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Gastroprotective Strategies in Chronic NSAID Users: A Cost-Effectiveness Analysis Comparing Single-Tablet Formulations with Individual Components

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ABSTRACT

Objectives: To evaluate the cost-effectiveness of competing gastroprotective strategies, including single-tablet formulations, in the prevention of gastrointestinal (GI) complications in patients with chronic arthritis taking nonsteroidal anti-inflammatory drugs (NSAIDs). **Methods:** We performed a cost-utility analysis to compare eight gastroprotective strategies including NSAIDs, cyclooxygenase-2 inhibitors, proton pump inhibitors (PPIs), histamine-2 receptor antagonists, misoprostol, and single-tablet formulations. We derived estimates for outcomes and costs from medical literature. The primary outcome was incremental cost per quality-adjusted life-year gained. We performed sensitivity analyses to assess the effect of GI complications, compliance rates, and drug costs. **Results:** For average-risk patients, NSAID + PPI cotherapy was most cost-effective. The NSAID/PPI single-tablet formulation became cost-effective only when its price decreased from €0.78 to €0.56 per tablet, or when PPI compliance fell below 51% in the NSAID + PPI strategy. All other strategies were more costly and less effective. The model was highly sensitive to the GI complication risk, costs of PPI and NSAID/PPI single-tablet formulation, and compliance to PPI. In patients with a threefold higher risk of GI complications, both NSAID + PPI cotherapy and single-tablet formulation were cost-effective. **Conclusions:** NSAID + PPI cotherapy is the most cost-effective strategy in all patients with chronic arthritis irrespective of their risk for GI complications. For patients with increased GI risk, the NSAID/PPI single-tablet formulation is also cost-effective.

Keywords: compliance, cost-effectiveness, cost-utility, dyspepsia, gastrointestinal bleeding, nonsteroidal anti-inflammatory drugs, proton pump inhibitors.

Introduction

The prevalence of osteoarthritis and rheumatoid arthritis is high, and the incidence of these chronic and expensive conditions is rising. Empirical treatment for osteoarthritis and rheumatoid arthritis often begins with nonsteroidal anti-inflammatory drugs (NSAIDs) for symptom relief [1,2].

NSAIDs are associated with a wide spectrum of gastrointestinal (GI) side effects, including dyspepsia, peptic ulcers, peptic ulcer bleeding (PUB), and ulcer perforations. NSAIDs cause an approximately three- to fourfold increase in these upper GI complications [3]. GI complications are expensive; for example, a Dutch observational study showed that for each €1.00 spent on NSAIDs, an additional €0.68 is needed for the treatment of GI adverse events [4].

Gastroprotective agents (GPAs) can reduce GI complications of NSAIDs, and are therefore widely recommended for use in high-risk users [5]. Physicians can choose between several gastroprotective strategies, including coprescription of NSAIDs with acid-suppressive medication (proton pump inhibitors [PPIs] and histamine-2-receptor antagonists [H2RAs]), misoprostol (prostaglandin analogue), or selective cyclooxygenase-2 inhibitors (coxibs). Previous analyses revealed that PPI cotherapy is cost-effective [6,7], especially in patients with a high risk of GI complications. Several guidelines recommend PPI coprescription for patients with moderate-to-high risk profiles [5,8]. The National

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Institute for Health and Clinical Excellence guidelines even recommend PPI coprescription in all patients on chronic NSAID therapy [1]. H2RA may be cost-effective when used in high doses. Only one study directly compared H2RA versus PPI cotherapy and concluded that PPI cotherapy was more effective in healing ulcers [9]. Misoprostol is also equally efficacious to PPIs, although common GI side effects (e.g., diarrhea and dyspepsia) reduce compliance and possibly its effectiveness. Another alternative is to replace nonselective NSAIDs with coxibs, which maintain anti-inflammatory capability while reducing GI complications through selective cox-2 inhibition [10,11]. Cost-effectiveness analyses reveal that coxibs provide an acceptable cost-effectiveness ratio compared with NSAID + PPI combination therapy in high-risk patients with a history of bleeding ulcers [12].

Although physicians are more aware than ever regarding the clinical and economic burden of NSAIDs, adherence to prescribing guidelines for GPA use remained low; up to 60% of high-risk patients are not prescribed adequate gastroprotection [13,14]. Furthermore, patient compliance with GPAs is inadequate, leading to suboptimal gastroprotection [15]. The risk of NSAID-related GI complications increases by 16% for every 10% decrease in GPA compliance [16].

Because of the low compliance with effective and cost-effective GPAs, efforts have been made to enhance patient adherence with prescribed therapies. In particular, new single-tablet formulations (i.e., NSAID/PPI or NSAID/H2RA) have been developed, which may limit poor clinical outcomes associated with noncompliance by ensuring that GPA is administered with each NSAID dose. Recent randomized controlled trials have shown that both esomeprazole + naproxen and ibuprofen + famotidine single-tablet formulation are superior to placebo in reducing gastric ulcers [17,18]. Previous data also found that the single-tablet formulation of diclofenac + misoprostol is effective in protecting patients at medium and high risk for GI complications [19].

