Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis

Sheena Derry, Yoon Kong Loke

Abstract

Objectives To assess the incidence of gastrointestinal haemorrhage associated with long term aspirin therapy and to determine the effect of dose reduction and formulation on the incidence of such haemorrhage.

Design Meta-analysis of 24 randomised controlled trials (almost 66 000 participants).

Intervention Aspirin compared with placebo or no treatment, for a minimum of one year.

Main outcome measures Incidence of gastrointestinal haemorrhage.

Results Gastrointestinal haemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo (odds ratio 1.68; 95% confidence interval 1.51 to 1.88); the number needed to harm was 106 (82 to 140) based on an average of 28 months' therapy. At doses below 163 mg/day, gastrointestinal haemorrhage occurred in 2.50% of patients taking aspirin compared with 1.45% taking placebo (1.59; 1.40 to 1.81). Meta-regression showed no relation between gastrointestinal haemorrhage and dose. For modified release formulations of aspirin the odds ratio was 1.93 (1.15 to 3.23).

Conclusions Long term therapy with aspirin is associated with a significant increase in the incidence of gastrointestinal haemorrhage. No evidence exists that reducing the dose or using modified release formulations would reduce the incidence of gastrointestinal haemorrhage.

Introduction

The use of aspirin in the prevention of cardiovascular disease is now well established; an estimated 50 million Americans have started taking aspirin over the past two decades. However, aspirin causes haemorrhagic complications. A systematic review in 1993 showed that the risk of gastrointestinal haemorrhage was significantly increased by long term aspirin. Only four of the 21 trials included in that review, however, used doses below 300 mg a day. Since then, new data have become available from eight studies involving 24 964 patients taking aspirin doses of 50-162.5 mg a day.

Recent trends towards the use of lower doses have been driven by the belief that these offer a better safety profile while retaining equivalent therapeutic efficacy. Is there evidence that the risk of gastrointestinal haemorrhage is substantially reduced at lower doses, and if so, how much? Expensive "modified release" formulations have been developed in an attempt to reduce the likelihood of adverse gastrointestinal effects. What is the evidence that they do so?

We reviewed the safety of aspirin, studying the effect of dose and formulation and incorporating the new data from the eight studies mentioned above.

Methods

The review was conducted using a defined protocol.

Inclusion criteria

Studies—We included reports if they were full journal publications of randomised controlled trials of aspirin used as an antplatelet agent. Trials were excluded if the term "randomised" was not specifically mentioned in the report or if the investigators clearly used non-random allocation, such as by date of birth. Abstracts, review articles, case reports, clinical observations, and unpublished data were not included. Trials with fewer than 50 patients in each arm were not included in the analysis because they were unlikely to be able to detect uncommon or rare adverse effects.
We did not include studies designed to assess the effects of aspirin in special groups—such as pregnant women, children, and patients with pre-existing platelet disorders.

**Intervention**—We included trials in which patients in one treatment arm were allocated to oral aspirin alone and patients in the control arm to either placebo or no treatment, provided that the scheduled duration of treatment was at least 12 months. Crossover studies and those in which aspirin was used in conjunction with other antiplatelet agents or anticoagulants were excluded. Trials that compared aspirin at different doses or with other antiplatelet agents or anticoagulants, without a placebo or “no treatment” control arm, were also excluded.

**Outcome measures**—Only trials that provided numerical data on all gastrointestinal haemorrhages in both the treated and the control group were included. If specific terms were used to describe bleeding complications, we accepted data on patients with “haematemesis” or “melana,” or with both of these, but not with “proctorrhagia.” We did not use data from trials that reported only on selected categories of gastrointestinal haemorrhage—for example, major bleeds and patients needing admission to hospital or blood transfusion—as trials varied considerably in their definition and reporting of such categories.

**Search strategy**
The search was performed separately by each author. Relevant trials were identified through a combination of electronic searching and manual checking of reference lists from previous review papers and retrieved trials. We applied no language restrictions.

