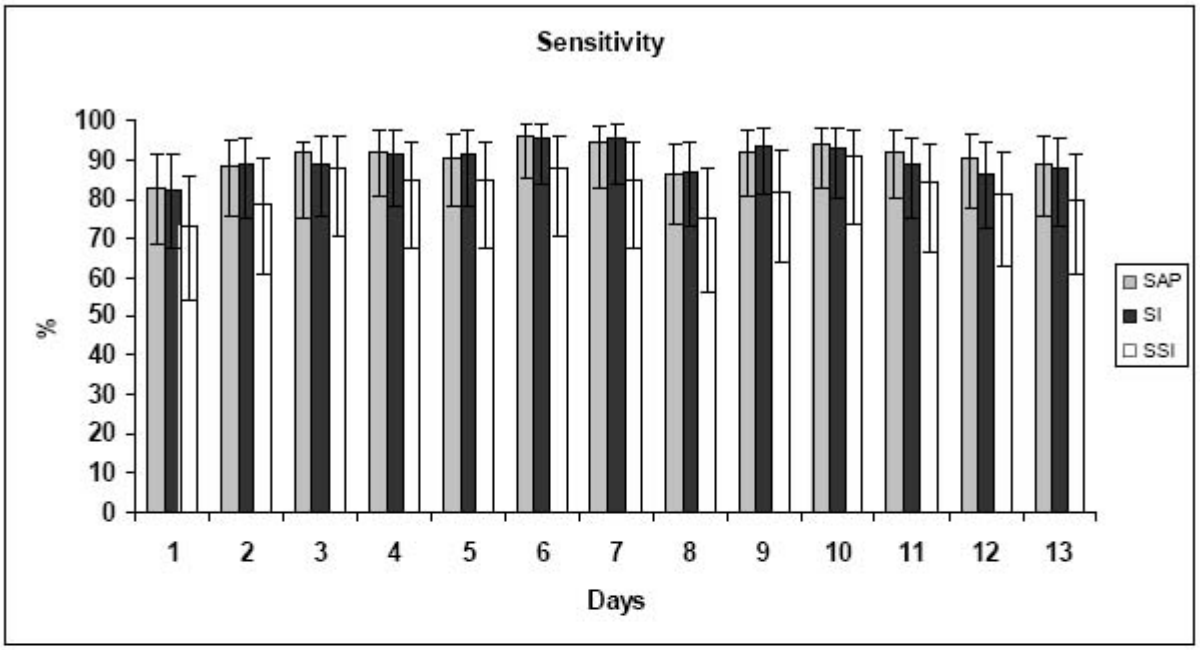


Figure 2
Sensitivity (A) and specificity (B) of the PPI test in percentages with SAP, SI and SSI as reference test for GORD for each of the 13 test days.