To assist the clinical decision-making process for patients with rheumatoid arthritis or osteoarthritis requiring chronic NSAID treatment, we aimed to evaluate the costs and effectiveness of eight different treatment strategies, including (co)prescription of GPAs and single-tablet formulations while accounting for patient compliance.

Methods

Decision Model Framework

We developed a Markov model by using decision-analysis software (TreeAge Pro 2009, TreeAge Software, Inc., Williamstown, MA). We evaluated eight strategies for managing a hypothetical cohort of 60-year-old patients with rheumatoid arthritis or osteoarthritis and requiring chronic NSAID therapy: 1) NSAID monotherapy (naproxen 500 mg b.i.d.); 2) NSAID + PPI (naproxen 500 mg b.i.d. and omeprazole 20 mg q.d.); 3) NSAID/PPI single-tablet formulation (naproxen 500 mg combined with esomeprazole 20 mg b.i.d.); 4) NSAID + H2RA (naproxen 500 mg b.i.d. and cimetidine 400 mg b.i.d.); 5) NSAID/H2RA single-tablet formulation (ibuprofen 800 mg combined with famotidine 26.6 mg t.i.d.); 6) NSAID + misoprostol (naproxen 500 mg b.i.d. and misoprostol 200 μg b.i.d.); 7) NSAID/misoprostol single-tablet formulation (diclofenac 75 mg combined with misoprostol 200 μg b.i.d.); 8) coxib monotherapy (celecoxib 100 mg b.i.d.) (Fig. 1). Coxib in combination with PPI was left out of the model because no literature is available for this strategy. The model tracked differential rates of compliance with these competing strategies, and evaluated variations in compliance (Table 1). In our base-case analysis, patients entering the model were 60 years old and did not have any GI symptoms or a history of peptic ulcer disease. Through a series of 3-month Markov transition cycles, we followed the cohort over a 5-year time horizon. During each cycle, patients could develop GI complications, including dyspepsia, ulcer complications (bleeding), and related mortality. After these initial health states, patients either could become symptom free, or go to a health state in which dyspepsia persists. In the "dyspepsia persists" health state, patients had different costs because of physician visits and medication, but comparable utilities. If a patient got a PUB, he or she will thereafter transfer to a "post" health state (post-PUB) in which he or she remained at a higher risk for a recurrent event, had a different utility, and higher health care costs compared with "no complications." In a post health state, the patient could still develop other complications (e.g., dyspepsia or recurrent PUB), yet he or she could never return to a "nonpost" health state (Fig. 2).

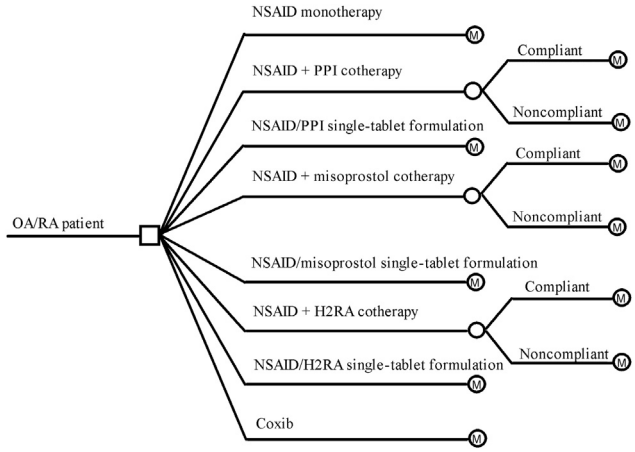

Fig. 1 – Decision model. The "M" is where the Markov model was incorporated in the decision tree. H2RA, histamine-2-receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PPI, proton pump inhibitor; RA, rheumatoid arthritis.

Model Assumptions

We applied the following assumptions regarding physician and patient behavior. To closely simulate clinical practice, we based these assumptions on a combination of clinical guidelines and expert opinion.

1. If dyspepsia develops, patients first visit their primary care provider. Patients will be prescribed a 4-week trial of PPI therapy. If dyspepsia persists despite this treatment, the patient is referred to a gastroenterologist and undergoes diagnostic endoscopic examination and testing for *Helicobacter pylori*. In case of *H. pylori* positivity, a 1-week course of triple therapy is prescribed and a 13C urea breath test is subsequently performed to confirm *H. pylori* eradication.
2. If dyspepsia persists in patients without endoscopic findings or *H. pylori* negativity, patients visit their primary care provider again and receive another 3 months of PPI therapy.
3. Patients presenting with GI bleeding visit the emergency department and are admitted to the hospital. If necessary, patients are stabilized with blood transfusion. A therapeutic endoscopy is then performed. The patient is treated with intravenous PPI therapy for 72 hours, followed by indefinite PPI therapy. Survivors are tested for *H. pylori*, and treated with triple therapy if positive. If the bleeding recurs, a second endoscopy is performed and endoscopic treatment is used if