Determination of candidates for adjunctive 'gastroprotective' prostaglandins

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Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) is now recognized as being frequently associated with asymptomatic gastric ulceration and its complications. Such adverse effects on the gastric mucosa have recently been found to occur with even greater frequency in certain NSAID-treated patients. Synthetic prostaglandin analogues have been shown to be cytoprotective of the gastric mucosa. This benefit has been evidenced by the reduced risk of gastric ulceration and gastric bleeding in patients taking NSAIDs on a prolonged basis. The first synthetic prostaglandin to be approved for this indication is misoprostol (Cytotec).

To determine which and how many patients receiving NSAIDs should be treated adjunctively with a cytoprotective prostaglandin to reduce risk of NSAID-induced gastropathy, a clinical study of 100 consecutive patients seen in a rheumatology practice was undertaken. Patients were assessed by interview and chart review. Of these patients, 19% to 30% were considered potential candidates for adjunctive prostaglandin therapy. The rationale for use of the "gastroprotective"

prostaglandins appears to lie in the identification of those patients who are especially at high risk for gastric ulcers.

Salicylates and the other nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common class of antiarthritic agents prescribed, with more than 67 million prescriptions written each year in the United States. The NSAIDs make up a market that exceeds \$2 billion.¹

The widespread use of NSAIDs is due to their clinical effectiveness. There are several postulated mechanisms of action for NSAIDs, with the classical hypothesis being that of prostaglandin synthesis (via inhibition of the enzyme cyclo-oxygenase).²

Most of the adverse effects of the NSAIDs are, likewise, due to the inhibition of prostaglandin synthesis and include NSAID-induced gastropathy (ie, gastric erosions, gastric ulcers, and accompanying upper gastrointestinal [GI] tract bleeding).³

Prostaglandins of the E series (PGEs) are essential to cytoprotection of the gastric mucosa because they inhibit gastric acid secretion, stimulate gastric mucous and bicarbonate production, and regulate mucosal blood flow.⁴ Knowledge of these mechanisms of action has provided a good rationale for the development of synthetic prostaglandin analogues and their adjunctive use with NSAIDs in selected patients at high risk for gastric ulcers.

Research studies of several prostaglandin analogues have been conducted and their find-

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ings published.^{3,5-8} Misoprostol (Cytotec) is the first of the oral "gastroprotective" (cytoprotective) prostaglandins to be approved for use in preventing NSAID-induced gastric ulcers and concomitant GI blood loss. Studies by Graham and coworkers⁴ and others⁹⁻¹³ have shown the clinical efficacy of misoprostol for this indication.

Taking into account some of the known risk factors for NSAID-induced gastropathy, Fries and coworkers¹⁴ studied patients being treated at a rheumatology outpatient office to determine the incidence of potential candidates for adjunctive therapy with an oral gastroprotective prostaglandin.

Patients and methods

One hundred consecutive patients treated at a university rheumatology outpatient office during January and February 1989 were assessed via an interview and a chart review to identify those who currently used NSAIDs and those who were at high risk for NSAID-induced gastropathy. High-risk subgroups were defined as (1) patients with a previous GI intolerance to NSAIDs, (2) those with dyspepsia related to current NSAIDs therapy, (3) those with a history of peptic ulcer or upper GI tract bleeding, and (4) those more than 65 years old during current NSAID therapy. The study population largely comprised long-standing patients of the investigator, many of whom he had personally followed up for several years.

Assessments of the patients revealed various rheumatologic diagnoses in both the population that was receiving NSAIDs and the one that was not. The most common definitive diagnoses were osteoarthritis, systemic lupus erythematosus, and rheumatoid arthritis (Table). All of the patients had rheumatologic complaints either at the time of the study or during previous visits.

The average age of the entire study group was 55.1 years, with patients who were currently receiving NSAIDs being slightly older (56.4 years) than those who were not (54.2 years). There was a 3:1 female preponderance.

Results

Of the 100 consecutive patients evaluated, 42

Table
Primary Rheumatologic Diagnoses of
Study Population*

Diagnosis	No. of patients taking NSAIDs	No. of patients not taking NSAIDs
Osteoarthritis	11	10
Rheumatoid arthritis	10	5
Juvenile rheumatoid arthritis	1	
Systemic lupus erythematosus	5	19
Mixed connective tissue disease	1	
Bursitis/tendinitis	4	2
Arthralgia of undetermined origin	6	3
Carpal tunnel syndrome	1	2
Osteoporosis	1	5
Psoriatic arthritis	1	1
Arthropathy of inflammatory bowel disease	1	
Scleroderma		2
Pseudogout		1
Gout		1
Polyarteritis nodosa		2
Hypersensitivity vasculitis		1
Polymyalgia rheumatica		1
Temporal arteritis		1
Erythema nodosum		1
Purpura of undetermined origin		1
Total	42	58

*Based on evaluations of 100 consecutive patients.

were taking NSAIDs at the time of the study. Of these, 19 (45%) were categorized into one of the four previously defined high-risk subgroups for NSAID-induced gastropathy (Fig 1). Additionally, 11 (11%) other patients of the total study group were not taking NSAIDs at the time; however, they could have been considered to be at high risk and therefore candidates for cytoprotective prostaglandins (Fig 2).

