The Use of COX-1–Sparing Agents in the Federal Health System

David S. Silver, MD

ABSTRACT

The use of cyclooxygenase (COX-1)–sparing agents has revolutionized the treatment of rheumatic diseases. Because of the significant safety advantages of these drugs, patients at high risk for gastrointestinal (GI) side effects from using traditional nonsteroidal anti-inflammatory drugs (NSAIDs) can now achieve pain relief with a lower risk of GI adverse events. However, the costs of these drugs has placed an enormous strain on already stretched formulary budgets.

The judicious use of COX-1–sparing agents has the potential to reduce the morbidity and mortality associated with NSAID therapy while saving health systems tens of millions of dollars. To allow for appropriate use of these medications in the federal health system, the author has developed an algorithm based on an analysis of the available GI safety data of the COX-1–sparing agents, the GI SCORE tool to determine GI bleeding risks, and the current cost structure of these agents.

OVERVIEW

Nonsteroidal anti-inflammatory drugs (NSAIDs) have served as the cornerstone of treatment for patients with many types of inflammatory and noninflammatory conditions. They are recommended for use in a wide variety of disease states, such as rheumatoid arthritis, systemic lupus erythematosus, and osteoarthritis, as well as nonsystemic conditions like acute and chronic muscle pain, joint pain, and ligamentous pain. With more than 100 million prescriptions written each year, NSAIDs represent the most commonly prescribed drug class. Concerns about their safety, however, have led to their limited use in older and high-risk patients, who are often the patients most in need of the drugs.

The use of the COX-1–sparing agents, with their improved gastrointestinal (GI) safety profile, has alleviated some of the concerns imposed by the older agents. Although these medications are now available for patients at a high risk for GI adverse drug events (ADEs), their significantly higher costs have led insurers to examine ways to control access to these agents. Consumer awareness of the COX-1–sparking medications, fueled partially by large direct marketing campaigns and possible misconceptions about their improved efficacy, has led patients, many of whom are at low risk for GI complications, to request prescriptions for these drugs.

Traditional NSAIDs have been used to help reduce the signs and symptoms of arthritis and to diminish common aches and pains. More than $6 billion is spent each year on prescription NSAIDs; for every prescription written, almost 10 people obtain these medications over the counter.

Although the efficacy of NSAIDs, in terms of symptom relief, has not been questioned, significant morbidity and mortality rates related to these drugs (even in a nonprescribed form) have been reported. In 1997, approximately 16,500 residents of the U.S. died as a result of NSAID-induced GI bleeding. This is equivalent to the number of patients who died as a result of human immunodeficiency virus (HIV) infection during the same year. In addition, more than 100,000 people were hospitalized.

More than 35% of the direct costs of treating patients with arthritis are related to NSAID-associated GI bleeding. Because none of these agents is considered to be a “disease-modifying drug,” these figures are even more disturbing. The average cost of hospitalization for a patient with GI bleeding in the federal health system is approximately $20,000, an expense that adds an enormous burden to an already strained health care budget. Theoretically, the careful use of COX-1–sparing agents can lower morbidity and mortality rates and reduce expenses in the long run.

Because NSAIDs effectively relieve the symptoms of the pain and stiffness of arthritis, and even though the need for these agents is clear (despite their significant side effects), searches for safer, equally effective agents have been undertaken. In the late 1980s, the COX-2 theory was advanced. The theory was that the pain and inflammation triggered by prostaglandins and other substances could be safely and effectively blocked by inhibiting the COX-2 enzyme while limiting any inhibition of COX-1 activity. The COX-1 enzyme is responsible for much of the “housekeeping” functions of the prostaglandins and thromboxanes, including protection of the gastric mucosa and maintenance of platelet function. The last several years have seen the development of more selective agents that preferentially bind to COX-2 without binding to COX-1. This has resulted in the availability of several new therapeutic regimens that appear to have safety advantages in the GI system.

The need for more than one agent in this new selective class is illustrated by the fact that approximately 30% of all patients who eventually find that NSAIDs are efficacious in relieving symptoms do not find success with the first agent. “Class switching” is common. In fact, many patients try two to four drugs before they find one that is effective for them; the reason might be related to differences in chemical structure or body composition, although the true answer to this question remains unknown.

