Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin – analysis of gastrointestinal bleeding during the UK-TIA trial

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Abstract

From 1979 to 1985 2435 patients having had transient ischaemic attacks (TIAs) or minor ischaemic strokes, were enrolled in the UK TIA trial and were randomised to receive either aspirin 300 mg, daily or aspirin 1200 mg or placebo. Analysis of reported upper gastrointestinal bleeding events (defined as haematemesis or melaena, or both) showed a risk of bleeding in a dose dependent manner, odds ratios (95% CI) for 300 mg of aspirin=3.3 (1.2 to 9.0) and for 1200 mg=6.4 (2.5 to 16.5) and, as would be expected, an increased risk of hospitalisation because of bleeding also in a dose dependent manner, odds ratio=3.6 (0.7 to 17.2) for 300 mg and 8.7 (2.0 to 37.6) for 1200 mg. Further analysis suggested greater risks of bleeding from duodenal ulcers than gastric ulcers and that bleeding is more likely early in the course of treatment with aspirin used as secondary prevention. There was also an increased risk of lower gastrointestinal bleeding, defined as fresh blood per rectum for both doses of aspirin, odds ratio 1.8 (0.5 to 6.1) for 300 mg of aspirin, and 1.5 (0.4 to 5.3) for 1200 mg of aspirin.

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The past 12 years have seen increasing use of aspirin in secondary prevention following vascular events such as transient ischaemic attacks (TIAs), minor ischaemic strokes, cerebral infarcts, myocardial infarction, and unstable angina.¹ Early studies used high doses of aspirin but the dose has been progressively reduced until the most commonly used dose nowadays is around 75 mg although substantial bodies of evidence concerned with efficacy relate to higher doses. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) used as simple analgesics, and in the treatment of rheumatic diseases, are well known to cause adverse gastrointestinal events including bleeding and perforation. Individual studies suggest a relative risk of upper gastrointestinal bleeding of between 3 and 5.² Some evidence also suggests that bleeding is more likely to occur early in the course of such treatment.^{3,4} Risks of lower gastrointestinal bleeding with NSAIDs and aspirin used in this way remain

less well defined, although NSAID treatment has been associated with a raised risk, of the order of a doubling or tripling, of colonic haemorrhage or perforation.⁵

On the other hand, the risks, sites, and timing of gastrointestinal bleeding with aspirin used as secondary prevention of vascular events remain poorly defined. Although case control studies show dose dependently increased risks of gastrointestinal bleeding it has been suggested that this method of examining risks may be prone to exaggerate any problems because of biases inherent in the methods. We have therefore examined the frequency of adverse gastrointestinal events occurring during the UK TIA trial of aspirin prophylaxis.

Methods

The results of the UK TIA study have been published both as an interim and a final report.^{6,7} Briefly, 2435 patients were randomised to receive aspirin 300 mg (806) or 1200 mg (815) daily as unbuffered and uncoated tablets or an apparently identical placebo (814). Patients developing indigestion were switched to enteric coated tablets so that drug and placebo could be continued in as many patients as possible. The study was conducted double blind and during the trial patients were reviewed four monthly by a physician or sometimes a general practitioner. Major outcome events of the trial were stroke, myocardial infarction, and death but adverse gastrointestinal events (for example, abdominal pain, nausea, gastrointestinal bleeding, etc) were recorded as they occurred and any reports of bleeding followed up, as far as possible by letter to the collaborating neurologist. All reported episodes of gastrointestinal bleeding were divided into haematemesis or melaena (upper gastrointestinal), or both, or bright red rectal bleeding (lower gastrointestinal). Patients without clinical evidence of bleeding (that is, those developing iron deficiency anaemia during the trial) have not been included in the analysis. Where possible upper gastrointestinal bleeds were divided into those from gastric ulcers, duodenal ulcers, oesophageal in origin or of unknown cause.

Data were examined on an intention to treat basis, and to determine the severity of bleeding the episodes were divided according to whether hospital admission was required.