When analyzed together, the patients from the two main high-risk groups represented 30% of the total study population who were candidates for adjunctive prostaglandin therapy. When patients with current or previous NSAID-induced GI intolerance were excluded, and only those with a history of peptic ulcer/upper GI tract bleeding or those older than 65 years were considered, then the percentage of the total study population who were candidates for adjunctive prostaglandin therapy was 23%.

Figure 1. Patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) at high risk for NSAID-induced gastropathy. (Note: Some patients may have been categorized in more than one high-risk subgroup.)

Figure 2. Patients not taking nonsteroidal anti-inflammatory drugs (NSAIDs) who also were possible candidates for gastroprotective prostaglandins. (Note: Some patients may have been categorized in both high-risk subgroups.)

Discussion

According to data provided by the American Rheumatism Association Medical Information System (ARAMIS), an estimated 2500 deaths at the least occur annually from NSAID-associated GI tract bleeding.^{1,14} In patients taking NSAIDs, mortality associated with peptic ulcer complications has been shown to be more than double that in patients not taking NSAIDs.¹⁵ Also, NSAIDs are taken twice as

often by patients older than 60 years found to have bleeding ulcers as compared with an age-matched community control or hospital inpatient control population.¹⁶

Various endoscopy studies have shown the incidence of peptic ulcers in patients taking NSAIDs to be approximately 20%.^{1,4,17} Generally, a poor correlation has been found between complaints of GI symptoms and endoscopic confirmation of pathoses.^{17,18} Another problem related to NSAID-induced gastropathy has been recognized relatively recently: in patients taking NSAIDs, ulcers and other significant endoscopic lesions typically occur *asymptotically*. Larkai and coworkers¹⁸ found that more than 90% of the patients who had endoscopic gastric lesions while taking NSAIDs were asymptomatic. This finding may be attributed to the anti-inflammatory/analgesic properties of the NSAIDs themselves.

The concept of NSAID-related gastropathy and the identification of those patients particularly at risk were succinctly reviewed in 1988 by Roth,¹ and more recently by Fries and coworkers.¹⁴ Certainly patients who are elderly or who have a history of gastric ulcers or gastric bleeding should be considered to be at significant risk. According to Fries and coworkers,¹⁴ there is an increased risk of NSAID-induced gastropathy also in patients who are taking corticosteroids; those who have been diagnosed as having rheumatoid arthritis; those

who have had upper abdominal pain in the past 6 months; those who have discontinued any NSAID because of adverse GI effects; those who have taken antacids, H-receptor antagonists, or sucralfate in the past 6 months; and those who smoke cigarettes.

Most NSAIDs (except perhaps the nonacetylated salicylates) alter the cytoprotective mechanisms of the stomach by reducing endogenous prostaglandin production. Misoprostol, a prostaglandin E₁ analogue, has been shown to effectively prevent gastric ulcers in patients taking aspirin as well as in patients taking other NSAIDs.⁸⁻¹³ The drug may also help alleviate dyspepsia or abdominal pain associated with NSAIDs, but this benefit has not been adequately or consistently demonstrated.^{4,5} Therefore, it remains debatable whether to consider patients experiencing these side effects as potential candidates for adjunctive prostaglandin therapy.

An important question, then, for the physician prescribing NSAIDs is, Which patients should receive adjunctive therapy with a gastroprotective prostaglandin? In view of the favorable safety profile of misoprostol (administration to pregnant women excluded), it would seem beneficial to prescribe this drug for those patients at high risk for NSAID-related gastropathy, especially elderly patients or patients with a history of peptic ulcers or upper GI tract bleeding. In the current study, these made up 23% of the patient population.

It must be noted that although approximately 19% to 30% of the patients in the current study were potential candidates for a cytoprotective prostaglandin as an adjunct to arthritis therapy, these percentages may be conservative. Not all the risk factors as delineated by Roth¹ and Fries and coworkers¹⁴ were considered (eg, patients who took corticosteroids, smoked cigarettes, etc). Also, although it is believed that the majority of the current study population had taken NSAIDs at one time or another (this was not specifically evaluated), only 42% were taking NSAIDs at the time of the study. This percentage may have already reflected, in part, the curtailed use of NSAIDs by the elderly and by those with a history of peptic ulcers.

In conclusion, misoprostol, and eventually

other cytoprotective prostaglandins, should be considered—especially for those patients at high risk—to reduce the morbidity and mortality associated with NSAID-induced gastric complications.

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