Approximately 20% of patients who take NSAIDs demonstrate an intolerance of the drug that is evidenced by GI symptoms, such as dyspepsia, reflux, and diarrhea. In addition, the rate of NSAID intolerance has been increasing by 1% to 4% annually. These symptoms appear to be independent of the COX-2 mechanism of action, but they still cause patients to either stop or limit their intake of the medication.

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COX-1–Sparing Agents

ALGORITHM FOR THE USE OF COX-1–SPARING AGENTS

The P&T formulary committees in large managed care facilities have struggled to balance the theoretical improved safety of the COX-1–sparing medications against their significantly increased acquisition costs. Although attempts have been made to determine their overall cost-effectiveness on a global basis, no one seems to have examined this problem in a way that practitioners can use in a clinical setting.

In the interest of providing a solution to this complex situation, I have attempted to develop a logical and applicable algorithm for the use of these COX-1–sparing agents in a large managed care system—the federal health system—in which the need for effective cost containment resulting from an ever-shrinking formulary budgets is most urgent (Table 1).

For an algorithm to be effective, it not only needs sound scientific and pharmacoeconomic backing but also must be easy to use. By studying the best data available on reducing the risk of GI events and on the current costs of the medications on the federal formulary, one can establish a model for use throughout a diverse network of clinics and hospitals within the federal system and as a potential model in other large managed care networks.

The problems with effective use of the COX-1–sparing medications are more pronounced in closely managed, large formularies (e.g., in the federal health system) than in the private sector. Although these agents do have the potential to decrease mortality and costly hospitalizations, their indiscriminant use would lead to tens of millions of dollars of unnecessary formulary costs in an atmosphere of steadily increasing budgetary constraints.

THE GI SCORING TOOL

Generic NSAIDs cost pennies per day, and for younger individuals at low risk, the additional expense of COX-1–sparing agents might not be justified. In an ideal world, cost would not be a concern and COX-1–sparing drugs would be used for every patient who needed them; however, with the current emphasis on cost containment, physicians can use the GI SCORE to stratify a patient’s risk of significant GI events.

Developed by Singh and colleagues at Stanford University, the GI scoring tool includes six simple questions to calculate a person’s annual risk of GI bleeding as a result of NSAID therapy (Table 2). This instrument has been validated in more than 40,000 patients. The model clearly predicts the risk of GI bleeding in patients at all levels of risk, and the clinician can determine the risk of a significant GI event in less than 30 seconds with information that is easily obtained from a patient’s chart. An intake nurse can calculate the GI SCORE. The instrument is already being used in Veterans Affairs (VA) medical centers, in the federal health system, and in many large managed care networks.

The next step in developing a simple algorithm for the use of COX-1–sparing agents is to calculate the costs of the drug against the costs of the ADEs. From the current data, GI bleeding episodes are not completely eliminated by the use of COX-1–sparing medications. Several factors account for this finding, including:

- the inherent COX-1 activity of even the most selective agents.
- other causes of GI bleeding, such as Helicobacter pylori–induced peptic ulcer disease.
- the concomitant use of aspirin.

The GI SCORE can be used to weigh the cost of medication against the probable risk reduction in any given population and at a given risk level.

According to the best clinical data, a reduction in significant GI events of approximately 50% can be expected with COX-1–selective inhibitors in place of standard NSAIDs. This figure is supported by the VIOxx Gastrointestinal Outcomes Research (VIGOR) trial, which examined the risk of GI events with rofecoxib (Vioxx®, Merck), and by several studies, such as the SUCCESS trial with celecoxib and a meta-analysis of meloxicam (Mobic®, Boehringer Ingelheim); all of these tri-

