Histamine H2-receptor antagonists for decreasing gastrointestinal harms in adults using aspirin: Systematic review and meta-analysis

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Abstract

Background: It is unclear if H2 blockers prevent gastrointestinal harm across a variety of different harm outcomes for patients taking aspirin over long periods of time.

Methods: Electronic databases (e.g., MEDLINE, EMBASE, Cochrane from inception to November 2010) and references of retrieved articles were searched. Randomized controlled trials (RCTs) assessing the efficacy of H2 blockers in reducing gastrointestinal harms (bleeding, ulcers) among adults taking aspirin 2 weeks or longer were included. Study and patient characteristics were abstracted and study quality was appraised using the Cochrane risk of bias tool by two reviewers, independently. Peto odds ratio (OR) meta-analysis and 95% confidence intervals (CIs) were calculated and heterogeneity was assessed using the I^2 and ^{2} statistics.

Results: Seven RCTs (five major publications and two companion reports) including 566 patients (healthy volunteers, arthritis, diabetes, cerebrovascular or cardiovascular disease) met the eligibility criteria. One trial adequately reported allocation concealment (4 scored unclear) and sequence generation (3 scored unclear, 1 scored no). After a median of 8-10 weeks follow-up, H2 blockers were effective in reducing gastrointestinal hemorrhaging (n=2 studies, OR: 0.07, 95% CI: 0.02, 0.23) and peptic ulcers (OR: 0.18, 95% CI: 0.11, 0.29) versus placebo among patients taking aspirin for two weeks or longer. Sub-group analysis found significant results for duodenal ulcers (n=2 studies, OR: 0.15, 95% CI: 0.06, 0.38). One study reported gastric ulcers; hence meta-analysis was not possible. Substantial clinical heterogeneity was noted across the studies, including types of H2 blockers, dosing of aspirin, and underlying conditions and statistical heterogeneity was low to moderate

Interpretation: H2 blockers reduced gastrointestinal harm among patients taking aspirin for 2 weeks or longer. Given the large proportion of patients taking long-term aspirin, H2 blockers should be considered.

Introduction

Aspirin is one of the most widely used medications in the world [1]. It is recommended for use among high-risk vascular patients due to its antiplatelet effects [2-8]. Surveys of physicians show that more than 85% prescribe aspirin post-myocardial infarction [9,10]. Aspirin also has analgesic, antipyretic, and anti-inflammatory properties. It is often prescribed for patients with migraine [11], acute pain [12], osteoarthritis [13], and post-operative pain[14].

Prolonged use of aspirin is associated with harms including dyspepsia, gastrointestinal mucosal injury, and bleeding, especially among the elderly [15]. Commonly used medications for reducing gastrointestinal harm associated with prolonged aspirin use include prostaglandin analogues, H2-receptor antagonists (H2 blockers), and proton pump inhibitors. It is unclear if H2 blockers prevent gastrointestinal harm across a variety of different harm outcomes for patients taking aspirin over long periods of time. Since H2 blockers are used for treating acid-related gastrointestinal conditions, including dyspepsia, peptic ulcer disease, and gastroesophageal reflux, it might be plausible that they are useful for preventing aspirin-induced gastrointestinal adverse events. We aimed to evaluate the role of concomitant administration of H2 blockers with aspirin in decreasing gastrointestinal harm.

Methods

A systematic review protocol was used to guide the methods of our review, based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement [16]. A draft version was compiled, circulated to clinicians and systematic review methodologists, and revised as necessary (available upon request).

Eligibility criteria

Inclusion criteria were randomized controlled trials (RCTS) and quasi-RCTs of H2 blockers for gastrointestinal harms among adults (aged ≥18 years) using aspirin for at least 2 weeks continuously. Studies were included regardless of the patient's condition and comorbidities. Only studies published in English were included. The primary outcome was the incidence of clinically relevant bleeding. Secondary outcomes were the incidence of ulcers (peptic ulcers overall and sub-group analysis of duodenal ulcers and gastric ulcers) and incidence of dyspepsia.

