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Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin

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SUMMARY

Background: Aspirin is valuable for preventing vascular events, but information about ulcer frequency is necessary to inform risk-benefit decisions in individual patients.

Aim: To determine ulcer prevalence and incidence in a population representative of those given aspirin therapy and evaluate risk predictors.

Methods: Patients taking aspirin 75–325 mg daily were recruited from four countries. Exclusions included use of gastroprotectant drugs or other non-steroidal anti-inflammatory drugs. We measured point prevalence of endoscopic ulcers, after quantitating dyspeptic symptoms. Incidence was assessed 3 months later in those eligible to continue (no baseline ulcer or reason for gastroprotectants).

Results: In 187 patients, ulcer prevalence was 11% [95% confidence interval (CI) 6.3–15.1%]. Only 20% had dyspeptic symptoms, not significantly different from patients without ulcer. Ulcer incidence in 113 patients followed for 3 months was 7% (95% CI 2.4–11.8%). *Helicobacter pylori* infection increased the risk of a duodenal ulcer [odds ratio (OR) 18.5, 95% CI 2.3–149.4], as did age >70 for ulcers in stomach and duodenum combined (OR 3.3, 95% CI 1.3–8.7).

Conclusions: Gastroduodenal ulcers are found in one in 10 patients taking low-dose aspirin, and most are asymptomatic; this needs considering when discussing risks/benefits with patients. Risk factors include older age and *H. pylori* (for duodenal ulcer).

INTRODUCTION

Low-dose aspirin is widely used because it reduces the risk of vascular events and death in patients with coronary and cerebrovascular disease,[1, 2] and has the advantages of both low cost and long duration of anti-platelet action.[3]

Although there is substantial net benefit from the use of aspirin – at least in high-risk vascular disease patients – it comes at the cost of an increased risk of peptic ulcer bleeding. Serious ulcer complications are about two- to fourfold higher in patients taking 75–300 mg daily than controls.[4, 5] As even a very low dose of aspirin (10 mg daily) decreases gastric mucosal

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prostaglandin levels and causes significant gastric lesions,[6] it is likely that the increased risk of ulcer bleeding is due to increased prevalence of ulcers. However, some or even much of the increased bleeding rate might result from the antiplatelet effect, increasing the probability of bleeding from incidental ulcers (i.e. ulcers caused by factors other than aspirin). As the frequency of ulcer in a representative population of those taking low-dose aspirin is not known, the relative contributions of these two mechanisms cannot be dissected out.

We therefore aimed at measuring the prevalence and incidence of gastric and duodenal ulcers in patients taking low-dose aspirin for vascular prophylaxis for any reason. We also evaluated several factors that might modulate the risk for such lesions.

METHODS

Study design and recruitment

The JUPITER study (Judging Ulcer Prevalence In aspirin Therapy: Endoscopic Rates) was conducted between March and December 2001 in Melbourne and Sydney, Australia; Edmonton, Canada; Zaragoza, Spain; and Nottingham, UK. Patients had an endoscopy at baseline to determine ulcer prevalence, then those who were eligible (see below) continued in the study (still taking aspirin) to have a second endoscopy 3 months later to assess ulcer incidence.

Patients

We aimed at recruiting 40 adult patients at each centre, who had been taking aspirin 75–325 mg daily for at least the preceding 28 days. They were stratified *pre hoc* into a higher risk group (aged ≥60 years and/or with a previous history of peptic ulcer) and a lower risk group (<60 years without ulcer history). Each centre was constrained to recruit between 30% and 70% in each stratum.

The major exclusion criteria for the prevalence study were: treatment with other non-selective non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, bisphosphonates, anticoagulants, acid suppressants (histamine H_2-antagonists or proton pump inhibitors) or prostaglandin analogues within the last 28 days; unstable angina, myocardial infarction, completed stroke or transient ischaemic attack within the 3 months prior to endoscopy, or any other condition considered to pose a risk for endoscopy.

