AstraZeneca

Clinical Study Report Synopsis

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The risk of uncomplicated peptic ulcer in the general population

Study dates:	Retrospective observational cohort study covering the period January 1997 – December 2005
Phase of development:	Therapeutic use
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Study centre(s)
UK

Publications
None published at the time of writing this report.

Objectives
- To estimate the relative risk of uncomplicated peptic ulcer (UPU) associated with use of low-dose aspirin (ASA) and other anti-inflammatory drugs (non-steroidal anti-inflammatory drugs [NSAID] and steroids) in the general population
- To estimate the dose-response and duration-response associated with use of these drugs
- To estimate the relative risk of UPU associated with naive/non-naive use of low-dose ASA in the general population
- To evaluate the effect of proton pump inhibitors (PPI) (alone or in combination with anti-inflammatory drugs) on the occurrence of UPU in the general population
- To investigate the management of low-dose ASA and other oral antiplateletet drugs after UPU
- To estimate the relative risk of UPU associated with use of other common drugs (anticoagulants, antiplatelets, serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, antihypertensives, lipid-lowering agents, hormone replacement therapy [HRT])

Study design
A retrospective, observational cohort study with nested case–control analysis performed using data from The Health Improvement Network (THIN) primary care database in the UK.

Study population
Individuals were identified who were aged 40–84 years old between January 1997 and December 2005 who had been enrolled with their PCP for at least 2 years, and who had at least 1 year of computerized prescription history. Individuals with a diagnosis of cancer, Mallory–Weiss disease, or peptic ulcer (PU; complicated or uncomplicated), or a history of upper gastrointestinal bleeding, esophageal varices, alcohol abuse, liver disease, or coagulopathies were excluded. Any individuals aged 70 years or older at their start date who had at least 1 year of follow-up with one or fewer data points recorded during that time (proxy for incomplete data recording) were also excluded. All remaining individuals were included in the study population (N=1,049,689).

Case ascertainment

Individuals were followed up until the detection of UPU (index date), the end of the study period (December 2005), or until they reached the age of 85 years old, died, or met any of the exclusion criteria (including receiving a diagnosis of complicated PU). Of the individuals who had a Read code suggestive of a diagnosis of UPU, true cases (n=3,914) were considered those that had been diagnosed during a specialist visit or hospitalization. In addition, 9,969 control individuals with no diagnosis of UPU were sampled from the study cohort and frequency matched to cases by age, sex and calendar year of qualification for inclusion in the study population.

Data collection and analysis

Demographic (age, sex, body mass index [BMI]), lifestyle (e.g. smoking and alcohol intake) and comorbidity data were collected, as well as current/recent/past medication use at index date, for all cases and controls. Simultaneous exposure to ASA and gastroprotective drugs (PPIs and histamine 2 receptor antagonists [H_2RA]) was also determined. The group of current ASA users was subdivided for some analyses, with naive current ASA users being defined as those receiving ASA at the index date and having received their first ASA prescription during the study period after an interval of more than 365 days during which they received no ASA prescription. All other ASA users were defined as non-naive.

For patients who received a diagnosis of UPU, use of ASA, NSAID and PPIs was also ascertained in the year following their date of diagnosis (as recorded in their medical records).

Statistical methods

A nested case-control analysis was carried out using unconditional logistic regression analysis models, adjusted (when appropriate) for sex, age, calendar year of index date, number of primary care physician (PCP) visits and specialist referrals in the year before the index date, smoking status, and use of gastroprotective drugs (PPIs or H_2RAs), paracetamol, ASA, and NSAIDs.

Summary of results

Patient characteristics and comorbidities

The demographic and lifestyle characteristics and the comorbidities that were significantly associated with the development of UPU are shown in Table 1. UPU was significantly associated with being a current or former smoker, having had at least two PCP visits or one or more specialist referrals in the year before the index date, and having a score of at least 3 on the Townsend deprivation index. Among the comorbidities, stress, depression, gastroesophageal reflux disease (GERD), and upper gastrointestinal (GI) symptoms were also all significantly associated with UPU development.

Risk of UPU development and medication use

UPU development was associated with current use of ASA, NSAIDs, paracetamol, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, antihypertensives, or gastroprotective medications (PPIs and H_2RAs), compared with non-use (Table 2). The risk of UPU was increased 1.5-fold (adjusted odds ratio [OR]: 1.54; 95% confidence interval [CI]: 1.37, 1.74) for current ASA use, and approximately 2.5-fold (adjusted OR: 2.62; 95% CI: 1.12, 6.11) for current dual antiplatelet therapy use (ASA and clopidogrel).

