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Prevention of ulcer bleeding in high-risk patients: is the enthusiasm for COX-2 selective NSAIDs justified?

Key Message

Among patients with previous ulcer bleeding, celecoxib is comparable to the combination of diclofenac plus omeprazole for the prevention of recurrent bleeding.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs worldwide, with nearly US\$2 billion per year being spent on them in the United States alone.¹ However, NSAID-induced gastro-intestinal toxicity is common; in the United States, it is estimated that 107 000 patients are hospitalised and 16 500 die each year from such complications.² Patients with a history of ulcer bleeding who use NSAIDs are at highest risk for ulcer complications.^{3,4}

Current guidelines recommend prophylaxis with a proton pump inhibitor (PPI) for patients receiving NSAIDs at risk for ulcer.^{5,6} However, PPIs are expensive and patients are required to take extra tablets. Moreover, non-compliance may limit the usefulness of this strategy.

An alternative strategy advocated to reduce the ulcer risk is to replace conventional agents with selective for cyclooxygenase-2 (COX-2 selective) NSAIDs. There is good evidence that COX-2 selective NSAIDs (eg celecoxib) are effective anti-inflammatory agents with minimal gastric toxicity.⁷ In patients at risk for ulcer, the American College of Rheumatology Guidelines for the management of osteoarthritis recommend these agents as an alternative to a non-selective NSAIDs.⁸

However, the gastric safety profile of COX-2 selective NSAIDs in high-risk patients is less well-defined than in those with average risk levels.¹ Whether COX-2 selective NSAIDs are comparable to the combination of a non-selective NSAID plus a PPI for patients at high risk of ulcer complications has not been investigated.

Aims and hypothesis

Our 6-month, prospective, randomised, double-blind trial set out to compare celecoxib with the combination of therapeutic doses of diclofenac plus omeprazole in patients presenting with ulcer bleeding. We hypothesised that treatment with celecoxib would not be inferior to combined therapy with diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in high-risk patients. The secondary aim was to evaluate the economic impact of these two strategies for the treatment of arthritis in high-risk patients, from the perspective of a public health organisation in Hong Kong.

Methods

Setting and subjects

We screened consecutive patients with arthritis presenting with endoscopically confirmed ulcer bleeding. Inclusion criteria were: ulcer healing confirmed by follow-up endoscopy, a negative test for *Helicobacter pylori* or successful eradication of *H pylori* based on histology, and anticipated regular use of NSAIDs for the duration of the trial. Exclusion criteria were concomitant use of anticoagulants or corticosteroids, previous gastric or duodenal surgery other than patch repair, erosive oesophagitis, gastric outlet obstruction, renal failure (serum

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creatinine of >2.26 mg/dL), terminal illness, or cancer.

Study design

The protocol was approved by our institutional ethics committee, and all participants provided written informed consent. Before enrolment, patients underwent physical examination, laboratory testing, and assessment of their arthritis. The latter included: global assessment of disease activity, scored on a scale of 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities), and patients' assessment of arthritis pain using a visual analogue scale.

Randomisation

Eligible patients were randomly assigned to receive 200 mg celecoxib (Celebrex, Pharmacia Corp, NJ, US) twice daily plus omeprazole placebo daily or 75 mg diclofenac SR (Voltaren SR, Novartis AG, Basel, Switzerland) twice daily plus 20 mg omeprazole (Losec, AstraZeneca, Mölndal, Sweden) daily for 6 months. Double blinding was achieved through repackaging of diclofenac SR and celecoxib as identical-appearing red-coloured capsules, and omeprazole and its placebo as identical-appearing green-coloured capsules. Consecutively numbered, sealed bottles of study drugs were dispensed.

Patients were permitted antacids, paracetamol, and disease-modifying anti-rheumatic drugs. Non-study NSAIDs (except for low-dose aspirin up to 325 mg daily), misoprostol, histamine H₂-receptor antagonists, sucralfate, PPIs, were prohibited during the study.

Assessments

After randomisation, the patients were contacted by telephone at month 1 and returned to the Endoscopy Centre at month 2 and every 2 months thereafter until the end of the study. At each visit, haemoglobin levels, serum biochemical values, drug compliance, efficacy, and safety were assessed. Drug compliance was assessed by pill counts. Treatment efficacy was gauged by global assessment of disease activity and patients' assessment of arthritis pain. Safety was based on physical examination, laboratory tests, observed/reported adverse events. A direct telephone line was provided enabling reporting of serious adverse events between the scheduled patient visits. Patients discontinuing study drugs before the study ended were similarly followed up.