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>First-Line Agent</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (GI SCORE 0–10)</td>
<td>Formulary nonselective NSAID</td>
<td>If the nonselective NSAID is not tolerated or if it is ineffective, patients may use a second nonselective NSAID. If this is not tolerated or is ineffective, patients may use meloxicam (Mobic®).</td>
</tr>
<tr>
<td>Moderate risk (GI SCORE 11–15)</td>
<td>Formulary nonselective NSAID</td>
<td>If there is no response to the nonselective NSAID or if intolerance develops, patients may use another COX-1–sparing agent, such as meloxicam, celecoxib (Celebrex®, Vioxx®, or valdecoxib (Bextra®).</td>
</tr>
<tr>
<td>High risk (GI SCORE 16–20)</td>
<td>Meloxicam</td>
<td>If there is no response to meloxicam or if intolerance develops, patients may use a different COX-1–sparing agent, such as celecoxib, rofecoxib, or valdecoxib.</td>
</tr>
<tr>
<td>Substantial high risk (GI SCORE &gt;20)</td>
<td>COX-1–sparing agent (e.g., meloxicam, celecoxib, rofecoxib or valdecoxib)</td>
<td>If there is no response or if intolerance develops, patients may use a different COX-1–sparing agent, such as meloxicam, celecoxib, rofecoxib, or valdecoxib.</td>
</tr>
</tbody>
</table>

COX = cyclooxygenase; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.
als indicated a risk reduction of at least 50%.

If we were then to estimate the anticipated risk reduction with any given score, we could predict the number of GI bleeding episodes that would be prevented. By comparing the cost of medication per 100 patients, based on actual usage, versus the cost of a GI event, we would be able to determine, according to a particular GI SCORE, whether the use of a COX-1–sparing agent would be cost-negative, cost-neutral, or cost-saving. If we determined, at a given score, that a drug was either cost-neutral or cost-saving, we would implement the use of that medication.

The cost of each medication was determined directly from the federal supply pricing schedule. The practice of “pill-splitting” was considered if it was deemed to be cost-saving; today this is a common procedure in federal, military, and VA hospitals. Clearly, if changes in the pricing schedule occurred, it is possible that the algorithm might change.

WHICH PATIENTS SHOULD TAKE COX-1–SPARING AGENTS?

Low Risk. A GI SCORE below 10 with a one-year risk of GI ulceration below 0.3% is considered low risk. At this level, there is probably little, if any, role for the COX-1 sparing agents, because the annual risk of GI bleeding in this population is below 0.3%.

When patients are unable to tolerate two previously prescribed traditional nonselective NSAIDs, a more selective COX-2 agent should be considered. Although dyspepsia and NSAID-induced GI bleeding are marginally related at best, the COX-1–sparing medications, compared with their traditional counterparts, are associated with a rate of GI side effects that is approximately one-third lower.13,14

Moderate Risk. A GI SCORE of 11 to 15 with a one-year GI ulceration risk of 0.3% to 1% is considered moderate risk. The costs of all of the COX-1–selective agents are still prohibitive for patients at this risk level and should be considered only when therapy with at least one or two traditional nonselective NSAIDs has failed.

High Risk. A GI SCORE of 16 to 20 with a one-year GI ulceration risk of 1% to 2% is considered high risk. With the average cost of a significant GI bleeding episode estimated at $20,000 per patient, a cost analysis based on risk can determine the cost-effectiveness of these medications. According to current prices, the less expensive COX-1–sparing drugs, such as meloxicam, are cost-effective.

COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug.

Courtesy of Singh G, et al.10,11

| Table 2 | Gastrointestinal (GI) Risk Assessment Tool (GI SCORE) |

This scoring tool, developed by Dr. G. Singh and colleagues at Stanford University, is based upon data from 566 hospitalizations for serious GI injury from 6,386 patients with rheumatoid arthritis or osteoarthritis who were monitored prospectively. The authors used COX proportional hazard models to determine risk factors. The GI SCORE is calculated from individual patient responses to six questions. Each question is assigned a certain number of points. After the points have been added up, a GI risk score from 1 to 4 is assigned (1 = lowest risk, 4 = highest risk).

