Clinical and Humanistic Outcomes in Patients With Gastroesophageal Reflux Disease Converted From Omeprazole to Lansoprazole

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Background: Omeprazole and lansoprazole are 2 proton pump inhibitors (PPIs) currently available in the United States. Both PPIs are approved for the treatment of gastroesophageal reflux disease (GERD) and are commonly converted in therapeutic interchange programs.

Objective: To measure clinical and humanistic outcomes in patients with GERD converted from treatment with omeprazole to treatment with lansoprazole through a managed care plan policy.

Methods: Patients with heartburn or GERD receiving omeprazole covered by a local health plan were surveyed by telephone. Data collected included symptom frequency, severity, over-the-counter heartburn preparation use, diet, lifestyle, and overall satisfaction. Patients were then converted to therapy with lansoprazole and again interviewed after at least 30-day use of the new PPI. Demographic data were obtained from the health plan database for analysis.

Results: A total of 105 patients completed both telephone surveys. After the conversion, 37% of the patients experienced more frequent symptoms while awake. Symptom severity score was significantly higher (more severe) after conversion (mean score of 1.34 vs 2.26). Thirty-three percent of study patients consumed more over-the-counter heartburn preparations, and 13% changed their diet more frequently due to heartburn symptoms after conversion. Overall patient satisfaction score decreased significantly (less satisfied) after conversion (mean score of 9.0 vs 7.2). There were no significant differences in alcohol and tobacco consumption before and after conversion, while patients consumed significantly less caffeine after conversion.

Conclusions: After the PPI therapeutic interchange from omeprazole to lansoprazole, patients with GERD or heartburn previously stabilized while receiving omeprazole experienced more severe symptoms and expressed decreased patient satisfaction. These results suggest a need to monitor symptoms after similar interchange programs.

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PATIENTS AND METHODS

DESIGN AND CONDUCT OF THE STUDY

The therapeutic interchange program initiated by Unity required that all patients receiving omeprazole be converted to lansoprazole at dosages determined by the prescribers. The study protocol was approved by the Human Subject Committee of the University of Wisconsin Hospital and Clinics, Madison. Patients receiving long-term omeprazole therapy were identified in the Unity prescription database. A notification letter was sent to these patients advising them on the details of the interchange, and informing them of the study. Upon receipt of the letter, patients who did not wish to participate in the study were allowed to contact the investigators and be removed from the sampling pool. Participation in the study involved 2 telephone interviews. The first interview took place before the therapeutic interchange occurred, and the second took place at least 30 days after the patients had been converted to lansoprazole. In cases when therapeutic strategies other than lansoprazole were used, only qualitative information were collected during the telephone interviews.

Data collected during the telephone interviews were combined with demographic data such as age and sex, pharmacy data, and pertinent medical history extracted from health plan records for analysis. Assessment of compliance was not included in the study design because it is one of many factors that could lower effectiveness. Therefore, it was decided that the measurement of effectiveness through evaluation of symptom severity and the measurement of patients' satisfaction were sufficient to address the study objectives.

PATIENTS

The focus of this study was on patients with GERD or heartburn receiving long-term or high-dose omeprazole therapy. The International Classification of Diseases, Ninth Revision (ICD-9) codes used to identify eligible patients were as follows: 53011, reflux esophagitis; 53081, esophageal reflux; 5368, dyspepsia; and 7871, heartburn. Enrollment was limited to patients 18 years or older who received omeprazole for more than 30 days. All other health plan patients receiving long-term, high-dose omeprazole therapy (≥40 mg/d), regardless of diagnosis, were also included. Indications for the use of omeprazole were verified during the telephone interviews. Patients were excluded if the indications were peptic ulcer only, Barrett esophagus, or Ellison-Zollinger disease. Patients were also excluded if the interchange had already occurred at the time of the first interview.

INSTRUMENT DEVELOPMENT

A literature review was performed to identify a suitable survey instrument for heartburn symptom assessment. However, the existing instruments were not suitable for the study due to various reasons. Investigators of PPI clinical trials assessed symptoms during face-to-face clinic visits and by diary cards kept by patients.6-9 Other published health-related quality of life questionnaires designed specifically for GERD were either too long for telephone interview or not specific enough to detect the change in outcomes relevant to the study objectives. Therefore, it was necessary to develop a questionnaire based on the objectives of this study.