Effect of dose and duration of treatment

The risk of UPU was more pronounced for current users of multiple NSAIDs (adjusted OR: 3.82; 95% CI: 2.16, 6.73), compared with those using a single NSAID (adjusted OR: 1.64; 95% CI: 1.43, 1.87). The risk increased with increasing duration of NSAID treatment (adjusted OR: 2.46; 95% CI: 1.92, 3.16 for >3 years versus 1.07; 95% CI: 0.84, 1.35 for <3 months).

The risk of UPU associated with current ASA use was similar for low (<100 mg, adjusted OR: 1.52; 95% CI: 1.33, 1.73); medium (100–200 mg, adjusted OR: 1.61; 95% CI: 1.27–2.04) and high (>200 mg, adjusted OR: 1.70; 95% CI: 1.12, 2.57) doses, and was increased irrespective of duration of therapy (adjusted OR: 1.82; 95% CI: 1.38, 2.41 and 1.53; 95% CI: 1.26, 1.86 for <3 months and >3 years, respectively). Adjusted odds ratios for the risk of developing UPU were 1.50 (95% CI: 1.29, 1.75) and 2.41 (95% CI: 1.25, 4.63) in naive and non-naive users of ASA, respectively.

There was also an association between UPU development and current oral corticosteroid use with a duration longer than 3 years (adjusted OR: 1.92; 95% CI: 1.04, 3.53).

Effect of gastroprotective medication on the occurrence of UPU

There was a significant association between use of gastroprotective agents and the risk of UPU (PPIs, adjusted OR: 2.05; 95% CI: 1.77, 2.36; H_2RAs, adjusted OR: 2.99; 95% CI: 2.47, 3.63). These findings may be due to confounding by indication; that is, an association may be observed because gastroprotective medications were prescribed to treat PU symptoms.

A subgroup of naive ASA users was analysed to investigate this hypothesis further. Patients were classified into 3 groups, PPI non-users, those prescribed a PPI at the same time as their first ASA prescription, and those prescribed a PPI during follow-up after their first ASA prescription. There was a significantly increased risk of developing UPU in patients who received a PPI during follow up, compared with PPI non-users (adjusted OR: 2.29; 95% CI: 1.45, 3.63). In contrast, this association was not seen among patients who received a PPI at the same time as their first ASA prescription, compared with PPI non-users (adjusted OR: 0.86; 95% CI: 0.42, 1.78 for patients with continuous PPI use until the index date).

The management of ASA and NSAIDs after UPU diagnosis

In total, 52.9% of current ASA users at the date of UPU diagnosis received ≥1 ASA prescription within 60 days of the diagnosis date, and 42.7% received ≥2 ASA prescriptions during this time period (proxy for continuous use); this had increased to 70.1% and 61.4%, respectively, by 1 year after the diagnosis date. The majority (82.9%) of the patients who received ASA within 60 days of the diagnosis date also received a PPI prescription. Of current chronic NSAID users (duration of treatment ≥1 year) at the date of diagnosis, 49.6% received at least one NSAID prescription in the 60 days after diagnosis; the majority of these patients (84.7%) also received at least one PPI prescription in this time period.

Table 1. Demographic and lifestyle characteristics at the index date and comorbidities significantly associated with uncomplicated peptic ulcer development

	UPU cases (n=3,914) n (%)	**Controls (n=9,969) n (%)**	**Association Adjusted OR[a] (95% CI)**
Smoking[b]			
Current	1,151 (29.4)	1,852 (18.6)	1.90 (1.72, 2.10)
Former	680 (17.4)	1,431 (14.4)	1.30 (1.15, 1.45)
PCP visits[c]			
2-5 visits	1,463 (37.4)	3,537 (35.5)	1.17 (1.06, 1.29)
≥6 visits	1,034 (26.4)	1,697 (17.0)	1.48 (1.31, 1.67)
Specialist visits[d]			
1-2 visits	804 (20.5)	1,537 (15.4)	1.26 (1.13, 1.40)
≥3 visits	425 (10.9)	610 (6.1)	1.34 (1.16, 1.56)
Townsend deprivation index[e]			
3	782 (20.0)	1,926 (19.3)	1.16 (1.03, 1.31)
4	741 (18.9)	1,573 (15.8)	1.27 (1.12, 1.45)
5 (most deprived)	589 (15.0)	1,094 (11.0)	1.35 (1.18, 1.56)
Comorbidities[f]			
Stress	246 (6.3)	430 (4.3)	1.23 (1.03, 1.47)
Depression	900 (23.0)	1,615 (16.2)	1.23 (1.11, 1.36)
GERD	716 (18.3)	971 (9.7)	1.19 (1.06, 1.34)
GI symptoms[g]	2,050 (52.4)	2,845 (28.5)	1.88 (1.72, 2.04)