1. How old are you?

<table>
<thead>
<tr>
<th>Age</th>
<th>Points</th>
<th>Age</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 years</td>
<td>0</td>
<td>56–60</td>
<td>10</td>
</tr>
<tr>
<td>21–25</td>
<td>1</td>
<td>61–65</td>
<td>12</td>
</tr>
<tr>
<td>26–30</td>
<td>3</td>
<td>66–70</td>
<td>13</td>
</tr>
<tr>
<td>31–35</td>
<td>4</td>
<td>71–75</td>
<td>14</td>
</tr>
<tr>
<td>36–40</td>
<td>5</td>
<td>76–80</td>
<td>16</td>
</tr>
<tr>
<td>41–45</td>
<td>6</td>
<td>81–85</td>
<td>17</td>
</tr>
<tr>
<td>46–50</td>
<td>8</td>
<td>85+</td>
<td>18</td>
</tr>
<tr>
<td>51–55</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Points: ______

2. How do you rate your current health status on the following scale?

<table>
<thead>
<tr>
<th>Rating</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Poor</td>
<td>4</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
</tr>
<tr>
<td>Fair</td>
<td>2</td>
</tr>
<tr>
<td>Well</td>
<td>1</td>
</tr>
<tr>
<td>Very Well</td>
<td>0</td>
</tr>
</tbody>
</table>

Points: ______

3. Has a physician ever told you that you have rheumatoid arthritis (not osteoarthritis or other forms of arthritis)?

<table>
<thead>
<tr>
<th>Response</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>

Points: ______

4. If you are taking prednisone or another corticosteroid, for how many months have you taken it in the past year?

<table>
<thead>
<tr>
<th>Duration</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1–3</td>
<td>1</td>
</tr>
<tr>
<td>4–6</td>
<td>3</td>
</tr>
<tr>
<td>7–10</td>
<td>4</td>
</tr>
<tr>
<td>11–12</td>
<td>5</td>
</tr>
</tbody>
</table>

Points: ______

5. Have you ever been hospitalized for a stomach or intestinal problem, such as bleeding or an ulcer? (if the answer is yes, skip the next question).

<table>
<thead>
<tr>
<th>Response</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>

Points: ______

6. If no, have you ever had gastrointestinal side effects (heartburn, stomach pain, nausea, vomiting) when taking NSAID pain relievers?

<table>
<thead>
<tr>
<th>Response</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>

Points: ______

Total Points: ______
Table 3  Costs of COX-1–Sparing Agents per Hundred Patients According to Actual Prescribing Patterns

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam (Mobic®, Boehringer Ingelheim)</td>
<td>$20,075.00</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx®, Merck)</td>
<td>$37,275.62</td>
</tr>
<tr>
<td>Celecoxib (Celebrex®, Pharmacia/Pfizer)</td>
<td>$93,987.50</td>
</tr>
<tr>
<td>Valdecoxib (Bextra®, Pharmacia/Pfizer)</td>
<td>$31,207.50</td>
</tr>
</tbody>
</table>

Figures are based on “tablet splitting,” when possible, as commonly practiced in the Veterans Affairs health system.

Table 4  Proposed Algorithm for the Veterans Affairs Health System: Evaluation of Risk for a Serious NSAID-Induced Gastrointestinal Event within the Next Year

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Points</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No risk</td>
<td>0–10</td>
<td>Patients may use a nonselective formulary NSAID; if therapy fails, they may use meloxicam (Mobic®, Boehringer Ingelheim)</td>
</tr>
<tr>
<td>2 Moderate</td>
<td>11–15</td>
<td>Patients may use a nonselective formulary NSAID; if therapy fails, they may use meloxicam</td>
</tr>
<tr>
<td>3 Significant</td>
<td>16–20</td>
<td>For patients receiving therapy for less than 30 days or for those using therapy intermittently, a standard NSAID may be used. For patients receiving therapy for more than 30 days, salsalate (e.g., Disalcid®, 3M; Salflex®, Amarin) or meloxicam may be used. If therapy is unsuccessful or intolerance to the agent develops, a COX-2 inhibitor may be used.</td>
</tr>
<tr>
<td>4 Substantial</td>
<td>&gt;20</td>
<td>Meloxicam or a COX-2 inhibitor may be used.</td>
</tr>
</tbody>
</table>

COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug.

for preventing GI bleeding in this population.

