Prophylactic aspirin and risk of peptic ulcer bleeding

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Abstract

***Objective*—To determine the risks of hospitalisation for bleeding peptic ulcer with the current prophylactic aspirin regimens of 300 mg daily or less.**

***Design*—A case-control study with hospital and community controls.**

***Setting*—Hospitals in Glasgow, Newcastle, Nottingham, Oxford, and Portsmouth.**

***Subjects*—1121 patients with gastric or duodenal ulcer bleeding matched with hospital and community controls.**

***Results*—144 (12·8%) cases had been regular users of aspirin (taken at least five days a week for at least the previous month) compared with 101 (9·0%) hospital and 77 (7·8%) community controls. Odds ratios were raised for all doses of aspirin taken, whether compared with hospital or community controls (compared with combined controls: 75 mg, 2·3 (95% confidence interval 1·2 to 4·4); 150 mg, 3·2 (1·7 to 6·5); 300 mg, 3·9 (2·5 to 6·3)). Results were not explained by confounding influences of age, sex, prior ulcer history or dyspepsia, or concurrent non-aspirin non-steroidal anti-inflammatory drug use. Risks seemed particularly high in patients who took non-aspirin non-steroidal anti-inflammatory drugs concurrently.**

***Conclusion*—No conventionally used prophylactic aspirin regimen seems free of the risk of peptic ulcer complications.**

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Introduction

The risks of peptic ulcer complications, particularly bleeding, are raised in association with aspirin [1-4] and other non-steroidal anti-inflammatory drug use.[5-8] Most information about aspirin use concerns doses of more than 300 mg daily and intermittent use.[9-20] Less is known about risks associated with regular use of doses below 300 mg, which are increasingly being used as prophylaxis against vascular disease. As standard doses seem to be associated with substantial risks, it is important to know whether these lower doses are significantly safer. We report a case-control study conducted to see if important differences in the risks of hospital admission for ulcer bleeding existed between different non-steroidal anti-inflammatory drugs.

Patients and methods

Patients studied and methods used were as detailed elsewhere.[8] Briefly, prior drug intake of all types was determined by questioning patients aged 60 and over admitted with haematemesis and melaena due to gastric and duodenal ulceration to hospitals in Glasgow (200), Newcastle (124), Nottingham (506), Oxford (144), and Portsmouth (170) between April 1987 and January 1991. Cases were as far as possible consecutive and were diagnosed by conventional clinical criteria. Findings were compared with those in age and sex matched hospital and community controls. Hospital controls were chosen from among all acute medical admissions (excluding patients with acute myocardial infarction, acute rheumatic diseases, and active non-bleeding ulcers); community controls were selected as the next person of the same sex and age (within five years) on the alphabetically ordered register of the same general practitioner as the case.

Standard questionnaires, in addition to seeking information about all prescribed and self administered drug intake, also asked (among other things) about alcohol consumption, smoking, and any history of gastrointestinal disease. Results were analysed by calculating odds ratios and 95% confidence intervals by means of unconditional logistic regression. Conditional methods were rejected because initial analysis suggested that similar results but with tighter confidence intervals were achieved by unconditional methods. This mainly arose because the matching code for triplets went missing at one of the centres, so reducing the number of triplets available. In addition, because the referent groups chosen were cases and controls not exposed to non-aspirin non-steroidal anti-inflammatory drugs or aspirin, a large number of triplets became incomplete because of the high overall rate of non-aspirin non-steroidal anti-inflammatory drug or aspirin use.

Of the 1144 cases intially included, 23 showed no evidence of ulcer haemorrhage on review and were therefore excluded. Results in the remaining 1121 were compared with those in the 1126 hospital controls selected and the 989 community controls who agreed to take part.

Results

Table I shows that 144 (13%) cases were daily users of aspirin (defined as at least five days a week) compared with 101 (9%) of 1126 hospital controls and 77 (8%) of 989 community controls. In addition, 42 cases and 14 hospital and five community controls had been daily users of aspirin for less than a month. Odds ratios calculated by logistic regression to take account of confounding factors were consistently slightly greater in comparisons with community than with hospital controls, but all suggested raised risk (table II). Odds ratios increased progressively with aspirin dose in people who had been daily users for at least a month.