[a]Adjusted when appropriate for sex, age, year of index date, number of PCP visits and specialist referrals in the year before the index date, smoking status, and use of gastroprotective drugs (PPIs or H_2RAs), paracetamol, ASA, and NSAIDs.

[b]Compared with non-smokers.

[c]In the year before the index date, compared with 0–1 PCP visits.

[d]In the year before the index date, compared with no specialist visits.

[e]Compared with a Townsend deprivation index of 1.

[f]Relative to being free from the respective comorbidity. Only significantly associated comorbidities are listed.

[g]Including nausea, vomiting, dyspepsia, heartburn, and epigastric pain.

CI, confidence interval; GI, gastrointestinal; OR, odds ratio; PCP, primary care physician; UPU, uncomplicated peptic ulcer

Table 2. Medications for which current, past or recent use was significantly associated with uncomplicated peptic ulcer development

	Cases (n= 3,914) n (%)	**Controls (n=9,969) n (%)**	**Association[a]**	
			OR	**95% CI**
ASA				
Current	725 (18.5)	1,133 (11.4)	1.54	1.37, 1.74
Recent	65 (1.7)	89 (0.9)	1.74	1.23, 2.46
Past	142 (3.6)	233 (2.3)	1.28	1.01, 1.61
NSAIDs				
Current	560 (14.3)	734 (7.4)	1.70	1.49, 1.94
Recent	103 (2.6)	212 (2.1)	1.04	0.80, 1.34
Past	560 (14.3)	1,303 (13.1)	1.03	0.91, 1.16
Oral anticoagulants				
Current	85 (2.2)	154 (1.5)	1.21	0.91, 1.61
Recent	14 (0.4)	27 (0.3)	1.31	0.66, 2.62
Past	32 (0.8)	34 (0.3)	1.81	1.09, 3.02
Paracetamol				
Current	649 (16.6)	868 (8.7)	1.56	1.38, 1.78
Recent	190 (4.9)	281 (2.8)	1.45	1.18, 1.78
Past	651 (16.6)	1,140 (11.4)	1.32	1.17, 1.49
PPIs				
Current	451 (11.5)	524 (5.3)	2.05	1.77, 2.36
Recent	79 (2.0)	53 (0.5)	4.21	2.92, 6.08
Past	334 (8.5)	278 (2.8)	2.89	2.42, 3.44
H_2RAs				
Current	261 (6.7)	215 (2.2)	2.99	2.47, 3.63
Recent	67 (1.7)	34 (0.3)	4.62	2.99, 7.12
Past	344 (8.8)	237 (2.4)	3.25	2.71, 3.89
SSRIs				
Current	159 (4.1)	216 (2.2)	1.37	1.09, 1.72
Recent	20 (0.5)	52 (0.5)	0.80	0.46, 1.38
Past	108 (2.8)	212 (2.1)	0.92	0.72, 1.19

	Cases (n= 3,914) n (%)	Controls (n=9,969) n (%)	Association[a] OR	95% CI
Tricyclic antidepressants				
Current	205 (5.2)	279 (2.8)	1.29	1.05, 1.57
Recent	15 (0.4)	34 (0.3)	0.77	0.39, 1.49
Past	145 (3.7)	214 (2.1)	1.28	1.01, 1.61
Antihypertensives				
Current	1,494 (38.2)	2,938 (29.5)	1.13	1.02, 1.26
Recent	68 (1.7)	186 (1.9)	0.82	0.60, 1.11
Past	165 (4.2)	310 (3.1)	1.27	1.03, 1.57

[a]Relative to non-use. Adjusted (when appropriate) according to sex, age, year of index date, number of PCP visits and specialist referrals in the year before the index date, smoking status, and use of gastroprotective drugs (PPIs or H_2RAs), paracetamol, ASA, and NSAIDs.

ASA, acetylsalicylic acid; CI, confidence interval; H_2RA, histamine 2 receptor antagonists; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; PCP, primary care physician; UPU, uncomplicated peptic ulcer