The survey instrument developed for the study contained 21 items, with the skip patterns to allow omission of questions as appropriate. The approximate duration of an interview was 5 to 8 minutes. The survey was fully scripted, and all telephone interviewers were trained prior to the calling sessions to minimize interrater variability.

After the initial development of the survey, cognitive interviews were conducted to ensure patient comprehension and face validity of the questions. Published methods for cognitive interviews were used to design the process.14-15 Two patients with GERD not covered by the health plan who were receiving long-term omeprazole therapy were recruited for the cognitive interview process. During the hour-long, face-to-face interviews, the patients were presented with the survey questions and their remarks on the contents were recorded. Their insights were incorporated into the final version of the survey.

The interview survey focused on 7 domains: heartburn symptoms while awake; nighttime symptoms of heartburn; use of over-the-counter (OTC) heartburn preparations; diet changes due to heartburn symptoms; alcohol, caffeine, and tobacco consumption; overall patient satisfaction; and satisfaction with the therapeutic interchange. (The questionnaire is available from the authors upon request.)

Patients were asked to report presence of heartburn while awake and at night within 7 days prior to the telephone interviews. If patients experienced any heartburn, they were also asked the frequency of heartburn. Heartburn symptoms were rated on a scale of 1 to 10, with 1 being very mild heartburn and 10 being the worst heartburn the patient had ever felt. Patients were also asked to report whether heartburn symptoms were intermittent or continuous while they were awake.

Patients were asked to report the use of OTC heartburn preparations (liquid antacids, tablet antacids, and histamine2 antagonists) and any change in their diet due to heartburn symptoms within 7 days of the interviews. Use of OTC preparations was determined by the number of days that a patient used at least 1 dose of the preparation in the past 7 days. The results were collected categorically, namely, in categories of none, 1 to 2 days, 3 to 4 days, 5 to 6 days, and every day. Overall patient satisfaction (before and after conversion) and satisfaction with the therapeutic interchange program (after conversion only) were rated by a scale of 1 to 10, with 1 being not at all satisfied and 10 being completely satisfied. Consumption of substances that may worsen heartburn symptoms, including caffeine, tobacco, and alcohol, was recorded. Patients were also asked to estimate the amount of alcohol consumed per week and amount of caffeinated beverages consumed per day.

STATISTICAL ANALYSIS

The t test was used to compare the mean age, and 2-sample z test was used to compare patient sex and concomitant medication use. Symptom severity and patient satisfaction scores were analyzed by paired 2-sample sign test (2 sided). The amount of alcoholic and caffeinated beverages consumed was analyzed by Wilcoxon signed rank test (2 sided). The Mann-Whitney rank sum test (2 sided) was used to analyze differences in mean satisfaction and mean symptom scores between patients whose symptoms worsened and those whose remained stable. The χ2 test of independence was used to analyze dose conversion data. Pearson correlation was used to determine relationships between variables, such as overall satisfaction scores and daytime symptom score.
relief of reflux-related symptoms, and incidence of adverse events. These equivocal data may create controversies in organizations where therapeutic interchange policies are implemented.

Unity Health Plans (Unity) is an 80,000-member, group/independent practice association–model managed care organization that provides services to members in approximately half of all Wisconsin counties. Based on comparable safety and efficacy of omeprazole and lansoprazole demonstrated in clinical studies, the Pharmacy and Therapeutics Committee of Unity declared these drugs to be therapeutically interchangeable. After a financial bidding process, lansoprazole was chosen as the preferred formulary product, and a therapeutic interchange process in which patients were converted from omeprazole to lansoprazole was implemented in the ensuing months.

This prospective, observational outcomes study measured rates of clinical and humanistic outcomes of patients with GERD who were converted from omeprazole to lansoprazole. Our hypothesis was that clinical and humanistic outcomes did not differ between patients with GERD treated with omeprazole and lansoprazole pre-scribed under a therapeutic interchange policy. Clinical and humanistic outcomes before the conversion were compared with outcomes after the conversion.