Daily users appeared to be at increased risk, by a doubling or more, if they had been users for less than a month compared with users for a month or more. There were also greater proportions of other regular or irregular users of aspirin among cases than among controls, defined respectively as used once to four times a week for more than a week and less than a month, and less than one day a week or only in the four days before admission. Table III shows that in all takers of aspirin, irrespective of dose, odds ratios

compared with combined controls calculated by logistic regression tended to be greatest in those who had taken aspirin for a week or less and differed little in those who had taken it longer.

Table IV shows the numbers of aspirin takers according to formulation in cases and controls, but irrespective of the dose taken, with the odds ratios calculated by logistic regression compared with the combined controls. Odds ratios were significantly raised for all comparisons except for those with enteric coated aspirin and benorylate. Data on dosage (table V) showed that average daily aspirin doses were similar in cases for enteric coated and soluble aspirin, and for aspirin tablets, and slightly greater for other commercial varieties.

Tables VI and VII show the risks associated with daily aspirin use in the previous month together with non-aspirin non-steroidal anti-inflammatory drug use. The odds ratios were raised almost eightfold in those who took both drugs, the difference compared with users of aspirin alone being significant ($P<0.05$).

TABLE I—*Aspirin intake in month before admission according to dose and duration of use*

		No (%) of cases	No (%) of controls	
			Hospital	Community
Daily use:				
For one month or more	Any dose	144 (12·8)	101 (9·0)	77 (7·8)
	75 mg	27 (2·4)	30 (2·7)	16 (1·6)
	150 mg	22 (2·0)	21 (1·9)	15 (1·5)
	300 mg	62 (5·5)	35 (3·1)	24 (2·4)
	Others	33 (2·9)	15 (1·3)	22 (2·2)
For less than one month (any dose)		42 (3·7)	14 (1·2)	5 (0·5)
Other regular use:				
Once a week to four days a week for more than one month		55 (4·9)	17 (1·5)	30 (3·0)
Irregular use:				
Less than one day a week or only in the four days before admission		63 (5·6)	31 (2·8)	45 (4·6)
Total users		304 (27·1)	163 (14·5)	157 (15·9)
Non-users of aspirin		817 (72·9)	963 (85·5)	832 (84·1)
Non-users of aspirin or non-steroidal anti-inflammatory drugs		457 (40·8)	807 (71·7)	657 (66·4)
Grand total		1121 (100·0)	1126 (100·0)	989 (100·0)

TABLE II—*Odds ratios and 95% confidence intervals (in parentheses) examining relation between aspirin intake and admission with peptic ulcer bleeding (calculated by logistic regression to take account of other non-steroidal anti-inflammatory drug use, previous ulcer or dyspepsia, and smoking and alcohol intake). Referents were non-takers of aspirin or any other non-aspirin non-steroidal anti-inflammatory drug*

	Combined controls	Hospital controls	Community controls
Daily aspirin use for one month or more:			
Any dose	3·2 (2·3 to 4·4)	2·7 (1·9 to 3·8)	4·2 (2·8 to 6·3)
75 mg	2·3 (1·2 to 4·4)	1·7 (0·8 to 3·4)	4·0 (1·6 to 9·2)
105 mg	3·2 (1·7 to 6·5)	2·6 (1·3 to 5·5)	4·1 (1·7 to 9·6)
300 mg	3·9 (2·5 to 6·3)	3·3 (1·9 to 5·6)	5·2 (2·8 to 9·7)
Daily aspirin use for less than one month:			
Any dose	9·2 (2·3 to 160·1)	6·5 (3·2 to 25·2)	19·2 (2·3 to 160·1)

TABLE III—*Numbers of aspirin takers during previous month in cases and controls according to duration of use, together with odds ratios and 95% confidence intervals calculated by unconditional logistic regression for association with bleeding peptic ulcers, taking account of other factors*

Time aspirin started before admission†	No of cases	No of hospital controls	No of community controls	Odds ratio			95% Confidence interval
				Hospital controls	Community controls	Combined controls	
One week	68	21	21	5·5	5·8	4·8	2·9 to 7·9
Between one week and one month	67	25	31	3·4	2·5	2·9	1·8 to 4·7
Between one and three months	45	37	25	2·3	3·9	2·9	1·7 to 4·9
More than three months	124	80	80	3·3	3·4	3·2	2·3 to 4·5

†Or interview in community controls.