End-points

The primary end-point was recurrent ulcer bleeding within 6 months according to pre-specified criteria. These were: haematemesis or melena documented by the admitting medical officer, with bleeding ulcers or erosions confirmed by endoscopy or a decrease in the haemoglobin level of at least 20 g/L in the presence of endoscopically proven ulcers or erosions. An ulcer was defined as a circumscribed mucosal break of at least 0.5 cm in diameter and a perceptible depth, and erosions were defined as flat mucosal breaks of any size

in the presence of blood in the stomach. Endoscopy was performed in a treatment-blinded fashion. Members of an independent, blinded adjudication committee determined whether recurrent bleeding had occurred according to the pre-specified criteria. Only events that were confirmed by the adjudication committee were included in the analysis. Secondary end-points included efficacy of treatments, recurrent ulcer bleeding in patients not taking low-dose aspirin, and other adverse events.

Statistical analysis

The sample size calculation assumed that about 4% of patients receiving diclofenac plus omeprazole would develop recurrent ulcer bleeding in 6 months,⁹ and that celecoxib would not be inferior to diclofenac plus omeprazole if the upper limit of the 95% confidence interval for the difference in recurrent bleeding did not exceed 6 percentage points. A sample size of 132 patients in each treatment group would give the study a power of 80% at a 5% significance level with the use of a one-sided equivalence test of proportions. Assuming that 10% of patients could not be evaluated, an overall sample size of 290 patients would be required.

One planned interim analysis was performed in September 2000 to compare the safety of the two treatments. The first interim analysis, which included data for 130 patients, did not justify early termination.¹⁰ The final analysis was performed in June 2002, after 287 patients had completed the study. Data analyses were carried out exclusively by a data review committee.

Efficacy variables were analysed using repeated measures analysis of variance. The Kaplan-Meier method was used to estimate the likelihood of reaching the end-point of recurrent ulcer bleeding within 6 months, based on an intention-to-treat population, defined as all patients who had taken at least one dose of study medication. The log-rank test was used to compare time-to-event curves between treatment groups. Failure to take at least 70% of the study drugs or use of prohibited drugs was considered as protocol violation. All P values and 95% confidence intervals were two-sided.

Economic analysis

The direct medical cost of each study patient was estimated from the perspective of a public health organisation. The health care resources utilised by each patient for routine follow-up during the 6-month study period and for management of recurrent ulcer bleeding were retrieved from medical records. The target types of health care resources included medications (study drugs and drugs used for the management of recurrent ulcer bleeding), diagnostic tests, endoscopy, clinic visits, visits to the accident and emergency department, and hospitalisation.

The direct costs of the two treatment strategies were estimated for each patient: routine management and management of recurrent bleeding. The cost of routine

management included the resources utilised by the patient for routine follow-ups and investigation of suspected bleeding while the patient was receiving the study medications. When a diagnosis of recurrent bleeding was confirmed, the resources utilised to manage the bleeding event were recorded to calculate the cost of managing recurrent bleeding.

In Hong Kong, the Hospital Authority (HA) is the largest public health organisation. It assumes the role of both the payer as well as the provider of health care services. The charges of itemised health care services of public hospitals are published in the Hong Kong Gazette. As the HA is a non-profit making organisation, the charges listed in the Gazette may be regarded as a close estimate of actual costs. Therefore, the costs assigned to the target resources were approximated using charges for public hospitals listed in the Hong Kong Gazette. Drug costs were based on HA-specific acquisition costs.

Data analysis and sensitivity analysis

The direct medical costs were expressed as medians with ranges when their distributions were skewed. A comparison of the direct medical cost between the two study groups was conducted by using a Mann-Whitney *U* test; $P < 0.05$ was considered significant. Generic oral omeprazole recently became available in Hong Kong, so the effect of generic pricing on the direct medical cost of the diclofenac plus omeprazole was examined by sensitivity analysis. The data and sensitivity analyses were conducted using Microsoft Excel 97 (Microsoft) and GraphPad Prism Version 3.03 (GraphPad Software).