Information sources

Medical Subject Headings and text words related to H2 blockers (e.g., ranitidine, cimetidine, famotidine) for adults taking aspirin were used to search MEDLINE (OVID interface, 1950 to November 2010), EMBASE (OVID interface, 1980 to November 2010), CINAHL (EBSCOhost interface, 1997 to November 2010), and the Cochrane Central Register of Controlled Trials (Wiley interface, inception to November 2010). The search was supplemented by searching a clinical trial registry (MetaRegister, http://www.controlled-trials.com/mrct/), the reference lists of included studies, the authors' personal files, and contacting experts in H2 blockers.

Search

An experienced information specialist conducted all of the literature searches. The search strategy for the main electronic search (MEDLINE) is presented in the Appendix; details on the other searches are available from the authors on request.

Study selection

Two independent reviewers screened the search results for inclusion using a pre-defined relevance criteria form and obtained the full-text of potentially relevant articles and screened

them to determine inclusion. Discrepancies at any stage were resolved by discussion or the involvement of a third reviewer. The level of agreement during screening was assessed using a kappa statistic [17]. We determined *a priori* that an acceptable level of agreement would be ≥60% [17].

Data collection process

A draft data extraction form was developed, piloted, and modified as necessary. Two reviewers extracted all of the data using the standardized data extraction form, independently. Discrepancies were resolved by discussion or the involvement of a third reviewer. When multiple study publications reported data from the same population (i.e., companion reports) the trial reporting the primary outcome of interest was considered the major publication and the other report(s) was used for supplementary data. If the included study was a cross-over RCT, only data for the first period before the cross-over were abstracted.

Data items

The extracted data included study characteristics (e.g., study period, sample size, trial arms, setting), participant characteristics (e.g., population, medical condition, mean age, gender), and results from the primary and secondary outcomes.

Risk of bias

The risk of bias in individual studies was assessed using the Cochrane Risk of Bias tool [18]. This tool consists of six items pertaining to sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Two

reviewers assessed study quality independently and discrepancies were resolved by discussion or the involvement of a third reviewer.

Statistical Analysis

The studies were plotted in a forest plot to examine heterogeneity visually. Statistical heterogeneity was examined using the I^2 and χ^2 statistics [19]. Peto odds ratios were calculated, as few patients were included in the meta-analyses [18]. Ninety-five percent confidence intervals were derived based on a normal distribution. All analyses were conducted in Review Manager Version 5 [18].

Results

Study selection

The literature search yielded 645 citations (i.e., titles and abstracts; Figure 1). From this, 394 citations were excluded because they did not examine H2 blockers, 116 because aspirin was not the comparator, 99 because they were not RCTs, and nine because they did not include adult patients. Twenty-six full-text articles were retrieved and examined for relevance and five RCTs fulfilled the inclusion criteria [20-24] (Figure 1). One RCT [24] had two companion reports [25,26], which were used for supplemental data. Twelve articles were excluded at the full-text level of screening because they examined aspirin use for less than 2 weeks, five because they did not have any relevant outcomes, and two because they were not RCTs. There was moderate agreement between reviewers at level 1 screening (kappa=0.60, 95% CI: 0.41 to 0.72).

Study and patient characteristics

All of the included studies were RCTs conducted between 1978 and 2009 in the United States, United Kingdom, and Japan (Table 1). The number of participants ranged from 18 to 404 and the duration of follow-up ranged from 4 weeks to 12 weeks. The types of H2 blockers examined included ranitidine, cimetidine, famotidine, lafutidine, and nizatidine. The aspirin dosage ranged from low (e.g., <325 mg) to high (e.g., >1900 mg).