We concentrated specifically on selecting trials from a detailed list of over 200 antiplatelet studies identified in a systematic review that included trials published up to 1993. In view of the comprehensive search strategies used in that review, we chose not to repeat an electronic search for most of this period but carried out a search of Medline and Embase for 1990-9 to identify new trials and to provide a three year overlap. We found no discrepancy between the two lists of the trials identified in the overlap period.

We used a sensitive search string for randomised controlled trials, based on that of the Cochrane Collaboration, in combination with the following free text terms: “aspirin” or “acetylsalicylic*” or “salicylic*”. This gave a yield of over 7000 hits on Medline and over 10 000 hits on Embase for 1990-9. We made no attempt to limit the yield by introducing terms for adverse effects or haemorrhage as we knew that this strategy would lead to the loss of relevant trials.

**Appraisal of study quality and data abstraction**
We did not anonymise the reports before assessment. All potentially relevant studies were checked independently by both reviewers to determine eligibility for inclusion and to extract data. A list of trials which were excluded is available from the authors.

We sought information on participants, blinding, type of control, assessment of compliance, and duration of treatment and follow up, in addition to data on the numbers of participants with and without gastrointestinal haemorrhage. We also recorded the formulation of aspirin used—modified release or standard. Any discrepancies were resolved by discussion.

**Statistical analysis**
Pooled odds ratios and heterogeneity were analysed using the RevMan program, version 4.04, with Meta

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Aspirin formulation</th>
<th>Dose (mg/day)</th>
<th>Average treatment duration (months)</th>
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SALT-Swedish aspirin low dose trial; TPT-thrombosis prevention trial; USPHS-US physicians health study; EAFIT-European atrial fibrillation trial; UK-TIA-UK transient ischaemic attack aspirin trial; COPA-coronary drug project aspirin study; PARIS-persantine-aspirin reinfarction study; AMIS-aspirin myocardial infarction study; CCSG-Canadian Cooperative Study Group.
intestinal haemorrhage.

one additional patient to be harmed by a gastro-

"metareg" command.

effects meta-regression was performed with the STATA

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effects model. Meta-regression is a technique used to assess

similar results were obtained with the random effects

aspirin—rather than with placebo or no treatment—for

number of patients who need to be treated with

odds ratio to the pooled control event rate. In our

intervals) was calculated by applying the calculated

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further table and the references for the 24 trials

Study

No of subjects/Total No in study

Treatmnet | Control | Peto odds ratio (95% confidence interval, fixed) | Weight (%) (95% confidence interval, fixed)

Aspirin (50 – 162.5 mg/day)

Diener et al11,12 25/1649 19/1649 3.5 1.32 (0.73 to 2.39)

Hansson et al13 107/9399 55/9391 12.9 1.91 (1.40 to 2.60)

Petersen et al14 1/336 0/336 0.1 7.39 (0.15 to 372.41)

SALT15 11/676 4/684 1.2 2.60 (0.94 to 7.19)

TPT16 22/1268 10/1272 2.5 2.14 (1.07 to 4.30)

Wallerlin et al17 0/399 0/397 0.0 Not estimable

Silay et al18 6/200 0/200 0.5 7.58 (1.51 to 37.93)

USPHS19 402/11 037 274/11 034 52.6 1.48 (1.27 to 1.72)

Subtotal (95% CI) 832/33 622 462/32 365 73.3 1.59 (1.40 to 1.81)

z²=8.41 (df=6, P=0.21; Z=7.02, P<0.0001)

Aspirin (162.5 – 1500 mg/day)

Elwood et al20 26.7 1.96 (1.16 to 3.29)

UKT1A21 75/2267 45/2257 4.2 2.26 (1.32 to 3.89)

Gavaghan et al22 2/127 0/110 0.2 6.51 (0.40 to 105.53)

Olivotto et al23 26.9 1.77 (0.91 to 3.42)

CDPA24 23/727 13/727 1.0 2.05 (0.64 to 6.82)

PARIS25 22/1268 10/1272 2.1 1.64 (0.68 to 3.91)

Hess et al26 4/80 1/80 0.13 (0.01 to 2.08)

AMIS27 107/9399 55/9391 4.2 3.42 (0.58 to 20.22)