The cost of meloxicam in the federal health system is $0.44 per day for the 7.5-mg dose (half that of the 15-mg tablet). Because approximately 75% of patients taking meloxicam stay with the 7.5-mg dose and 25% of patients increase their dose to 15 mg, the estimated annual cost per 100 patients for meloxicam is $20,075.15 In this high-risk population, the ability to prevent an episode of GI bleeding, even in only one of 100 patients treated per year, would justify the additional expense. A reduced incidence of GI bleeding not only affects direct medical costs but also results in indirect cost advantages related to decreased morbidity and improved quality of life.

Very High Risk. A GI SCORE above 20 with a one-year GI ulceration risk of 2% or higher is considered extremely high risk. For patients at this level, any of the COX-1–sparing agents at that dose would be considered cost-effective, according to the costs of these medications in the federal health system (Table 3). An algorithm based on these cost considerations for use in the federal health system is shown in Table 4.

Other Considerations: Note that the risk of GI bleeding with the COX-1–sparing agents is not reduced to zero; therefore, before prescribing any of these medications, physicians and pharmacists should consider the risks and benefits of these drugs in the patients with the highest potential for GI bleeding (e.g., patients with a history of bleeding, those of advanced age, and those with concomitant medical conditions).

Patients who have experienced significant GI ADEs within the last five years should probably start taking a COX-1–sparing drug regardless of their GI SCORE. Cardiovascular prophylaxis with aspirin should not influence the decision as to whether or not to use a COX-1–sparing medication, because the risk of GI events in patients taking low-dose aspirin (up to 325 mg/day) does not approach that of a full-prescription-strength NSAID.16

WHO IS AT HIGH RISK FOR GI BLEEDING?

The data clearly show that COX-1–sparing agents, such as celecoxib (Celebrex®, Pharmacia/Pfizer) meloxicam, rofecoxib, and valdecoxib (Bextra®, Pharmacia/Pfizer) reduce the risk of significant GI adverse events. However, because these drugs are much more expensive than comparative NSAIDs, they should be used prudently.

Patients at the highest risk for GI bleeding are most likely to benefit from the COX-1–sparing drugs. Risk factors for GI bleeding include:1,6,7,17

• advanced age (older than 65 years).
• a history of GI bleeding.
• corticosteroid use.
• other comorbidities.

Physicians and pharmacists are often reluctant to incorporate “clinical tools” into their practices because they often find them cumbersome and tedious and are concerned that such tools might be used as a substitute for clinical judgment. However, with the significant restrictions placed on the use of COX-1–sparing agents, simple methods that enable practitioners to avoid unnecessary paperwork, and the annoyance of going through the process of preauthorization, are usually welcomed. The first step in developing an algorithm that is widely accepted and easily used is to have a method of estimating risk.
COX-1–Sparing Agents

for individual patients and for the population as a whole.

Both in vitro and in vivo data are necessary to determine whether an agent is COX-1–sparing. Many assays have been developed in an attempt to determine COX-2 selectivity and specificity (i.e., the COX-1–sparring effects) of a variety of new agents. This effort has led to much confusion regarding the selectivity of these drugs. By using various assays, almost any drug might be considered a “COX-2–selective inhibitor,” including drugs that are widely accepted as not being COX-2–selective (e.g., indomethocin).

At present, the most widely accepted test is the human whole blood assay, which uses an ex vivo model; this method specifically mimics in vivo activity. Warner et al. developed an examination that uses the human whole blood assay to determine the selectivity of various NSAIDs and other COX-1–sparing agents. They stated that the use of a so-called effective concentration at 80% (EC-80), rather than an EC-50, was more applicable for these patients (i.e., 80% inhibition of the COX-2 enzyme is necessary to provide the full therapeutic effect and is therefore more clinically relevant). After accessing all available NSAIDs, they determined that four existing agents—celecoxib, meloxicam, rofecoxib, and etodolac (valdecoxib was not available when this study was performed)—were more selective for the COX-2 enzyme than the COX-1 enzyme. In addition, models with these and other medications showing selectivity in therapeutic dosing ranges have been established.