Results

Patients

Between January 2000 and December 2001, we screened 396 users of NSAIDs who presented with ulcer bleeding and enrolled 290 patients. The reasons for exclusion were: no indication for prolonged NSAID use ($n=34$), renal failure ($n=26$), cancers ($n=14$), failure to obtain consent ($n=14$), oesophagitis ($n=10$), unhealed ulcers ($n=4$), and concomitant use of anticoagulants ($n=4$). Three patients who withdrew their consent after randomisation and did not take any study medication were excluded. Two hundred and eighty-seven patients were included in the intention-to-treat analysis; 144 were assigned to receive celecoxib, and 143 to diclofenac plus omeprazole. The median follow-up was 6.0 (range, 0.5-6) months for both groups. Rates of discontinuation were also similar: 13% in the celecoxib group (11% because of adverse events, 1% due to lack of efficacy, and 1% for other reasons) and 11% in the other group (10% because of adverse events, 1% due to a lack of efficacy, and 1% for other reasons). Patients who withdrew early did not have recurrent ulcer bleeding or anaemia in 6 months. One patient in each group was lost to follow-up. Ninety-two percent of the patients in two treatment groups took at least 70% of the study drugs.

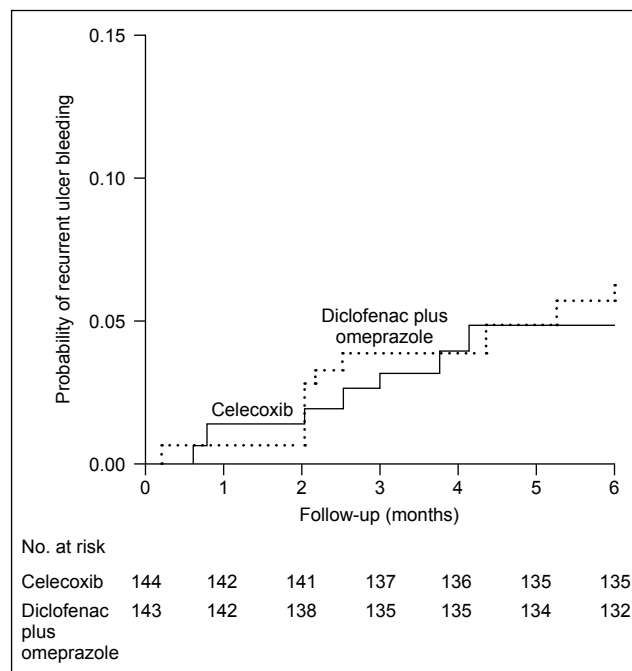


Fig 1. Cumulative probability of recurrent ulcer bleeding in the groups receiving celecoxib versus diclofenac plus omeprazole

Efficacy

Patients' global assessment of disease activity and patients' assessment of arthritis pain did not differ between the two treatment groups at any visit. The proportions of patients who withdrew treatment or used non-study NSAIDs owing to a lack of efficacy were low (2.8% in the celecoxib group and 2.1% in the omeprazole group).

Serious gastro-intestinal events

In all, 24 events were evaluated by the adjudication committee, which identified 16 patients with recurrent ulcer bleeding—seven in the celecoxib group and nine in the controls. In all except one recurrent bleeding was from gastric ulcers, and in 13 they were at the same site. The median size of recurrent ulcers was 1.5 (range, 0.5-4.0) cm. Six patients underwent endoscopic therapy to secure haemostasis and four received transfusion (2-4 units). The probability of recurrent bleeding during the 6-month study was 5% for patients who received celecoxib and 6% in the controls (difference, -1.5%; 95% confidence interval for the difference, -6 to 3.8%) [Fig 1]. Of the 260 patients not taking concomitant low-dose aspirin, six in the celecoxib group and seven in the omeprazole group had recurrent ulcer bleeding. The probability of recurrent bleeding was 5% in the celecoxib group and 6% in the omeprazole group (difference, -1.2%; 95% confidence interval for the difference, -6.3 to 3.9%).

One patient who received diclofenac plus omeprazole developed peritonitis and died after 4 weeks of treatment; necropsy revealed small bowel infarction and perforations.