Table 1. Proton Pump Inhibitor Dose Conversions of 105 Patients

<table>
<thead>
<tr>
<th>Dose Conversions, mg</th>
<th>Omeprazole</th>
<th>Lansoprazole</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>15</td>
<td>13 (12)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>57 (54)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>15</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>30</td>
<td>20 (19)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>60</td>
<td>12 (11)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>60</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Results of Symptoms, Over-the-Counter (OTC) Drug Use, and Diet Change (N = 105)

<table>
<thead>
<tr>
<th>Survey Item</th>
<th>Response, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased frequency of OTC histamine2 antagonists</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Development of new heartburn while awake</td>
<td>30 (29)</td>
</tr>
<tr>
<td>Heartburn became continuous while awake</td>
<td>34 (32)</td>
</tr>
<tr>
<td>Increased symptom frequency while awake</td>
<td>37 (35)</td>
</tr>
<tr>
<td>New heartburn that kept patients from falling asleep*</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Increased frequency of heartburn that kept patients from falling asleep*</td>
<td>9 (9)</td>
</tr>
<tr>
<td>New heartburn that woke patients from sleep</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Increased frequency of heartburn that woke patients from sleep</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Increased frequency of OTC liquid antacids</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Increased frequency of OTC tablet antacids</td>
<td>23 (22)</td>
</tr>
<tr>
<td>Increased frequency of OTC histamine2 antagonists</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Increased frequency of any OTC heartburn preparations</td>
<td>35 (33)</td>
</tr>
<tr>
<td>Increased frequency of diet change due to heartburn symptoms</td>
<td>14 (13)</td>
</tr>
</tbody>
</table>

n = 104. There was 1 missing data point in this question.

RESULTS

RESPONSE RATES

A total of 339 patients who met the inclusion criteria were identified in the health plan database and each was sent the initial letter. Two patients contacted the investigators and chose not to participate after receipt of the letter. During the months of April and May 1998, approximately 600 telephone calls were made, resulting in the completion of 151 initial interviews. Most common reasons for nonresponse were incorrect telephone numbers, no answer at the residence after more than 4 attempts, and patient already having switched therapy. Demographics and prescription data were collected from responders and were compared with those of nonresponders. No differences were seen between responders and nonresponders in age, sex, mean number of prescriptions per month, and use of nonsteroidal anti-inflammatory drugs, salicylates, and corticosteroids.

Of the 151 patients who completed the preconversion interview, 105 completed the second interview (net response rate of 31%). Thirteen patients could not be reached for the second interview. Another 33 patients were contacted but did not participate in the second interview, of whom 21 had already switched back to omeprazole. The reasons for switching back were lack of efficacy (12 patients) and adverse events such as diarrhea and gastric cramps (9 patients). There were no significant age and sex distribution differences between patients who completed both interviews and patients who missed the postconversion interview.

OUTCOMES IN PATIENTS WHO COMPLETED PRECONVERSION AND POSTCONVERSION INTERVIEWS

Of the 105 patients who completed both interviews, 48 (46%) were men and 57 (54%) were women. Their mean ± SD age was 53. ± 11.9 years. Six patients (6%) were taking concomitant nonsteroidal anti-inflammatory drugs, and 8 (8%) were taking concomitant oral corticosteroids.

Table 1 displays PPI dose conversion distribution of the 105 patients. Table 2 displays combined survey results of symptoms, OTC drug use, and diet change. For daytime symptoms, while a majority of patients (66 patients, 63%) remained symptomatically stable, a number of patients had worsened or increased frequency of symptoms. Thirty patients (29%) developed new heartburn symptoms, 34 (32%) had heartburn that became continuous, and 37 (35%) had increased frequency of heartburn. Note that these experiences were reported by primarily the same group of patients (32 patients reported all 3 criteria of symptom worsening). Postconversion symptom severity measured by severity score was also significantly higher than that before conversion (mean ± SD score of 2.26 ± 2.63 vs 1.34 ± 2.28, respectively; P = .003).
Table 3. Consumption of Alcohol and Caffeine

<table>
<thead>
<tr>
<th>Interview</th>
<th>n</th>
<th>No. of Servings, Mean (Range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Preconversion</td>
<td>104*</td>
<td>2.20 (0-15)</td>
</tr>
<tr>
<td>(servings per week)</td>
<td>Postconversion</td>
<td>104*</td>
<td>2.22 (0-24)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Preconversion</td>
<td>105</td>
<td>2.02 (0-20)</td>
</tr>
<tr>
<td>(servings per day)</td>
<td>Postconversion</td>
<td>105</td>
<td>1.62 (0-12)</td>
</tr>
</tbody>
</table>

* One patient did not respond to questions regarding alcohol and tobacco use.