The patient population varied across the included RCTs (Table 2). Healthy adults were included in one RCT [20], two RCTs included patients with rheumatic diseases [21,23], and one RCT included patients with cardiovascular disease, cerebrovascular disease or diabetes [24]. All of the studies performed pre- and post-aspirin use endoscopy. The results of the pre-aspirin endoscopy were used to determine participant inclusion in several studies; one RCT included patients without mucosal injury [20], two RCTs included patients with ulcers or sores [23,24], and two RCTs excluded patients with ulcers or bleeds from inclusion [20,24]. Only one of the included studies reported the number of years that the patients were taking aspirin, which was at least one month before the trial [23].

Risk of bias

One of the included RCTs adequately generated (4 scored unclear) and concealed (3 scored unclear, 1 scored no) allocation (Table 3) [24]. Blinding was adequate in four of the RCTs (1 scored no [22]) and three of the RCTs adequately addressed incomplete outcome data (2 scored no [20,21]. Selective outcome reporting was unclear in four of the RCTs (1 scored no [23]) and most reports were free of other types of bias (1 scored unclear because it was funded by private industry [24]).

Primary outcome meta-analysis results

None of the studies reported the incidence of clinically relevant bleeding. However, two studies reported gastrointestinal hemorrhage as confirmed by endoscopy. After median of 8 weeks follow-up, patients who were administered an H2 blocker were significantly less likely to experience gastrointestinal hemorrhage compared with placebo (n=2 studies, odds ratio: 0.07, 95% CI: 0.02, 0.23; Figure 2) [20,24]. This means that patients who only took placebo had 14.2 times the odds of experiencing gastrointestinal hemorrhage compared to patients taking H2 blockers. Both of these studies examined low doses of H2 blockers (≤300 mg/day), yet one examined a low dose of aspirin (325 mg/day) [24] and the other examined a high dose of aspirin (2600 mg/day) [20]. Furthermore, one of the studies included healthy adults [20] and the other included patients with diabetes, cardiovascular disease or cerebrovascular disease [24]. One study excluded mucosal inclusion, ulcers or bleeds [20] and the other study included patients with gastric or duodenal scars or erosions but also excluded patients with ulcers or bleeds [24]. Despite this clinical heterogeneity, statistical heterogeneity was not observed (I^2=0%, p-value=0.047 on χ^2). We were unable to perform sensitivity analysis to explore the clinical heterogeneity, as only two studies were included in this analysis.

Secondary outcome meta-analysis results

After a median of 10 weeks follow-up, H2 blockers were effective in reducing the incidence of peptic ulcers (n=4 studies, odds ratio: 0.18, 95% CI: 0.11, 0.29) (Figure 2) [20-24]. Most of these studies examined low doses of H2 blockers (≤300 mg/day), yet one examined a high dose of H2 blockers (1200 mg/day) [23]. Two studies examined a low dose of aspirin (≤325 mg/day) [22,24] and the others examined high doses of aspirin (2600 mg/day) [20,23]. Furthermore, the patients included ranged from healthy adults [20] to patients with rheumatic disease [23] or those with

diabetes, cardiovascular disease or cerebrovascular disease [24]. Moderate statistical heterogeneity was noted (I^2=56%), yet it did not reach statistical significance (p-value =0.08 on χ^2).

Two of the studies excluded ulcers or bleeds [20,24] and the other two included ulcers or bleeds. A sensitivity analysis was conducted to examine the effects of ulcers or bleeds on the meta-analysis results. The meta-analysis results were unchanged when the analysis was conducted only including the two studies that excluded ulcers (n=2 studies, odds ratio: 0.19, 95% confidence interval: 0.11, 0.33, I^2=0%) [20,24], as well as only including the two studies that included ulcers (n=2 studies, odds ratios: 0.15, 95% confidence interval: 0.05, 0.43, I^2=85%) [22,23]. The results of the second sensitivity analysis should be interpreted with caution, as significant heterogeneity was observed (p-value=0.01 on χ^2) and this is likely because all of the participants in the O'Laughlin et al. study included patients with ulcers [23].