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TABLE I Overall number of drop outs by allocated treatment

Site of origin	Placebo (n=814) (%)	Aspirin	
		300 mg (n=806) (%)	1200 mg (n=815) (%)
Not stopping	403 (49.5)	412 (51.1)	394 (48.3)
Stopping without known adverse effect	314 (38.6)	288 (35.7)	261 (32.0)
Stopping with gastric event	58 (7.1)	73 (9.1)	136 (16.7)
Stopping with other adverse event	39 (4.8)	33 (4.1)	24 (2.9)

Results were examined by calculation of odds ratios with 95% confidence intervals using the logit method,⁸ or by χ^2 .

Results

Table I shows that 1226 of 2435 patients entered in the trial failed to complete the full treatment period, which ranged from about one to seven years. The overall drop out rate was slightly, but not significantly, higher with high dose aspirin (51.7%) than with the low dose (48.9%), or placebo (50.5%). The rates of drop out for gastrointestinal complaints were 16.7, 9.1, and 7.1% respectively ($p < 0.001$, and $p > 0.1$) for comparisons of high dose with placebo and of low dose with placebo.

Seventy three confirmed episodes of gastrointestinal bleeding were reported during the follow up period. The four associated with gastric cancer (all in aspirin takers) are not considered further. Fifty two of the remainder were of upper gastrointestinal bleeding and 17 of lower gastrointestinal origin, and all except five of the upper gastrointestinal episodes, and four of the lower gastrointestinal episodes occurred in aspirin recipients (Table IIA). Risks of upper gastrointestinal bleeding were raised significantly, and dose dependently, in aspirin takers. The risks of lower gastrointestinal bleeding were also increased although to a lesser degree, and the trend was not statistically significant. Hospital admission was required in 26 cases of upper gastrointestinal bleeding, with risks being raised dose dependently in aspirin takers (Table IIB).

Table III shows that 26 of 27 diagnosed first episodes of ulcer bleeding occurred in aspirin recipients, as did 18 of 22 episodes where a cause was not determined. Greater numbers of duodenal ulcer episodes than gastric ulcer episodes occurred at the lower dose of aspirin but differences from the 1200 mg dose takers may represent chance. In general, episodes of bleeding occurred more frequently early in

TABLE II(B) Hospital admissions with upper gastrointestinal bleeds

	Treatment allocation		
	Aspirin		
	Placebo	300 mg	1200 mg
Not admitted	3	9	14
Admitted – survived	1	7	15
Admitted – died	1	0	2
OR (95% CI) (for admission)	1.0	3.6 0.7 to 17.2	8.7 2.0 to 37.6

Abbreviations as Table II(A).

treatment courses. Eighteen of 52 first episodes of upper gastrointestinal bleeding occurred in the first 152 days of treatment. (This period was chosen for analysis because the nominal follow up times of the UK TIA trial were almost complete at this time). Assuming that drop outs completed half the period, rates of upper gastrointestinal bleeding were one in 59 000, 29 000, and 9700 treatment days respectively for placebo, low dose, and high dose aspirin. Assuming a mean four year follow up, rates of bleeding after the first 152 days were respectively one in 357 000, 96 000, and 54 000 treatment days (Table IV). Taken overall, after correction for drop outs, episodes of bleeding were three times as likely to be recorded in the initial 152 days period as later in the course, episodes occurring once in every 80 and 263 patient years of observation early and late during low dose aspirin treatment, and once every 27 and 148 patient years of observation early and late in high dose treatment courses.