Breddin et al28 10/406 4.2 3.42 (0.58 to 20.22)

CCSG29 3/317 0/309 0.2 6.25 (0.43 to 12.62)

Fields et al30 2/127 0/110 0.2 6.51 (0.40 to 105.53)

Fields et al31 2/65 0/60 0.2 6.51 (0.40 to 105.53)

Britton32 13/253 8/252 1.6 1.64 (0.68 to 3.91)

Ehresman et al33 2/215 0.2 6.51 (0.40 to 105.53)

Subtotal (95% CI) 574/24 964 362/24 963 73.3 1.59 (1.40 to 1.81)

x²=22.73 (df=20, P=0.30; Z=9.18, P<0.0001)

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Fig 1 Peto odds ratio for gastrointestinal haemorrhage with aspirin. SALT=Swedish aspirin low dose trial; TPT=thrombosis prevention trial; USPHS=US physicians health study; EAFTR=European atrial fibrillation trial; UK-TIA=UK transient ischaemic attack aspirin trial; CDPA=coronary drug project aspirin study; PARIS=persantine-aspirin reinfarction study; AMIS=aspirin myocardial infarction study; CCSG=Canadian Cooperative Study Group

View 4.0 and MetaView 3.01. We used the Peto fixed
effects model to calculate the pooled odds ratios as this is the most appropriate model for rare events. Closely similar results were obtained with the random effects model. Meta-regression is a technique used to assess statistically whether specific factors (covariates) influence the magnitude of effect across studies. Random effects meta-regression was performed with the STATA “metareg” command.3

The number needed to harm (with 95% confidence intervals) was calculated by applying the calculated odds ratio to the pooled control event rate. In our review the number needed to harm is the estimated number of patients who need to be treated with aspirin—rather than with placebo or no treatment—for one additional patient to be harmed by a gastrointestinal haemorrhage.

Results

We identified 24 randomised controlled trials of aspirin that fulfilled our inclusion criteria (table). (A further table and the references for the 24 trials are on the BMJ’s website.) The 65 987 participants were predominantly male (74%) and middle aged. Doses of aspirin used were 50-1500 mg/day for a mean duration of 28 months. Indications for aspirin extended from primary prevention in “healthy” individuals to secondary prophylaxis after stroke. In all trials patients were excluded if they had a history of peptic ulcer, previous gastrointestinal haemorrhage, or any other contraindication to aspirin.

All 24 trials were double blind and placebo controlled. Fourteen trials had sufficient data to extended from primary prevention in “healthy” individuals to secondary prophylaxis after stroke. In all trials patients were excluded if they had a history of peptic ulcer, previous gastrointestinal haemorrhage, or any other contraindication to aspirin.

Figure 1 shows the results of our meta-analysis. Overall, gastrointestinal haemorrhage occurred in 2.47% of the patients taking aspirin compared with 1.68 (95% confidence interval 1.51 to 1.88; P<0.0001), and the number needed to harm based on an average of 28 months of aspirin was 106 (82 to
Long term aspirin therapy, even at a low dose, carries a risk of gastrointestinal haemorrhage, with a number needed to harm per year of 248. Although it would be preferable, for the purposes of comparison, to have a number needed to harm and a number needed to treat from the same trial or review, this may not always be feasible. It is possible, however, to obtain some idea of the trade-off between benefit and harm when using aspirin in patients with different cardiovascular risk levels by weighing up the pooled estimate of the number needed to harm against the number needed to treat from individual trials.

In the secondary prevention of stroke, for example, the number needed to treat per year with aspirin to prevent a further event was 106. This means that if aspirin was used in patients with stroke who had similar baseline risks to those above, at least two recurrent strokes could be prevented at the cost of one gastrointestinal haemorrhage. The benefits of aspirin are less marked, however, in primary prevention of myocardial infarction—in the US physicians study, the number needed to treat per year was 555, whereas the number needed to treat per year in hypertensive patients was 794. Aspirin use in primary prevention could, depending on the baseline risks of the patients, cause two or three gastrointestinal haemorrhages for each myocardial infarction prevented.

