

Proton Pump Inhibitor Therapy: Preliminary Results of a Therapeutic Interchange Program

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Abstract

Objective: To analyze the experience of one Department of Veterans Affairs hospital in treating with lansoprazole all patients with acid-peptic disease requiring proton pump inhibitor therapy, including newly diagnosed patients and those who were previously stabilized on omeprazole.

Study Design: Retrospective analysis.

Patients and Methods: We evaluated the charts of 78 patients seen between March 17, 1997, and November 1998 by the Gastroenterology Section at the Togus Veterans Administration Hospital who were diagnosed with acid-peptic disease.

Results: Overall, side effects necessitated discontinuation of therapy in 10 (13%) of the lansoprazole-treated patients and none of the omeprazole-treated patients. Nine patients on lansoprazole suffered from persistent diarrhea and were placed on omeprazole, and one had lower back pain and was switched to cimetidine therapy. Additionally, 12 patients (15%) had their lansoprazole therapy discontinued because of lack of efficacy. Of the 78 lansoprazole-treated patients, 22 (28%) failed to respond to treatment.

Conclusions: Although this study represents preliminary findings and the statistics are observational in nature, important lessons can be learned. At this

particular institution, the potential 12% savings from a mandated therapeutic interchange program were quickly offset by the overall lansoprazole-associated failure rate of 28%. The reproducibility of these preliminary results from an omeprazole-to-lansoprazole therapeutic interchange program in other institutions is unknown but warrants further consideration and additional studies, including those evaluating cost efficacy.

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The need to moderate rising healthcare costs has contributed to the increased use of therapeutic interchange programs to aid in choosing cost-effective drug therapy when several drugs within the same therapeutic class exist. On June 16, 1997, the Department of Veterans Affairs (VA) announced the implementation, effective June 1, 1997, of a national drug formulary to provide system-wide consistency in drug dispensing policies and practices.¹ The stated objectives of this formulary included, in part, lowering pharmaceutical costs through enhanced competition and providing better patient care at a lower cost.

In the February 1997 VA National Acquisition Center newsletter, the Special Contract Section of the center's Pharmaceutical Products Division announced the awarding of 3 new national contracts promoting and supporting the VA drug standardization initiative. One multiyear, committed-use con-

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tract was for lansoprazole (Prevacid®, TAP Pharmaceuticals, Deerfield, IL), contributing to a combined estimated total savings of \$48.7 million annually over the next available source of supply, Federal Supply Schedule.¹ In the case of lansoprazole, the comparator drug that it replaced was omeprazole (Prilosec®, Astra Zeneca LP, Wayne, PA). At the time of the award, the side effect profiles of the 2 drugs were reported to be similar.

A recent abstract evaluated dose equivalency, cost, and failures after the conversion of omeprazole to lansoprazole in the VA system.² Total cost savings were projected based on successful conversions; the costs of side effects and treatment failures associated with switching were not considered. One VA hospital evaluated the treatment costs and percentage of outpatient prescriptions for peptic ulcer disease and gastroesophageal reflux disease (GERD).³ Maintenance therapy with lansoprazole accounted for 76% (\$1,366,200) of the estimated yearly cost.

An assessment of patient satisfaction after a formulary switch from omeprazole to lansoprazole revealed that omeprazole was preferred by patients for maintenance therapy of GERD.⁴⁻⁶ The study was conducted at a VA Hospital in San Diego, California. More patients reported side effects with lansoprazole ($P < .001$) than with omeprazole, and 64% of patients preferred omeprazole.

Recently published abstracts report an emerging pattern of treatment failures in the VA medical system with lansoprazole therapy because of poor symptom control and adverse effects (primarily diarrhea).⁶⁻⁹

The present report is from the Gastroenterology Section of a VA hospital in a US region different from those in previously published reports. The article describes the results of treating all patients diagnosed with acid-peptic disease requiring proton pump inhibitor therapy with lansoprazole, including those previously stabilized on omeprazole and those newly diagnosed with acid-peptic disease.