A



B

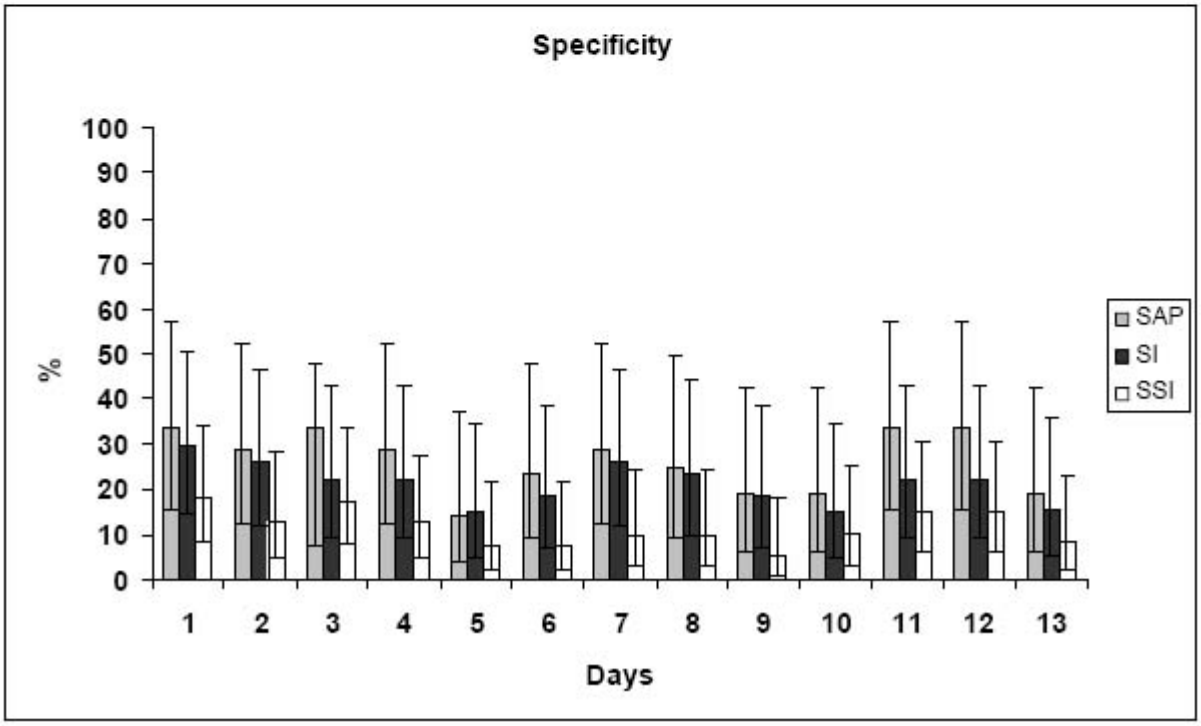


Figure 3
Likelihood ratio of the PPI test evaluated with the gold standards SAP, SI and SSI for each of the 13 test days.