TABLE IV—*Use of different aspirin preparations at any time in month before admission and risks of peptic ulcer bleeding. (Odds ratios and 95% confidence intervals calculated by unconditional logistic regression)*

Aspirin formulation	No of cases	No of hospital controls	No of community controls	Odds ratio* *v* combined controls	95% Confidence interval
Aspirin tablets	126	60	57	4·0	2·8 to 5·8
Soluble aspirin	84	56	51	3·3	2·2 to 4·9
Enteric coated	11	12	7	1·1	0·4 to 3·3
Alka-Seltzer	10	2	1	7·7	1·8 to 32·6
Benorylate	6	4	3	1·1	0·2 to 6·1
Other commercial	77	30	41	3·7	2·4 to 5·8

*For Alka-Seltzer, non-aspirin non-steroidal anti-inflammatory drugs were not included in model, as there were no cases of community controls also taking non-aspirin non-steroidal anti-inflammatory drugs.

Discussion

We found that no particular dose of aspirin between 75 mg and 300 mg daily currently used in cardiovascular prophylaxis is free of risk of causing bleeding from gastric or duodenal ulcers. Even very low (75 mg) doses of aspirin reportedly caused gastric bleeding in volunteers.[21] Nevertheless, evidence that low doses of aspirin may or may not be associated with risks of peptic ulcer bleeding is limited.

In the atrial fibrillation, aspirin, anticoagulation (AFASAK) and thrombosis prevention trials there were three major episodes of upper gastrointestinal bleeding in, respectively, 336 and 907 recipients of aspirin, compared with no episodes in 336 and 932 subjects given placebo.[22,23] In addition, in the Swedish aspirin low dose trial (SALT) there were nine episodes of severe gastrointestinal bleeding in subjects taking aspirin 75 mg daily and four in those taking placebo,[24] whereas in the physicians' health study the relative risk of bleeding requiring transfusion (site unspecified) was 1·71 (95% confidence interval 1·09 to 2·69) in takers of aspirin 325 mg every other day compared with placebo.[19]

By contrast, in the research group on instability in coronary artery disease (RISC) study there were apparently no episodes of gastrointestinal bleeding in 399 recipients of 75 mg aspirin daily,[25] and in the Dutch transient ischaemic attack trial there were no differences in the rates of gastrointestinal bleeding in those receiving 30 mg and 283 mg aspirin daily.[26] Case-control studies have been claimed to overestimate the risks of non-steroidal anti-inflammatory drug associated upper gastrointestinal bleeding compared with randomised trials,[27] but though we found higher risks for 150 mg and 300 mg than in some vascular prevention trials,[18,19] they were no higher than those in the United Kingdom transient ischaemic attack study.[28]

Comparisons between the two data sources are, however, difficult. Randomised trials can give complete sets of unbiased information, but exclusion criteria employed at trial entry may limit generalisation to the population at large. Case-control studies, provided that their frame is wide enough, give data from a general base, though biases—for instance, in questioning and in control selection—may skew conclusions.

Our study was conducted in five major urban centres and included large numbers of cases and both hospital and community controls. Precautions were taken to minimise selection and information bias. Thus drug histories were checked against hospital and general practitioner records and found to be in substantial agreement.[8] We believe that the design was robust, though there is evidence of selection bias, in that hospital controls were more likely to be exposed to aspirin than community controls. Even with this conservative bias the results showed a significantly increased risk of hospital admission for ulcer bleeding in association with all aspirin regimens used and compared with either set of controls.

