Addressing unmet needs for patients with previous upper gastrointestinal bleed requiring concomitant aspirin and non-steroidal anti-inflammatory drugs

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Title Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial

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Summary

The CONCERN trial was an industry-independent, double-blind, double-dummy randomised controlled trial performed in a single centre in Hong Kong between 24 May 2005 and 9 November 2015. There was a lack of data to address the choice of non-steroidal anti-inflammatory drugs (NSAIDs) in patients who were on low-dose aspirin and had a background of gastrointestinal (GI) bleed. The working hypothesis was that for prevention of recurrent GI bleed in these patients, cyclo-oxygenase(COX)-2 selective NSAIDs, in combination with proton-pump inhibitors (PPIs) were superior to non-COX selective NSAIDs plus PPIs. Participants had had an upper GI bleed but needed NSAIDs for chronic arthritis not relieved by simple analgesics; and at the same time needed aspirin for cardiac event prophylaxis.

Participants who had endoscopically confirmed ulcer healing and were negative for, or had completed eradication therapy for, Helicobacter pylori were randomly assigned to receive a combination of celecoxib 100 mg twice daily and esomeprazole 20 mg once daily, or naproxen 500 mg twice daily and esomeprazole 20 mg once daily. The NSAID dosing regime was decided after considering evidence showing similar analgesic efficacy between celecoxib 100 mg once daily and naproxen 500 mg twice daily; both of which were not associated with increased risk of serious cardiovascular events. The primary endpoint was recurrence of upper GI bleed within 18 months; secondary endpoints were serious cardiovascular events and patient's global assessment of disease activity. Initial screening of 1,158 patients who presented with haematemesis and/or malaena while on NSAIDs plus low-dose aspirin yielded 514 patients who met the inclusion criteria. Subjects were then randomised to the celecoxib plus PPI or naproxen plus PPI treatment arms while continuing aspirin at a dose of 80 mg daily, then followed up for 18 months.

The baseline characteristics of the participants were similar between both treatment arms, with a slight male preponderance (54% male). The mean age was approximately 72. Approximately 55% of patients in both groups had re-bleeding secondary to gastric ulcers, 32% due to duodenal ulcers and 11% due to both. The most common indication for NSAID use was osteoarthritis (70%). 43% of patients in both groups had previous *Helicobacter pylori* infection which had been eradicated. The dropout rates were similar in both groups with 46 (18%) of 256 in the celecoxib group and 50 (18%) of 256 in the naproxen group discontinuing treatment. About 70% of patients in both treatment arms continued taking aspirin throughout the study period, and about 90% of patients in both groups took at least 70% of the assigned study drug.

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From the modified intention-to-treat analysis, the proportion of patients with recurrent upper GI bleeding was significantly lower in the celecoxib group (5.6%, 95% CI 3.2–9.2) than the naproxen group (12.3%, 95% CI 8.8–17.1; p = 0.008). None of the recurrent bleeds caused death. There was no significant difference between the groups in the proportion of patients developing serious cardiovascular events. Significant improvement in the patient's global assessment of disease activity from baseline to the end of the study period was also noted in both groups; however, the improvement did not significantly differ between the groups. The authors concluded that celecoxib given with a PPI is the preferred choice of therapy to prevent recurrent upper GI bleeding in patients requiring low-dose aspirin and regular NSAIDs.

Opinion

There has been a lack of clear guidance on the choice of NSAIDs in patients who are at considerable risk for both gastrointestinal and cardiovascular events while requiring concomitant aspirin plus anti-inflammatory analgesia. Previously published guidelines and consensus statements have provided conflicting recommendations. While some guidelines do not address this issue at all,[1,2] there are several that acknowledge this but refrain from making any recommendations due to a lack of evidence.[3–5] Some have recommended the use of non-selective NSAIDs[6] while others advocate the use of naproxen or COX-2 selective NSAIDs depending on which risk factor (cardiovascular or GI) was prioritised.[7]

The CONCERN trial certainly provides clarity on the GI safety profile of using NSAIDs in a high-risk population as compared to the previously published PRECISION trial. The PRECISION trial, which was a randomised clinical trial comparing the safety of celecoxib as compared to ibuprofen and naproxen, reported that celecoxib at moderate dosage was non-inferior with regards to cardiovascular safety, and had lower rates of clinically significant GI events. However, the study was limited by 68.8% of patients stopping the study drug and 27.4% of them discontinuing follow-up. The proportion of patients having peptic ulcer or bleeding ulcer is also not known.[8]

The findings of the CONCERN trial are particularly useful in guiding treatment in a very select population of patients. This high-risk group has been largely excluded from previous studies, making it difficult to identify evidence-based strategies to reduce complications. Subjects in the study had a mean age of 72, which is the typical at-risk age group for developing upper GI bleed.[9,10] As elderly patients are also more likely to be on aspirin and NSAIDs owing to higher rates of comorbidities, the findings from this study are probably representative of 'real world' data.

Although the cumulative incidence of recurrent upper GI bleed over 18 months in the celecoxib group was lower than in the naproxen group, it is important to note that the risk of recurrent GI bleed in the celecoxib group of nearly 6% may not be clinically acceptable. Therefore, the concomitant use of aspirin and NSAIDs in patients with previous peptic ulcer bleed should be avoided in the first instance. Only when continuing both ulcerogenic drugs is unavoidable should a recommendation be made to choose a COX-2 selective NSAID over a non-selective NSAID, akin to choosing the lesser of two evils. However, this recommendation only applies if the duration of NSAID use extends beyond three months; this is based on the time-to-outcome analysis of recurrent upper GI bleeding reported in this study, whereby the cumulative incidence for both study drugs was the same for the first three months.

Limitations of the study include the lack of generalisability of the findings as it was performed in a single centre involving predominantly ethnic Chinese patients. Nearly 90% of patients continued taking the study NSAIDs at a non-variable high dose, compared to real life where patients more commonly take NSAIDs on a 'as needed basis'. This could lead to over estimation of the GI bleeding risk. The indications for the use of aspirin are not well-described and merely stated as 'cardiothrombotic diseases or multiple coronary risk factors'. With a 30% aspirin discontinuation rate, it raises the question of whether the patients had clear indications to be on antiplatelet therapy in the first place.

This study has certainly added novel information with regards to the choice of NSAIDs in a group of patients at risk for recurrent upper GI bleeding, who require aspirin for cardiac protection and NSAIDs for anti-inflammatory therapy. Thus, the findings should guide current practice on managing this complex group of patients often encountered in daily practice. We envisage it being incorporated into future guidelines on management of upper GI bleeding. Future, multi-centre, prospective studies to assess the reproducibility of the findings in other populations should ideally be undertaken.

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