Patients were excluded from continuing to the incidence study if they had gastric or duodenal ulcer or erosive oesophagitis at baseline (as they would need acid suppressant drugs), or upper gastrointestinal (GI) symptoms anticipated to require treatment during the study.

Demographic data

At baseline, we recorded patients' age, sex and race, duration and dose of aspirin therapy, aspirin formulation and indication for therapy, smoking history, previous history of gastric or duodenal ulcer and history of previous ulcer bleeding.

Gastrointestinal symptom assessments

Before each endoscopy, patients were questioned about GI symptoms (i) in a standardized way by the investigators, as detailed in the next paragraph, and (ii) by completion of the Gastrointestinal Symptoms Rating Scale (GSRS) questionnaire.

The investigator-recorded symptoms were: heartburn, acid regurgitation, nausea, upper abdominal bloating, epigastric pain, epigastric burning and epigastric discomfort during the previous 7 days (translated into Spanish for Zaragoza). They were graded as none, mild (awareness of sign or symptom but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities) or severe (incapacitating with inability to perform normal activities).

The GSRS covers 15 GI symptoms using a 7-graded Likert scale for each[7] – the lower the value, the less the symptoms – validated in both English and Spanish.

Endoscopic assessments

The primary variables were (i) the proportion of patients with gastric and/or duodenal ulcers at baseline, and (ii) the proportion developing an ulcer within 3 months, having been ulcer-free at baseline.

On the day of endoscopy, patients delayed taking their aspirin until after the procedure. An ulcer was defined as a mucosal break having significant depth, measuring 3 mm or more in its longest diameter; all other mucosal breaks were termed erosions (superficial lesions that do not extend below the mucosa). Ulcer size was measured with calibrated endoscopy forceps. The presence of

Helicobacter pylori was determined using a rapid urease test on an antral biopsy (or histology at the investigators' discretion).

Statistical methods

The proportions of patients with an ulcer at baseline and at the 3-month endoscopy were calculated with 95% confidence intervals (CI) based on the binomial distribution. Odds ratios (OR) with 95% CI and chi-square tests or Fisher's exact test on frequency data were performed using the SPSS statistical package. Mean values of continuous variables were compared with analysis of variance, *t*-test (or Mann–Whitney test when assumptions for *t*-test were not met). The sample size of 200 patients was calculated on the basis that a 95% CI of ±3% would be achieved if the observed proportion with an ulcer at baseline were 5%.

Ethical approval

This study was performed in accordance with the principles of good clinical practice[8] and the Declaration of Helsinki (1983 revision), with the approval of each institutional ethics committee. Written consent for participation was obtained from each participant.

RESULTS

Patient characteristics

A total of 206 patients were recruited. Of these, 19 failed to meet all eligibility criteria or withdrew their consent before the baseline endoscopy, leaving 187 eligible for calculation of ulcer point prevalence.

The main characteristics of these patients are shown in Table 1. These varied between countries, with the most notable differences being in *H. pylori* infection rates and age. The study population was middle-aged to elderly and predominantly male (except in Edmonton, where some younger women taking aspirin to reduce vascular risk from oral contraceptives were included).

Exactly 113 patients proceeded to a second endoscopy at 3 months. The most common individual reasons for withdrawal prior to this were presence of an ulcer ($n = 20$) or other GI findings ($n = 28$) (usually erosive oesophagitis) at baseline; a further 26 discontinued for a variety of reasons, including cessation of aspirin, commencement of prohibited medications, unwillingness to continue and loss to follow-up.

Prevalence and incidence of ulcers

At baseline, the point prevalence of ulcers was 10.7% (95% CI 6.3–15.1%)(Table 2). The mean (±s.d.) ulcer diameter was 4 ± 1.7 mm in the stomach (largest 8 mm) and 5 ± 2.5 mm in the duodenum (largest 10 mm). The proportions with ulcer in the predetermined 'higher risk' and 'lower risk' strata (see Methods) were, respectively, 11.6% and 9.3% ($P = 0.62$).