Discussion

These results show clearly that the risks of peptic ulcer bleeding and also of upper gastrointestinal bleeding of uncertain cause were increased in patients receiving prophylactic aspirin for TIAs. The risk associated with the lower dose of aspirin (odds ratio 3.6, confidence intervals 0.7 to 17.2) is similar to that recently found in a further retrospective case control study examining the chances of peptic ulcer bleeding in patients aged 60 and over receiving prophylactic aspirin in a dose of 300 mg daily (odds ratio 3.9, confidence intervals 2.5 to 6.3 compared with a combined hospital and community control).⁹

Case control studies have been claimed to overestimate the risks of NSAID associated upper gastrointestinal bleeding but divergences

TABLE II(A) Risks of upper and lower gastrointestinal bleeding

Site of origin	Treatment allocated		
	Placebo (n=814)	300 mg (n=806)	1200 mg (n=815)
Upper gastrointestinal	5	16	31
OR (95% CI)	1.0	3.3 (1.2 to 9.0)	6.4 (2.5 to 16.5)
Lower gastrointestinal	4	7	6
OR (95% CI)	1.0	1.8 (0.5 to 6.1)	1.5 (0.4 to 5.3)
Bleeds associated with cancer and omitted from analysis	0	2	2
Total	9	25	39

OR=odds ratio.

TABLE III Diagnoses established in patients with upper gastrointestinal bleeding

Diagnosis	Treatment allocation		
	Aspirin		
	Placebo (n=814)	300 mg (n=806)	1200 mg (n=815)
Haematemesis/melaena	4	7	11
? Cause			
Oesophageal	0	1	2
Gastric ulcer	1	1	9
Duodenal ulcer	0	7	9
Total	5	16	31

TABLE IV Timing of upper gastrointestinal bleeds

	No started	No stopped	No completed	No bleeds	Mean no of days per episode
<i>Interval 0–152 days</i>					
Placebo	814	70	744	2	59 000
Aspirin 300 mg	806	83	723	4	29 000
Aspirin 1200 mg	815	88	727	12	9700
Those stopping are assumed to have a mean follow up of 75 days.					
<i>Interval 153+ days</i>					
Placebo	744	341	403	3	357 000
Aspirin 300 mg	723	312	411	11	96 000
Aspirin 1200 mg	727	332	395	20	54 000
Assuming for all patients a mean four year follow up.					

in results seem likely to arise because the populations studied were obtained in completely different ways. Case control data, provided the sampling framework is representative, and methodological biases, such as recall bias, are minimised will reflect what happens in the population at large. Results of randomised trials are the products of the restricted circumstances in which they are obtained. The process of randomisation should minimise the effects, inter alia, of intersubject variability upon measured outcome but trial design is itself likely to influence adverse event rates significantly.

The adverse effects of aspirin are well known, and most trial designs have made specific allowance for these. Thus the exclusion of patients with histories of peptic ulceration, or those developing adverse effects with aspirin, can be expected to reduce the chances of adverse gastrointestinal events. The proportions of patients considered but never included in controlled trials can be substantial. Thus in the Physicians Health Study,¹⁰ 112 528 invitations were made to participate, with 22 071 enrolments, while in the RISC study¹¹ 945 of 3365 subjects with unstable angina were ultimately included. In the Physicians Health Study there was little difference in the frequency of dyspepsia in aspirin and placebo takers (26.1% and 25.6% respectively), although slightly more ulcers were detected in drug recipients (169 in 11 037 given aspirin and 138 in 11 034 given placebo). The lack of difference in gastric adverse effects between aspirin and placebo recipients almost certainly reflects the fact that all patients intolerant of aspirin were withdrawn during a preliminary run in period. The UK TIA study did not have explicit exclusion criteria related to any perceived propensity to gastrointestinal side effects. This may account in part for the clearly identified risks of such adverse events. In addition the patients were all starting

treatment, and, as we have shown, the risks of adverse events were greatly increased early in treatment, a pattern noted by others^{3,4} and ascribed by some to gastric adaptation.^{12,13}

Chance variation is the most probable explanation for the greater frequency of duodenal than gastric ulcer bleeding with low dose aspirin. The raised frequency of rectal bleeding may reflect the antiplatelet actions of aspirin making bleeding from occult lesions visible. There is evidence, however, that aspirin and non-aspirin NSAID use raises the risk of large bowel perforation and bleeding,⁵ which makes a direct mucosal effect likely.

The observed risks of overt bleeding must be set against the substantial benefits of aspirin use.¹ The use of enteric coated aspirin could, however, reduce risks while maintaining benefits.¹⁴

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