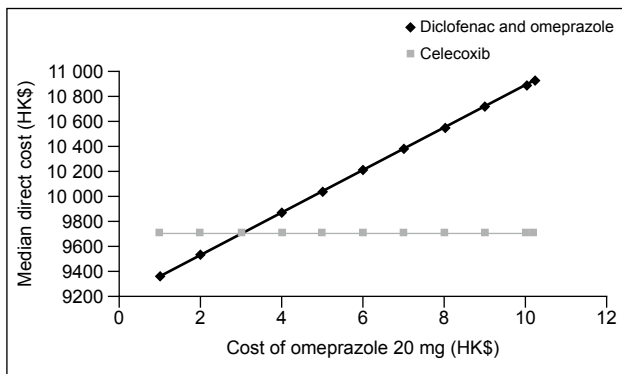


Fig 2. One-way sensitivity analysis using various unit cost of omeprazole (20 mg)

Other adverse events

Adverse events leading to discontinuation of treatment were similar in both groups; adverse sequelae, including hypertension, peripheral oedema, and renal failure were common. Among patients with renal impairment at baseline, 51% receiving celecoxib and 41% receiving diclofenac developed renal adverse events. One patient in the celecoxib group died of lung cancer and one in the omeprazole group had colon cancer during the study period.

Economic data

Compared with diclofenac plus omeprazole, the median total direct cost in the celecoxib group was significantly reduced by 11%, from HK\$10 915 (range, HK\$10 915-57 899) to HK\$9714 (range, HK\$9714-89 770) [$P < 0.0001$].

The effect of generic pricing of oral omeprazole on the median total direct medical cost was examined over a range of HK\$1 to HK\$10 per omeprazole 20 mg capsule (Fig 2). The median total direct cost in the diclofenac plus omeprazole arm would be the same or lower than that in the celecoxib arm when the unit cost of the oral omeprazole 20 mg capsule was HK\$3 or less.

Discussion

We set out to test the hypothesis that treatment with celecoxib would not be inferior to co-therapy with diclofenac plus omeprazole in preventing recurrent ulcer bleeding in high-risk patients. The patients enrolled in this study had more than one risk factor, including a recent history of ulcer bleeding, old age, and co-existing medical conditions. Among these high-risk patients, celecoxib administered at twice the maximal dose approved by the US Food and Drug Administration for osteoarthritis was comparable to diclofenac plus omeprazole.

While our findings indicate that celecoxib is an alternative to co-therapy of diclofenac with omeprazole, we cannot predict outcome beyond 6 months. However, about 5% of patients receiving either treatment still had recurrent ulcer bleeding within 6 months, which suggests

that neither approach adequately protects high-risk patients from recurrent ulcer complications.

We found that renal adverse events occurred in over 20% of patients receiving celecoxib, which has no advantage compared to the control treatment; co-existing medical conditions (renal diseases, diabetic nephropathy, and heart failure) probably accounted for the high incidence of renal adverse events. In susceptible individuals, COX-2 selective and non-selective NSAIDs probably share the same propensity to renal toxicity.

Our study had limitations. First, it was not powered to assess the effect of concomitant low-dose aspirin on the risk of recurrent bleeding. Second, the risk reduction achieved by celecoxib or omeprazole in high-risk patients could not be determined, because for ethical reasons we did not include a group taking NSAID plus placebo. After all, we had previously reported that about 19% of patients with a recent episode of ulcer bleeding who took a non-selective NSAID developed recurrent bleeding in 6 months.⁹

Economic considerations

According to our study, the median total direct cost per patient was significantly lower in the celecoxib group, mainly due to a lower rate of symptom-driven medical services (laboratory procedures and oesophagogastroduodenoscopy) during routine follow-up.

Using one-way sensitivity analysis, however, the median total direct cost of diclofenac plus omeprazole would be the same or lower than that of celecoxib when the unit cost of oral omeprazole 20 mg capsule was HK\$3 or less.

Conclusion

Among patients with a recent history of ulcer bleeding, treatment with celecoxib was comparable to that of diclofenac plus omeprazole in preventing recurrent bleeding. Moreover, the median total cost associated with celecoxib was lower than that of the diclofenac plus omeprazole.

Implications

Currently, the local expert panel in Hong Kong recommends NSAIDs plus a PPI but not COX-2 selective NSAIDs for arthritis patients at-risk for ulcer. Our results showed that although the two treatments were comparable in preventing recurrent ulcer bleeding, neither treatment eliminated the risk of ulcer complications in very-high-risk patients. The current guidelines on the prevention of NSAID-associated ulcers need revision. Studies are urgently required to address whether the combination of a COX-2 selective NSAID with a PPI can significantly reduce ulcer complication risks in such patients.

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