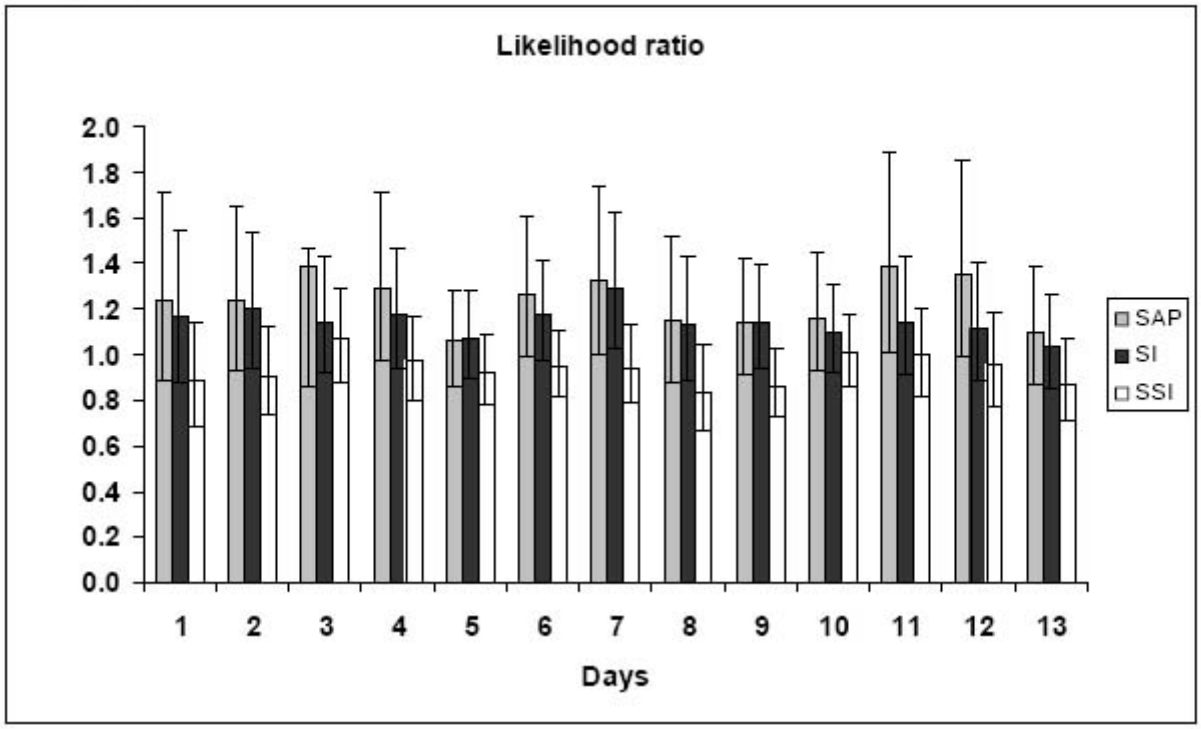
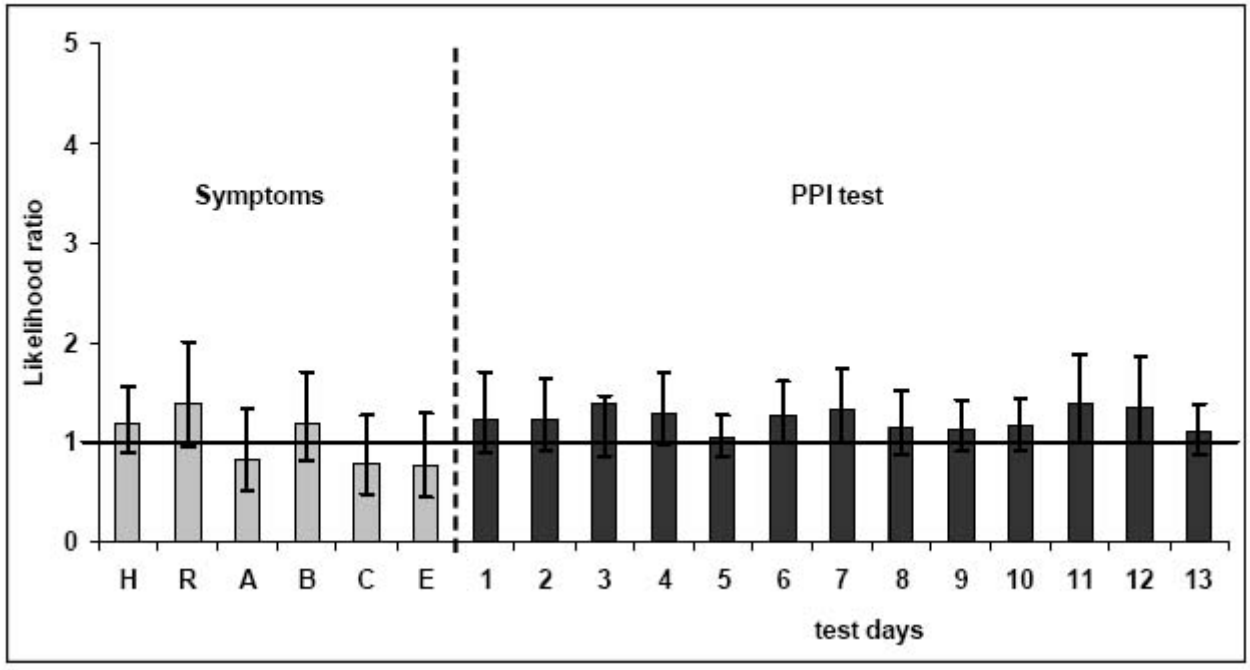


Figure 4



Likelihood ratios for the pre-test reflux symptoms (heartburn (H) regurgitation (R), acid taste (A), burning sensation in the epigastric region (B), chest pain (C) and epigastric pain (E)) and for the PPI test for each of the 13 days using the SAP as reference standard. A likelihood ratio of 1 (see line) indicates that the test result does not influence the final diagnostic outcome.

REFERENCE

Aanen MC et al. Aliment Pharmacol Ther 2006; 24:1377-1384

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.