Our main analyses took account of smoking and alcohol consumption as well as of prior histories of

TABLE V—*Average dosages of different aspirin preparations taken daily in month before admission. (Odds ratios and 95% confidence intervals calculated by unconditional logistic regression)*

Aspirin formulation	No of cases	Dose (mg)	No of hospital controls	Dose (mg)	No of community controls	Dose (mg)	Odds ratio *v* combined controls	95% Confidence interval
Aspirin tablets	82	300	49	170	38	249	3·4	2·2 to 5·3
Soluble aspirin	55	270	41	180	28	315	3·7	2·3 to 6·0
Enteric coated	11	296	12	267	5	672	1·6	0·5 to 4·9
Other commercial	34	419	10	952	11	613	5·8	3·0 to 11·1

*For Alka-Seltzer, non-aspirin non-steroidal anti-inflammatory drugs were not included in model, as there were no cases of community controls also taking non-aspirin non-steroidal anti-inflammatory drugs.

TABLE VI—*Numbers of daily aspirin takers and of takers of non-aspirin non-steroidal anti-inflammatory drugs alone and together*

	No of cases	No of hospital controls	No of community controls
Daily aspirin alone	140	101	71
Non-aspirin non-steroidal anti-inflammatory drug	340	137	142
Daily aspirin + non-aspirin non-steroidal anti-inflammatory drug	46	14	11
Neither	477	826	690

TABLE VII—*Odds ratios and 95% confidence intervals (in parentheses) calculated by unconditional logistic regression for risk in aspirin takers and of takers of non-aspirin non-steroidal anti-inflammatory drugs alone and together*

	Hospital controls	Community controls	Combined controls
Aspirin alone	2·8	4·5	3·3 (2·5 to 4·4)
Non-aspirin non-steroidal anti-inflammatory drug	5·4	4·7	4·9 (3·9 to 6·1)
Aspirin + non-aspirin non-steroidal anti-inflammatory drug	7·0	9·3	7·7 (3·6 to 16·4)

dyspepsia or peptic ulceration and of non-aspirin non-steroidal anti-inflammatory drug use. Further analysis of data showed that concurrent non-aspirin non-steroidal anti-inflammatory drug use roughly doubled risk. Table III indicates that risk tended to be greater when aspirin use had been of short duration. This increase associated with short term use may be explained by the taking of aspirin to alleviate symptoms arising from incipient peptic ulceration, but the substantially raised risk associated with daily aspirin use for less than a month (table II) suggests that there may be particular risks associated with prophylactic aspirin use early in treatment. These findings are consonant with results obtained elsewhere.[5 8 28]

Table IV suggests that enteric coated aspirin and the aspirin-paracetamol combination benorylate may be free of risk whereas the buffered perparation Alka-Seltzer may be associated with high risk. It should be noted, however, that confidence intervals were large and that because of its high buffering capacity Alka-Seltzer may have been used preferentially by people with gastric symptoms. There was no evidence of material differences in risk between aspirin tablets, soluble aspirin, and other commercial varieties.

Some 10 000 episodes of ulcer bleeding occur in people aged 60 and over each year in England and Wales. Other data of ours suggest that some 3500 of these will be takers of non-aspirin non-steroidal anti-inflammatory drugs and, if our current figures are representative, 1700 or 17% of the total will be taking prophylactic aspirin compared with 8% of community controls. It may be deduced that 900 of the 10 000 episodes could be associated with and ascribed to prophylactic aspirin use. A general change to low doses (75 mg) of aspirin would not eliminate risk but, again if our figures are soundly based, would reduce risk by about 40% compared with 300 mg doses and by 30% compared with 150 mg doses. It is unclear if substituting enteric coated aspirin would eliminate risk in view of evidence that non-steroidal anti-inflammatory drug use can cause haemorrhage, perforation, or stricture in the lower bowel.[29-31] Taken overall, benefit from prophylactic drug use is likely substantially to outweigh risk, but refinements to dosage and delivery would clearly be valuable.