Sub-group analysis indicated that H2 blockers were effective in reducing duodenal ulcers (n=2 studies, RR: 0.15, 95% CI: 0.06, 0.38) versus placebo (Figure 3) [20,24]. The duodenal and peptic ulcer meta-analysis results were not affected by statistical heterogeneity (I^2=0%), despite significant clinical heterogeneity. Sensitivity analysis was not conducted, as only two studies were included in this analysis. Only one of the included studies reported gastric ulcers (odds ratio: 0.20, 95% CI: 0.09, 0.47) [24] so sub-group analysis was not possible.

One of the included studies reported the proportion of patients experiencing dyspepsia, yet few patients experienced this outcome (n=4) and this result was not reported per treatment group [21]. None of the other included studies reported data on dyspepsia.

Harms related to H2 blockers

Two of the included studies reported adverse events [20,22] and 0 events were observed for patients receiving aspirin plus H2 blockers, as well as those taking aspirin plus placebo.

Discussion

Aspirin is one of the most common drugs prescribed to patients and the gastrointestinal harm associated with its prolonged use is well known. A recent systematic review found that 109 major cardiovascular events were prevented for every 10,000 diabetic patients treated with aspirin at the expense of 19 major bleeding events [27]. We found that H2 blockers were effective in reducing gastrointestinal bleeding and peptic ulcers, suggesting that these agents should be considered in routine practice among adults taking aspirin for two weeks or more. One of the included studies reported the proportion of patients experiencing dyspepsia so we were unable to assess this outcome.

Given that aspirin is such a common drug and the adverse effects are well known, it was surprising to note the dearth of studies that were identified on this topic. This could be because most of the research in this area has focused on other agents, such as proton pump inhibitors and misoprostol or on non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin. Indeed, a recent Cochrane review on a similar topic found double the number of studies evaluating misoprostol versus H2 blockers among patients concurrently taking a variety of NSAIDs [28]. In this Cochrane review, the relative benefits of these agents were unclear and future reviews should examine these differences, perhaps through indirect comparisons meta-analysis, as few head-to-head trials exist. Another issue to take into consideration in future reviews is the cost of H2 blockers, as a recent cost effectiveness analysis found that starting with antacids and H2

blockers was more cost effective than starting with proton pump inhibitors and moving to H2 blockers and antacids [29].

We found that H2 blockers were effective in reducing duodenal ulcers, which is consistent with a recent Cochrane review on a similar topic [28]. Although our review was more focused, we included four more RCTs and an important additional outcome (gastrointestinal bleeding) than the Cochrane review.

We found that many of the included RCTs had small sample sizes and were poorly reported. Furthermore, only one of the included RCTs reported adequately on more than three of the 6 risk of bias items [24], suggesting that our meta-analyses results should be interpreted with caution. Although statistical heterogeneity was not apparent, there was significant clinical heterogeneity across studies. For example, we combined studies regardless of aspirin dose, H2 blockers dose, and patient conditions. We were unable to fully assess these differences via subgroup analysis, as too few studies were included in the meta-analysis. This should be addressed in updates of this systematic review.

Our systematic review is limited because we did not include studies written in languages other than English. Furthermore, although we searched for unpublished material and contacted trial authors for unpublished material, we were unable to identify relevant unpublished material to include. Furthermore, we did not compare H2 blockers with more commonly used medication, such as proton pump inhibitors.

Across all of the included RCTs, the longest duration of follow-up was 12 weeks [24]. Although the prolonged use (i.e., >45 weeks) of H2 blockers has been found to be safe [30], the

long-term safety of concurrent aspirin and H2 blocker intake is unclear. Future RCTs should evaluate the efficacy and safety of using these agents concurrently over time.

In conclusion, H2 blockers reduced gastrointestinal harm among patients taking aspirin for 2 weeks or longer. Given the large proportion of patients taking long-term aspirin, H2 blockers should be considered. Future studies should examine the efficacy and safety of long-term use of H2 blockers among patients taking aspirin for greater than 2 weeks duration.