In the 113 patients eligible to continue to the 3-month endoscopy, a further 7.1% (95% CI 2.4–11.8%) developed an ulcer, the majority of which were in the stomach (Table 2). Assuming a linear rate of ulcer development, this translates to an annual ulcer incidence of 28%.

The distribution of ulcers across the five centres and the two visits was not homogeneous. At baseline, ulcers were found in 7 of 38, 6 of 33, 7 of 40, 0 of 37 and 0 of

Table 1. Demographic and other characteristics of the patients by centre

Patient characteristic	Edmonton ($n = 39$)	Melbourne ($n = 40$)	Nottingham ($n = 37$)	Sydney ($n = 38$)	Zaragoza ($n = 33$)	*P*-value*
Gender (% female)	79.5	22.5	16.2	15.8	45.5	<0.0001
Age (years; mean ± S.E.)	49.9 ± 2.1	61.0 ± 1.5	63.9 ± 1.7	61.3 ± 1.5	67.6 ± 2.0	<0.0001
H. pylori (% positive)	5.1	27.5	48.6	28.9	72.7	<0.0001
Smokers (%)	5.7	10.8	11.1	10.0‡	4.3‡	0.77
History of ulcer (%)	2.6	10.0	2.7	5.3	21.2	0.02†
Aspirin dose (mg; mean±S.E.)	160 ± 18	144 ± 9	103 ± 8	134 ± 9	124 ± 8	0.009

* Tested by chi-square for frequency data and one-way ANOVA for continuous variables.
† Fifty per cent of expected frequencies <5, so chi-square testing may be unreliable.
‡ Smoking status unknown in >10% of patients.

Table 2. Prevalence and incidence of ulcers and erosions in stomach and duodenum

	Stomach	Duodenum	Either site
Point prevalence			
Ulcers*	5.9 (11)	5.3 (10)	10.7 (20)
Erosions†	59.4 (111)	18.7 (35)	63.1 (118)
Incidence at 3 months			
Ulcers	6.2 (7)	0.9 (1)	7.1 (8)
Erosions†	56.6 (64)	14.2 (16)	60.2 (68)

Values are % (*n*).
* One patient at baseline had both gastric and duodenal ulcers.
† Proportion with any erosions at that site.

39, respectively, in Sydney, Zaragoza, Melbourne, Nottingham and Edmonton ($P = 0.004$). At the 3-month visit, the corresponding proportions with ulcers in these centres were 0 of 14, 2 of 14, 1 of 19, 3 of 29 and 2 of 37 ($P = 0.58$).

Risk factors for having an ulcer

Figure 1 shows the ORs for the presence of a baseline ulcer in relation to several possible risk factors. Ulcer risk was increased more than threefold in patients infected with *H. pylori*, or aged ≥70. The mean (±S.E.) ages of ulcer and non-ulcer patients were, respectively, 66.2 ± 2.6 and 59.8 ± 0.9 years ($P = 0.03$). Smoking, higher aspirin doses, previous ulcer history and gender were not significant risk factors in this study population. The increased risk in *H. pylori*-infected individuals was significant only for duodenal ulcers (OR 18.5; 95% CI 2.3–149.4), not gastric ulcers (OR 2.3, 95% CI 0.7–7.8).

Relation between symptoms and ulcers

The proportions of patients with epigastric symptoms in the week before each endoscopy are shown in Figure 2. Because few reported moderate or severe symptoms, these categories were amalgamated. At visit 1, only four of the 20 patients with an ulcer reported epigastric symptoms of *any* severity, and the distribution of symptom grades was similar to that in patients without ulcers. At the 3-month endoscopy, four of the eight patients with an ulcer reported symptoms (three mild, one moderate). There were also no significant differences between the ulcer and non-ulcer groups in the frequency and severity of the other investigator-recorded symptoms (nausea, acid regurgitation, heartburn, bloating) at either visit. Similarly, after adjusting for multiple testing, there were no significant differences between ulcer and non-ulcer patients in the scores on the five GSRS dimensions.

DISCUSSION

This study has demonstrated a high prevalence of ulcers in patients prescribed low-dose aspirin for vascular protection. The study group was large enough and sufficiently representative of the wider population taking low-dose aspirin to give a reliable estimate of ulcer risk in such patients.