Key messages

- Risks of peptic ulcer bleeding are significantly raised by prophylactic use of aspirin
- This finding applies to doses in common use of 75, 150, and 300 mg daily
- Despite these results, overall benefits of treatment are likely considerably to outweigh possible risks

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Case-control study of migraine and risk of ischaemic stroke in young women

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Abstract

***Objective*—To determine whether migraine is a risk factor for ischaemic stroke in young women.**

***Design*—A case-control study.**

***Setting*—Five hospitals in Paris and suburbs.**

***Subjects*—72 women aged under 45 with ischaemic stroke and 173 controls randomly selected from women hospitalised in the same centres.**

***Main outcome measures*—Ischaemic stroke confirmed by cerebral computerised tomography or magnetic resonance imaging; history of headache recorded with structured interview, and diagnosis of migraine assessed by reproducibility study.**

***Results*—Ischaemic stroke was strongly associated with migraine, both migraine without aura (odds ratio 3·0 (95% confidence interval 1·5 to 5·8)) and migraine with aura (odds ratio 6·2 (2·1 to 18·0)). The risk of ischaemic stroke was substantially increased for migrainous women who were using oral contraceptives (odds ratio 13·9) or who were heavy smokers (≥20 cigarettes/day) (odds ratio 10·2).**

***Conclusions*—These results indicate an independent association between migraine and the risk of ischaemic stroke in young women. Although the absolute risk of ischaemic stroke in young women with migraine is low, the reduction of known risk factors for stroke, in particular smoking and use of oral contraceptives, should be considered in this group.**

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Introduction

Few epidemiological studies have investigated the possible association between migraine and stroke. One of the main reasons for this was the lack of precise criteria for the diagnosis of migraine until 1988, when the International Headache Society established operational criteria.[1] Using these criteria, we found that migraine was not related to ischaemic stroke except in women aged under 45: 65% of young women with ischaemic stroke had migraine compared with 30% of controls (P=0·03).[2] This result, however, was questionable as it was extracted from a subgroup analysis with only 20 pairs of cases and controls.

The main aim of this study was to investigate the relation between migraine and ischaemic stroke in young women. It was also designed to study the relation between migraine, stroke, and two known vascular risk factors in this group: use of oral contraceptives and cigarette smoking.

Subjects and methods

We conducted a case-control study, cases being women aged under 45 who were hospitalised for an ischaemic stroke, in five neurological departments from January 1990 to December 1993. Three of the departments were in academic centres in Paris that were already involved in a study including all young patients consecutively admitted for ischaemic stroke. The two others were neurological departments of general hospitals located in small towns near Paris. Patients eligible for inclusion were women aged 18-44 with a diagnosis of first ischaemic stroke (codes 433, 434, and 436 of *International Classification of Diseases*, ninth revision). All cases were confirmed by cerebral computed tomography or magnetic resonance imaging. Of the 85 eligible patients admitted during the study period, two died after their stroke and one patient with dysphasia was excluded. Of the 82 remaining patients, 10 could not be located despite various efforts. Therefore, 72 patients were contacted and agreed to participate: 40 were hospitalised in the academic centres, and 32 were in the general hospitals. The mean elapsed time between stroke and interview was 19·5 months (SD 12·7).

Cervical ultrasound examination, electrocardiography, and usual laboratory studies were performed on all patients. Most patients underwent further investigations to determine the aetiology of the stroke: cerebral angiography (68), echocardiography (63), transoesophageal echocardiography (56 (92% of cases without arterial dissection)), transthoracic echocardiography (7), anticardiolipin antibodies (30), and coagulation studies (59). These investigations revealed various abnormalities associated with a higher risk of stroke: arterial dissection (22), carotid occlusion of unknown cause (5), carotid atheroma (5), anticardiolipin antibodies (6), essential thrombocytaemia (1), paroxysmal atrial fibrillation (1), mitral valve stenosis (2), patent foramen ovale (11), and atrial septal aneurysm (11). This last abnormality was diagnosed with transoesophageal echocardiography when the atrial septum presented an excursion of more than 6 mm in the right or left atrium. None of the patients was pregnant at the time of the stroke.

Controls were women randomly selected from