Author Contributions

ACT, AA, MM, and SES conceptualized and designed the study. AA, MT, ACT were involved in the acquisition of the data. ACT analyzed the data. ACT, AA, MM, and SES interpreted the data. ACT and AA wrote the first draft and it was revised for intellectual content by all other authors.

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Figure legends

Figure 1: Study flow

Figure 2: Gastrointestinal bleeding meta-analysis

Figure 3: Peptic ulcer meta-analysis

Figure 4: Duodenal ulcer meta-analysis

Table 1: Study characteristics

Reference	First author, year of publication	Type of trial	Total # patients	Setting	Duration of trial in weeks (longest duration of FU)	Trial arms (dose/day in mg)
[21]	Welch, 1978	Cross-over RCT*	26	Rheumatology clinic, University of Texas Health Science center at San Antonio, USA	8 (8)	Cimetidine (1200) + ASA (2600-3900); Placebo + ASA (2600-3900)
[23]	O'Laughlin, 1982	RCT	18	Rheumatology clinics and general medicine wards at the Harry S. Truman Memorial Veterans Hospital and the University of Missouri Medical Center, USA	8 (104)	Cimetidine (1200) + antacids (prn) + ASA (2600); Placebo + antacids (prn) + ASA (2600)
[20]	Berkowitz, 1987	RCT	50	Hospital, USA	4 (4)	Ranitidine (300) + ASA (2600); Placebo + ASA (2600)
[22]	Nakashima, 2009	RCT	68	Saitama Medical University Hospital, Japan	8 (8)	H2 blockers [9 patients taking famotidine (10-40), 2 patients taking lafutidine (20), 2 patients taking nizatidine (300), 1 patient taking ranitidine (75), 1 patient taking cimetidine (100)] + ASA (81-100); Placebo + ASA (81-100)
[24] (CRs: [25,26])	Taha, 2009	RCT	404	Gastroenterology Unit, Crosshouse Hospital, University of Glasgow, Kilmarnock, UK	12 (12)	Famotidine (40) + ASA (75-325); Placebo + ASA (75-325)

Notes: * Data from cross-over RCTs were abstracted prior to the groups crossing over to make the data consistent with the other RCTs. **Abbreviations:** ASA aspirin, CRs companion reports, prn *pro re nata* (i.e., as required), RCT randomized controlled trial, UK United Kingdom, USA United States of America.

Table 2: Patient characteristics

Reference	# patients	Medical reason for taking ASA	% Male	Age in years: mean (SD)	Pre-/post-ASA endoscopy?	Mucosal inclusion criteria	Excluded ulcers or bleeds?
[21]	26 (22 included in analysis)	RA or degenerative joint disease	NR	NR	Yes	NR	No
[23]	18 (ITT)	Rheumatic disease	NR	NR	Yes	Confirmed gastric ulcer included	No
[20]	50 (43 included in analysis)	None	100%	Ranitidine 28.5 (SE 2.2), Placebo 26.2 (SE 2.0); Range:18-57	Yes	No abnormality	Yes
[22]	68 (0 dropouts)	NR	66.2	Range: 25-88	Yes	NR	No
[24] (CRs: [25,26])	404 (ITT)	Cardiovascular, cerebrovascular, and diabetes	68.6	Famotidine 63 (range 36-86), Placebo 63 (range 37-86) Median age: 63 years	Yes	Patients with gastric or duodenal scars or erosions included	Yes (allowed erosions or scars to be included)

Abbreviations: ASA aspirin, NR not reported, RA rheumatoid arthritis, SD standard deviation, SE standard error, ITT intention-to-treat.

Table 3: Risk of bias results

Reference	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
[21]	Unclear	No	Yes	No	Unclear	Yes
[23]	Unclear	Unclear	Yes	No	No	Yes
[20]	Unclear	Unclear	Yes	Yes	Unclear	Yes
[22]	Unclear	Unclear	No	Yes	Unclear	Yes
[24]	Yes	Yes	Yes	Yes	Unclear	Unclear