Nighttime symptoms differed less when comparing preconversion and postconversion survey results. Most patients (85%, n = 89) had stable symptoms. Nine patients (9%) reported newly developed heartburn or increased frequency of heartburn that kept them from falling asleep. Twelve patients (11%) reported newly developed heartburn or increased frequency of heartburn that woke them from sleep. Of the patients with any nighttime symptom worsening, 5 experienced both definitions of nighttime symptoms.

There was an increase in use of OTC heartburn preparations in all 3 categories of product (liquid antacids, tablet antacids, and histamine2 antagonists). Overall, 35 (33%) of the patients consumed more OTC heartburn products (any category) after conversion. Tablet antacids seemed to be the most commonly used of the 3 categories, with 43 (41%) patients reporting some use.

Few patients noted the need to change their diet habits due to heartburn symptoms after conversion. Fourteen patients (13%) had increased frequency of diet changes due to heartburn symptoms after conversion.

There were no significant differences in the amount of alcohol consumed before or after the therapeutic interchange; however, patients consumed significantly less caffeinated beverages after the conversion (mean difference of 0.4 servings per day; P = .01). Table 3 shows alcohol and caffeine consumption of the patients. The consumption of caffeinated beverages decreased with increase of symptom score (r = −0.26, P = .006), which might indicate that patients lowered their caffeine intake when they had more symptoms. There were no significant differences in the pattern of tobacco use.

Two aspects of patient satisfaction were evaluated. The postconversion overall satisfaction score was significantly lower than the preconversion score (mean ± SD score of 7.24 ± 2.78 and 9.00 ± 1.49, respectively; P < .001). The mean satisfaction toward the medication switch program was 7.29 with an SD of 3.02. The program satisfaction score was assessed once during the second interview only. Patients were less satisfied with the therapeutic interchange program if their symptoms worsened (r = 0.46, P < .001).

The correlation of the preconversion and postconversion changes in the symptom severity score and the overall satisfaction score was examined. Linear regression of the net changes of the 2 scores indicates that the increase of symptom severity correlates with the decrease in overall satisfaction (r = −0.67, P < .001).

We performed further analysis on patients with worsened heartburn outcomes. Patients with any negative outcomes were considered to be “worsened” patients. The negative outcomes included new heartburn, heartburn that became continuous, increased frequency of heartburn while awake, increased frequency of nighttime symptoms, increased frequency of OTC heartburn preparation use, and increased frequency of diet change due to heartburn symptoms. The 55 patients who worsened (52%) were compared with the 50 patients with stable outcomes (48%). The patients who worsened were significantly younger (mean age of 49.7 years vs 57.3 years; P = .001). There were no sex distribution differences (P = .96). As physicians made the decisions of the eventual lansoprazole doses, several dose conversion schemes resulted. Worsening of symptoms was independent of dose conversion (P = .62), which indicated that no correlation was found between symptom worsening and specific dosing schemes. However, the relatively small sample size may have limited our ability to detect any differences. Mean daytime symptom score change was significantly different (+2.62 for the worsened group, −0.96 for the stable group; P < .001). Mean overall satisfaction score change was also significantly different (−3.07 for the worsened group, −0.32 for the stable group; P < .001).

The results of this study suggest the trend that, after the PPI therapeutic interchange, patients with GERD or heartburn experienced more severe symptoms and their satisfaction decreased. Of the 105 patients who completed the 2 telephone interviews, 52% experienced some aspects of worsened heartburn symptoms after conversion. Also, there were an additional 21 patients who had already switched back to omeprazole before the second interview took place. This group of patients should be considered lansoprazole treatment failures, of which lack of efficacy and adverse side effects both played significant roles.

Other evidence to support the trend of worsening symptoms includes the fact that smoking and alcohol use did not change, while patients appeared to consume less caffeinated beverages after conversion. As caffeinated beverages are known to contribute to heartburn symptom exacerbations, a decline in consumption is likely an indicator of worsening symptoms. Increased OTC use and diet change also correlated with worsening symptoms and lower level of satisfaction.

The worsening of outcomes was independent of PPI dose conversion, and therefore the equivalent doses of the 2 PPIs in patients with GERD remain unclear. The lack of statistical significance may be attributed to the small sample sizes in the dose conversion subgroups.