...METHODS...

Medical records were reviewed for those patients seen by the Gastroenterology Section at the Togus Veterans Administration Hospital with a diagnosis of acid-peptic disease that was managed with proton pump inhibitor therapy. Data were abstracted from medical records for all patients under treatment between March 17, 1999 and November 1998. All patients with acid-peptic disease stabilized on omeprazole were switched to lansoprazole therapy,

beginning in June 1997, and all new patients requiring proton pump therapy subsequent to March 17, 1997, received lansoprazole. Demographic data for all patients, including height, weight, sex, and race, were collected. Primary diagnosis, comorbid conditions, signs and symptoms of GERD, and history of diagnostic workups and results also were noted. Items noted from the patients' drug treatment history included the proton pump inhibitor prescribed before switching therapy, reasons for the switch (eg, formulary mandate, adverse effects), specific drug, dose, schedule, and duration of therapy.

Both clinical and economic issues were considered. Therapy was evaluated and classified by discontinuations or changes in the dose of a drug secondary to side effects or lack of efficacy. Frequency of dosing also was detailed. Clinical results were classified as 1) successful, 2) primary treatment failure (failed because of side effects, no response [no response is defined as a patient who fails to respond clinically to current drug therapy and is ultimately switched to alternate drug therapy], or required upward dose titration), or 3) therapeutic failure (failed because of side effects or no response). Patients who were switched under formulary mandate from omeprazole to inappropriate doses of lansoprazole and who needed dose increases were considered to have primary treatment failure because of the need for this titration. For example, a patient on omeprazole 20 mg might have required lansoprazole 30 mg but was placed on lansoprazole 15 mg and required a dose titration to achieve a therapeutic response. Medication costs were evaluated based on hospital acquisition costs, with the assumption that initial and subsequent treatment costs were assigned to the initial treatment group until therapeutic success was achieved. To be as conservative as possible in our estimates and to simplify our analysis, we did not weight the duration of time on lansoprazole therapy before dose escalation or change to another agent. Instead, we assigned a 1-month duration to all therapeutic courses before a change in therapy. We also did not evaluate the cost of professional services such as physician visits, patient telephone calls, or hospitalization costs. Baseline omeprazole treatment costs before the therapeutic interchange program were used as the comparator group.

...RESULTS...

Records for 78 patients with a diagnosis of acid-peptic disease were analyzed. There were 74 male

and 4 female patients whose average age was 58.4 ± 15.4 (mean \pm SD) years. All of the patients were Caucasian with the exception of one African-American man. Mutually nonexclusive patient diagnoses included GERD (n = 52), hiatal hernia (n = 23), esophageal stricture (n = 18), peptic ulcer disease (n = 13), erosive esophagitis (n = 7), duodenitis (n = 7), gastropathy (n = 1), and other gastrointestinal diagnoses (n = 27). By history, 6 patients had a diagnosis of gastrointestinal bleeding and 2 had gastrointestinal cancer. Each patient averaged 2.3 gastrointestinal-related diagnoses.

Of the 78 patients, 30 (38%) were considered to have primary treatment failure (Table). In summary, 8 (19%) of the 43 patients initially treated with lansoprazole failed by study definition: 5 because of side effects, 1 because of no response, and 2 because of increased dose. Of the 35 patients initially on omeprazole who were switched to lansoprazole by formulary

mandate, 22 (63%) were considered failures by study definitions: 5 because of side effects, 11 because of no response, and 6 because the doses had to be increased.

By definition of therapeutic or secondary failure (when the need for dose titration was eliminated as a cause of failure), 22 (28%) of the 78 patients failed, including 6 (14%) of the 43 patients initially treated with lansoprazole and 16 (46%) of the 35 patients switched from omeprazole to lansoprazole. Subgroup analysis is provided under specific headings below.