The structure of the COX-2–binding receptor site and the theoretical mechanisms of how agents selectively bind to this receptor, versus the COX-1 receptor site, have been elucidated. Molecular modeling has demonstrated that the COX-2 active site has a side pocket that allows drugs having an appropriate side chain to bind to this region without being able to bind to the COX-1 active site.

SAFETY PROFILE

The real proof of the potential beneficial GI effects of the COX-1–sparing agents is found not in test tubes but in clinical practice. There has been much discussion about GI safety issues and the use of endoscopy in revealing the reduced rate of ulceration. However, as clearly indicated in numerous studies, ulcers detected by endoscopy have little, if any, correlation with actual clinically significant ulcers. Up to 80% of patients who take traditional NSAIDs develop “endoscopic ulcers,” but only 1% to 4% of these patients ever have a clinically significant ulcer. This is one reason why the Food and Drug Administration (FDA) has not accepted the data on endoscopic erosion and ulcers as a rationale for drug selectivity. The overall improved safety of these drugs is better demonstrated in clinical models that have shown a reduction in significant GI events.

Rofecoxib

In the VIGOR Study, rofecoxib was compared with naproxen (Naprosyn®, Roche) in approximately 8,000 patients with rheumatoid arthritis. Aspirin for cardiovascular protection was not allowed. The patients who received rofecoxib—an agent that is more selective for the COX-2 enzyme than for the COX-1 enzyme—experienced a 55% reduction in significant GI events over one year compared with patients who received naproxen, a nonselective agent. Meta-analyses of the data on rofecoxib, which included data on patients with osteoarthritis and rheumatoid arthritis, demonstrated a significant reduction of GI events for patients taking rofecoxib versus traditional NSAIDs.

Celecoxib

In the Celecoxib Long-term Arthritis Safety Study (CLASS) trial, celecoxib—an agent that is more selective for the COX-2 enzyme—was compared with diclofenac sodium (Voltaren®, Novartis) and ibuprofen in approximately 8,000 patients with osteoarthritis and rheumatoid arthritis. In contrast to the VIGOR trial, the CLASS trial allowed aspirin use for cardiovascular prophylaxis (21% of patients were taking 325 mg of aspirin or less); the dropout rate in each of the three treatment arms was almost 60% (compared with 20% in the VIGOR study). Although the six-month data seemed to show a difference among the treatment arms, there was no significant difference among the groups at one year, a fact that might be related to the high number of patients who withdrew from the study.

In a subsequent study of more than 13,000 patients, Singh et al. described a comparison of celecoxib with diclofenac and naproxen over a three-month period. There was a significant reduction in GI events in the group receiving celecoxib (with ulcer complications occurring in 0.1% of patients) compared with the group receiving conventional NSAIDs (with ulcer complications occurring in 0.8%).

Meloxicam

Several pooled analyses assessing the GI safety of meloxicam have been conducted. In an analysis by Schoenfeld that included more than 20,000 patients, patients taking meloxicam experienced a 48% reduction in perforations, ulcers, and GI bleeding episodes, compared with patients taking traditional NSAIDs.

In a pooled analysis of more than 27,000 patients, Singh and colleagues found that the rate of GI events in patients taking meloxicam was reduced by more than 50%, compared with patients receiving comparator NSAIDs. These findings support the premise that meloxicam has greater selectivity for the COX-2 enzyme than for the COX-1 enzyme.

The two largest studies from Europe—The Meloxicam Large-scale International Study Safety Assessment (MELISSA) and the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trials—included approximately 9,000 patients in each. Patients who received meloxicam spent significantly fewer days in the hospital because of GI ADEs than did patients receiving diclofenac and piroxicam.

In a prospective, observational cohort study by Degner et al. that included more than 4,000 patients, patients with rheumatoid arthritis or osteoarthritis received either meloxicam or a comparator NSAID, such as diclofenac, ibuprofen, piroxicam (Feldene®, Pfizer), or indomethocin (Indocin®, Merck). A higher percentage of the meloxicam patients had a history of significant GI events (11%) than the comparator NSAID patients (6%), but they had significantly lower rates of GI adverse reactions (1.80%) and GI bleeding (0.08%) than the comparator NSAID group (3.20% and 0.50%, respectively).