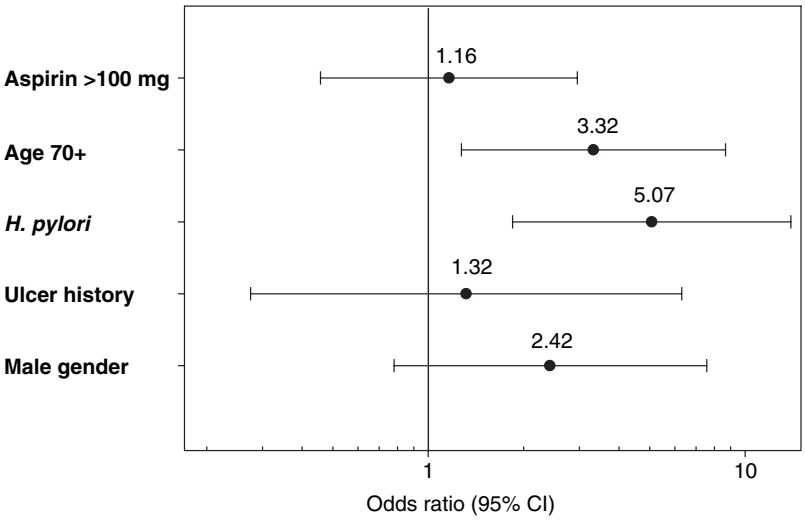

Figure 1. Odds ratios (with 95% confidence intervals) for presence of a gastric or duodenal ulcer at the baseline endoscopy, for several putative risk factors. The influence of *Helicobacter pylori* was significant only for duodenal ulcers (see text).

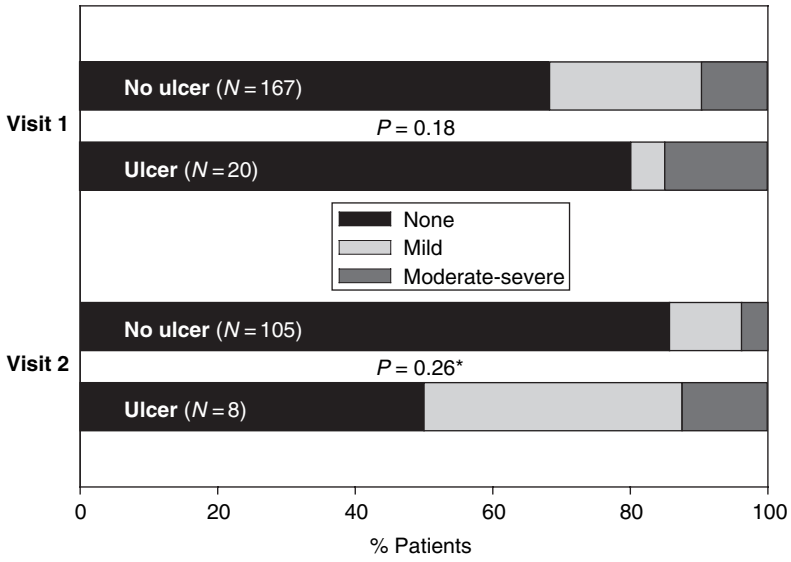

Figure 2. Epigastric symptoms (highest score reported by each patient on any of the three scales: epigastric discomfort, epigastric burning or epigastric pain) in the week prior to visit 1 and visit 2 endoscopies. *P*-values are for the comparison ulcer vs. no ulcer at each visit. * Tested with Fisher's exact test as expected frequencies (for chi-square) <5 in 50% of cells.