As there are relatively few deaths after gastrointestinal haemorrhage (estimated death rate 12%\(^{10}\)) compared with myocardial infarction, such a trade-off may be considered worth while. Doctors and patients involved in making decisions about aspirin therapy need to consider carefully whether the inconvenience of long term therapy and the associated risk of gastrointestinal haemorrhage are outweighed by the potential cardiovascular benefits. This is particularly so for those at low absolute risk of cardiovascular events (with correspondingly high numbers needed to treat), in whom the likelihood of harm is greater than that of therapeutic benefit (as shown in the example above for hypertensive patients).

Although doctors have hoped that changes in the dose or formulation of aspirin might reduce the problem of gastrointestinal haemorrhage, the results of this meta-analysis do not suggest that either approach offers clear benefits. Our findings are supported by those of two recent case-control studies, in which aspirin increased the risk of gastrointestinal haemorrhage, despite the use of low dose or modified release formulations.\(^{11,12}\) The results of our meta-regression are compatible with those of a large Dutch trial of transient ischaemic attack in which no significant difference in
the rate of gastrointestinal haemorrhage was found between two different doses of aspirin. In this study, aspirin was efficacious at a dose of 30 mg a day, but a threshold dose for either the therapeutic or adverse effects of aspirin has yet to be established, and further attempts at dosage reduction might compromise therapeutic efficacy before adverse effects are eliminated completely.

Insufficient evidence exists to support the view that modified release formulations are safer, in terms of gastrointestinal haemorrhage, than standard formulations. Here we have studied the effect of dose and formulation on the incidence of gastrointestinal haemorrhage only; it may be that other symptomatic gastrointestinal adverse effects, such as nausea and epigastric pain, can be significantly reduced.

The incidence of gastrointestinal haemorrhage with aspirin is relatively low, and to avoid factors that could have led us to underestimate the risk, we set inclusion and exclusion criteria such that only trials of a certain quality, with adequate numbers and follow up, would be selected. Although there is some asymmetry in the funnel plot (see figure on BMJ’s website), suggesting the possibility of selection bias, adjustment for the likely effect of bias using “trim and fill” gave a pooled odds ratio of 1.62, which is only a slight change from our estimate of 1.68. Our meta-analysis seems reasonably robust to the asymmetry observed in the funnel plot.

We believe that the findings of our study are relevant to everyday practice. No significant heterogeneity was found, even though the studies we analysed encompassed a broad selection of patients with varying clinical indications. All the trials excluded patients at increased risk of gastrointestinal haemorrhage or with aspirin intolerance, but this is consistent with current advice on the use of aspirin and does not invalidate the relevance of our findings. Nevertheless, aspirin is available over the counter, and the risk of gastrointestinal haemorrhage could be higher in patients who take it without consulting a doctor.

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Contributors: YKL conceptualised the review, developed the protocol, provided clinical interpretation of the trials, abstracted data, and undertook most of the statistical analyses. SD contributed to the development of the protocol, abstracted data, and prepared the manuscript. Both authors will act as guarantors for the paper.

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Wet combing versus traditional scalp inspection to detect head lice in schoolchildren: observational study
Jan De Maeseneer, Ineke Blokland, Sara Willems, Robert Vander Stichele, Filip Meerschaut

Lice infestation is a problem in local communities, probably because reservoirs remain undetected. Wet combing (combing systematically through wet, well conditioned hair with a fine toothed comb) has been presented as a cheap, ecological, self sufficient, and feasible technique for diagnosis and treatment of head lice. Compared with traditional scalp inspection it uses five elements to make living lice more visible, to better distinguish them from dandruff, and to assess the maturity of the infestation: water, conditioner, a fine toothed comb, a systematic sweep of the scalp, and a magnifying glass (10×). However, its efficacy as a diagnostic tool and as a therapeutic intervention has not been proved; hence it is not evidence based.

Subjects, methods, and results
We did an observational study comparing detection of head lice using traditional scalp inspection and wet combing. After ethical approval had been obtained, all 260 pupils, aged 2-12 years, of a primary school in a socially deprived urban area in Ghent, Belgium, were invited for a screening test during a three day campaign to detect head lice in November and


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