Patients who reported worsened outcomes were significantly younger. In our study, the mean age difference between the worsened patients and the nonworsened patients was 7.6 years. This is consistent with data from 2 other studies.16,17 Both studies included patients with dyspepsia and the authors found a negative association between age and reported symptoms. This age difference is likely reflecting that the perception of pain is age dependent. It is impossible to create policies or treat-
ment guidelines based on a small age difference that was related to a subjective measure. Although the finding was statistically significant, the age difference may not be a practical guide for health policy purposes.

Results of our study are somewhat contradictory to findings in clinical trials that have shown equal efficacy between the 2 PPIs. However, there are fundamental study design differences between our study and the clinical trials. The published clinical studies compared parallel groups of patients who received either lansoprazole or omeprazole. Patients who participated in these studies were also screened by strict inclusion and exclusion criteria and were followed with special monitoring schedules. In our study, patients previously stabilized with omeprazole were converted to lansoprazole. These patients served as their own comparison, and they also represented patients with a spectrum of GERD severity. These intrinsic differences in study design between clinical trials and outcomes studies are likely the primary reason for the result discrepancy. However, it is important to note that studies in naturalistic settings are designed to reflect outcomes under real-life conditions, and therefore more suitable when extrapolating into practice.

It is questionable whether a severity score difference of 0.92 on a scale of 1 to 10 is clinically significant. We believe the measurable decreases in effectiveness and patient satisfaction were not due to the clinical efficacy of the 2 PPIs, but were due to the administration of the interchange program, which nevertheless indicates that there is some room for improvement. For instance, the lack of personal interaction between physicians and patients during the therapeutic interchange process, which is common in managed care environments, might have contributed to the outcomes. In our setting, the interchange is often done at the pharmacy level, where the pharmacist obtained physician approval and dosage order over the telephone. Little patient involvement was present in the process. This could also be another reason for the discrepancies in results between our study and randomized clinical trials, that the 2 types of studies were conducted in vastly different environments, namely, the artificial but well-controlled vs the real but imperfect. Most important, the results of our study illustrate that efficacy does not always translate into effectiveness and that policy makers in managed care organizations should not assume therapeutic equivalence with only clinical trial data.

There are several limitations in this study. First, because the study was conducted in a naturalistic setting, we could not control for some patient characteristics. For example, we did not have the baseline disease severity data of the patients. Also, the level of interaction between the patients and their health care providers might have been varied. These limitations are common in outcomes research where internal validity is sacrificed in return for heightened external validity. Second, survey studies are subject to self-report bias. Patients may be dissatisfied with the therapeutic interchange as a managed care cost-saving technique. The perceived coercion to switch from one medication to another may have exacerbated their frustration as well. Finally, the post-conversion observational period may or may not be sufficient for patients’ symptoms to stabilize.

From a health policy perspective, this study serves as an important part of quality improvement in a managed care setting. Two strategies may be utilized to maintain quality of care when implementing a therapeutic interchange program. The interchange may apply only to new prescriptions for previously untreated patients, while patients stabilized with a nonformulary product in the same class may continue with the treatment, an arrangement often referred to as “grandfathering.” Under this policy, the immediate financial return of the program may be limited as the number of patients using the formulary product will increase slowly. The advantage, on the other hand, is that the impact to patient satisfaction is minimized when the nonformulary product is grandfathered as opposed to a mandatory change. Alternatively, a health plan may require all eligible patients to convert to the new drug, while having an approval process in place whereby patients may be switched back to the nonformulary product if the formulary product is ineffective. Obviously, the advantage and disadvantage of this method is opposite to that of grandfathering. Our health plan had been operating with the latter approach that allowed patients to switch back to treatment with omeprazole if lansoprazole therapy failed.

Results of this study were presented to members of the Quality Improvement Committee of our health plan, who decided to continue endorsement in the conversion, despite realizing that a subset of patients was dissatisfied. The results prompted follow-up efforts with patients who developed worsened symptoms. The members of the committee also emphasized the need to improve communication with patients and physicians in future therapeutic interchange initiatives.

The design of this study did not account for other clinical events such as hospitalization, extra clinic visits, use of specialists, visits to the emergency department, and medication wastage. Such events may have a significant economic impact. Future studies may explore such costs involved in a therapeutic interchange program. Nevertheless, our results demonstrate that it is critical for managed care organizations to measure patient outcomes in an organized fashion after implementation of health policy decisions and determine their impact in effectiveness and patient satisfaction.

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