The prevalence we observed is lower than the 29% reported in patients (89% taking low-dose aspirin) who were being worked up for cardiac surgery with an obligatory gastroscopy.[9] However, the presurgical morbid state in some of these patients may have put their gastric mucosae at higher than normal risk. The incidence rate of 7% we found at 3 months is not dissimilar to the 10% over the same time period observed by Cryer and Feldman in a small group of volunteers given aspirin 10–325 mg daily.[6] Their study was not powered to estimate incidence, though, so CIs were very wide. In a population different to that evaluated in our study, Laine *et al.* recently found an identical 7% ulcer incidence over 3 months in patients with osteoarthritis who were taking enteric-coated low-dose aspirin but no other NSAID.[10]

Without performing gastroscopy on control patients not taking aspirin, we cannot directly calculate the *incremental* ulcer risk due to low-dose aspirin. Two studies that sampled whole populations with gastroscopy can be used for comparison, though: one found a point prevalence of 1.3% for peptic ulcer in the adult population of Soreisa, Norway;[11] a second showed an ulcer incidence of 0.2% per annum in the 30–60 year age group in Denmark.[12] In Laine *et al.*'s study of osteoarthritis patients,[10] the 3 month cumulative ulcer incidence in those taking placebo was 5%, but some (possibly many) had been taking NSAIDs immediately before the study began, and there is evidence that the NSAID ulcer risk carries over for a period of months after cessation of NSAIDs.[13]

Taken together, it is likely that low-dose aspirin increases the risk of gastroduodenal ulcers, and this increased ulcer risk appears to be broadly in line with the relative risk of two- to fourfold,[4, 14, 15] and an absolute risk of around 1% per annum[16] for such patients presenting with an ulcer *bleed*. In very high-risk patients (those with a prior ulcer bleed on aspirin), the annual risk of re-bleeding may be as high as 15%.[17] No aspirin dose that has been shown to be effective in vascular protection is safe for the GI tract – even at 75 mg daily the ulcer bleeding risk is increased about twofold.[4] It is the magnitude of this background risk of ulceration and bleeding, in comparison with the size of the gain in vascular events prevented, that has led the US Food and Drug Administration (FDA Cardiovascular and Renal Drugs Advisory Committee Meeting, December 8, 2003)[18] and others[19] to not recommend low-dose aspirin prophylaxis for people at average cardiovascular risk. Our findings add further weight to this recommendation for caution.

Because prevalence (P), incidence (I) and duration (t) of each episode of a disease are related by $P = It$, we can attempt to estimate the 'lifespan' of ulcers occurring on low-dose aspirin. Assuming linear incidence with time, we calculate mean ulcer duration to be about 4–5 months. This may be an overestimate, due to the removal of susceptibles who had an ulcer at the first endoscopy and because some ulcers may have appeared then healed between the two endoscopies. There are very wide CIs around our calculated 'lifespan', and of

course many factors such as ulcer size are likely to influence how long each undiagnosed event persists.

Our observation that *H. pylori* increases the risk of duodenal ulcer is in keeping with some previous data on ulcer and ulcer-bleeding prevalence in aspirin or non-aspirin NSAID users;[20] however, the relationship with gastric ulcer has been highly controversial. Similarly, our finding that age >70 increased risk of low-dose aspirin ulcers is consistent with other studies showing that old age increases ulcer risk on non-aspirin NSAIDs.[21–23] The low prevalence of ulcers in the younger, mostly *H. pylori*-free, patients in Edmonton is in keeping with those factors playing a part in aspirin ulcer risk. We did not show a relationship with aspirin dose or previous ulcer history – but that may be simply because our study was not powered for those analyses, or because of reluctance of doctors to prescribe aspirin to patients with an ulcer history. Case–control studies have consistently found that an ulcer history *is* a predictor of increased risk,[14, 21, 24] but whether there is a dose relationship over the 75–325 mg/day range has been more controversial.[4, 25]

Previous studies have shown that patients often present with an NSAID ulcer complication without any dyspeptic symptoms.[26] We find that this is also true for low-dose aspirin, and our study had the advantage that symptoms were quantitated prospectively without patient or doctor knowing whether an ulcer was present. Holtmann *et al.* have shown that asymptomatic patients taking aspirin elevate their gastric sensory threshold so that they do not experience dyspepsia despite acute mucosal damage.[27] The present study suggests that this lack of awareness extends to aspirin-associated ulcers in the community.

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