Data from the United Kingdom’s pharmacovigilance surveillance program suggest that both meloxicam and rofecoxib reduce the number of significant GI events. No head-to-head
comparisons of these drugs and GI safety have been performed to date.

**Valdecoxib**

Although no long-term data on valdecoxib and the reduction of GI events have been published, this agent is clearly more selective for the COX-2 enzyme than for the COX-1 enzyme; its selectivity is similar in magnitude to that of rofecoxib. Endoscopic studies suggest that valdecoxib reduces the risk of ulcers in the upper GI tract.30

**Etodolac**

Although test tube data suggest that etodolac—an agent with an available generic equivalent—has a favorable selectivity profile for COX-2,31 few clinical data exist about the risk of endoscopy-detected ulcers or significant GI ADEs.

**RESULTS: THE P&T COUNCIL’S FORMULARY DECISION**

After examining the available data, the Department of Defense Pharmacy and Therapeutics Executive Council (DoD P&T Council), in a meeting held on August 7, 2002, voted to add meloxicam to the formulary but emphasized that it should be used only after a traditional nonselective NSAID has been unsuccessful.32 The Council acknowledged that although meloxicam was associated with fewer serious GI events than the less COX-2–selective NSAIDs were, its use in patients who are at low risk of GI ADEs is inappropriate.

Although the Council members were convinced that the evidence for a GI-sparing effect with rofecoxib was strong, they did not add it to the formulary because of its cost and because of concerns about its cardiovascular safety. However, the Council agreed that the evidence showing a reduction in the incidence of complicated upper GI events, compared with nonselective NSAIDs, was most conclusive with rofecoxib.

After analyzing the GI safety data, the Council concurred (1) that celecoxib and meloxicam were similar in terms of their GI-sparing effects and (2) that although available whole-blood assay and endoscopic erosion data showed valdecoxib to be highly COX-2–selective, further studies are needed. Because of the insufficient data concerning the clinical utility and GI-sparing effect of etodolac, the Council decided not to add it to the formulary despite its cost advantages.

The algorithm in its present form was presented to the DoD pharmacoeconomic committee in San Antonio, Texas, in August 2002. The DoD specifically requested the algorithm for its review and positioned meloxicam to follow generic NSAIDs.

Several hospitals and clinics in the federal system have already altered their formularies based on this analysis, including TriCare 11 (Northwest Military Region), Madigan Army Medical Center, Nellis Air Force Base Medical Center, Tripler Army Medical Center, and William Beaumont Army Medical Center.

The VA pharmacy benefit management is using the algorithm format with the GI SCORE, as developed three to four years ago, to include celecoxib and rofecoxib. Algorithms are now in place at various Veterans Integrated Service Networks (VISNs) throughout the U.S. These include VISNs 1, 2, 4, 18, and 22, which have implemented algorithms similar to the one described here.33 VISNs are regional VA formularies that encompass multiple VA hospitals and clinics within a region of the U.S.

**CONCLUSION**

When used for the appropriate patients, COX-1–sparing agents reduce the risk of the most common complication of NSAID therapy (GI bleeding), with potential savings of millions of dollars for acute hospitalization and management. Models that can help to estimate the risks of serious GI complications related to NSAID therapy are now available.10,11 By stratifying patients according to their risk of GI bleeding, P&T committee members will be able to compare the costs of more expensive medications versus the costs of treating complications that arise when the therapy is not utilized. When drug costs are taken into account, a “cut-off” point for the price of these more expensive and safer medications can be determined, and an algorithm can be developed to guide the use of these drugs. Such algorithms are presently being implemented in the regional VA formularies throughout the U.S. in efforts to control costs and to improve the quality of care.33

The advent of COX-1–sparing drugs has revolutionized the way in which physicians treat osteoarthritis and rheumatoid arthritis. Because of their significant costs, however, careful use of these medications is essential.

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COX-1–Sparing Agents