Of the total 78 patients, 14 overall required lansoprazole dosage titration. Patient's initial lansoprazole starting dose is found in the Table. Thirteen patients required upward titration. One patient in the initial lansoprazole group had his dose decreased from 30 mg to 15 mg. Among the 10 patients requiring upward dose titration in the group initially treated with omeprazole, 4 were also classified as nonre-

Table. Overall Results of Proton Pump Inhibitor Therapy After VA Formulary Conversion from Omeprazole to Lansoprazole

Variable	No. of Patients On Proton Pump Inhibitor Therapy* (n = 78)								
	Initial Lansoprazole Therapy (n = 43)				Initial Omeprazole Therapy (n = 35)				
	15 mg	30 mg	60 mg	Total	15 mg	30 mg	60 mg	90 mg	Total
No. of patients	4	17	22	43	7	19	8	1	35
Reason for failure									
Side effect		2	3	5	1	3	1		5
No response		1		1	2	7	2		11
Increase dose	2			2	4	2			6
Primary treatment failure				8					22
Therapeutic (secondary) failure				6					16
No. of patients experiencing lansoprazole dose titration	2	2		4	6	3	1		10
No. of patients ultimately maintained on lansoprazole	4	14	19	37	5	11	3		19

*All dosages given are for lansoprazole.

†For lansoprazole and omeprazole groups, dose is at the time of initiation of proton pump inhibitor therapy with lansoprazole (not resultant titrated dose).

sponders because their drug therapy was ultimately switched back to omeprazole and are included in this part of the analysis for completeness. The remaining 4 patients requiring upward dose titration with lansoprazole remained on lansoprazole therapy. Among the 4 patients requiring dose titration in the initial treated lansoprazole group, 1 patient was also classified as a nonresponder because his therapy was ultimately switched to omeprazole. The remaining 3 patients continued on lansoprazole—2 with increased and 1 with decreased dose. Overall among the 13 upward dose titration patients, 8 remained on lansoprazole. The remaining 5 patients were converted from a final titrated lansoprazole dose (3 on 30 mg/d and 2 on 60 mg/d) to omeprazole (2 on 20 mg and 3 on 40 mg).

Of the total 78 patients, 56 ultimately remained on lansoprazole therapy, 37 in the initial lansoprazole treated group and 19 in the initial omeprazole treated group.

Side effects necessitated discontinuation of therapy in 10 (13%) of the patients during lansoprazole therapy and none of the patients during omeprazole treatment. Nine patients (five on 30 mg/day and four on 60 mg/day) suffered from persistent diarrhea and were successfully switched to omeprazole. One patient receiving lansoprazole 15 mg/day complained of low back pain and was switched to cimetidine therapy. One patient who had diarrhea on lansoprazole 30 mg/day also had a history of diarrhea associated with numerous other medications. An additional 12 patients (15%) had their lansoprazole therapy discontinued because of reported lack of efficacy. Eleven of these patients had been switched from omeprazole to lansoprazole, and one was on initial lansoprazole therapy at the time of lansoprazole discontinuation (Table).

Patients Initially Treated With Omeprazole

Before March 17, 1997, 35 patients had been receiving omeprazole at various daily doses (26 at 20 mg, 7 at 40 mg, and 2 at 60 mg). Twenty-seven of those patients (77%) were treated with omeprazole on a once-daily dosing regimen. All 35 patients were converted to lansoprazole therapy because of formulary mandate; after the conversion, 22 (63%) of those patients were considered to have experienced primary treatment failure. Of those 22 patients, 16 (73%) required a change in therapy to a different agent, and 6 (27%) required an increase in the dosage of lansoprazole (Table). Thirteen of the 16 patients who required a change in therapy were placed back on omeprazole (10 from the group

that had no response and 3 from the group that had side effects), 1 nonresponder was placed on cispripide, and 2 patients who experienced side effects were placed on cimetidine and famotidine, respectively. The 2 patients placed on cimetidine or famotidine had diagnoses of GERD. Thirteen patients (37%) remained on their initially prescribed dose of lansoprazole after conversion from omeprazole.

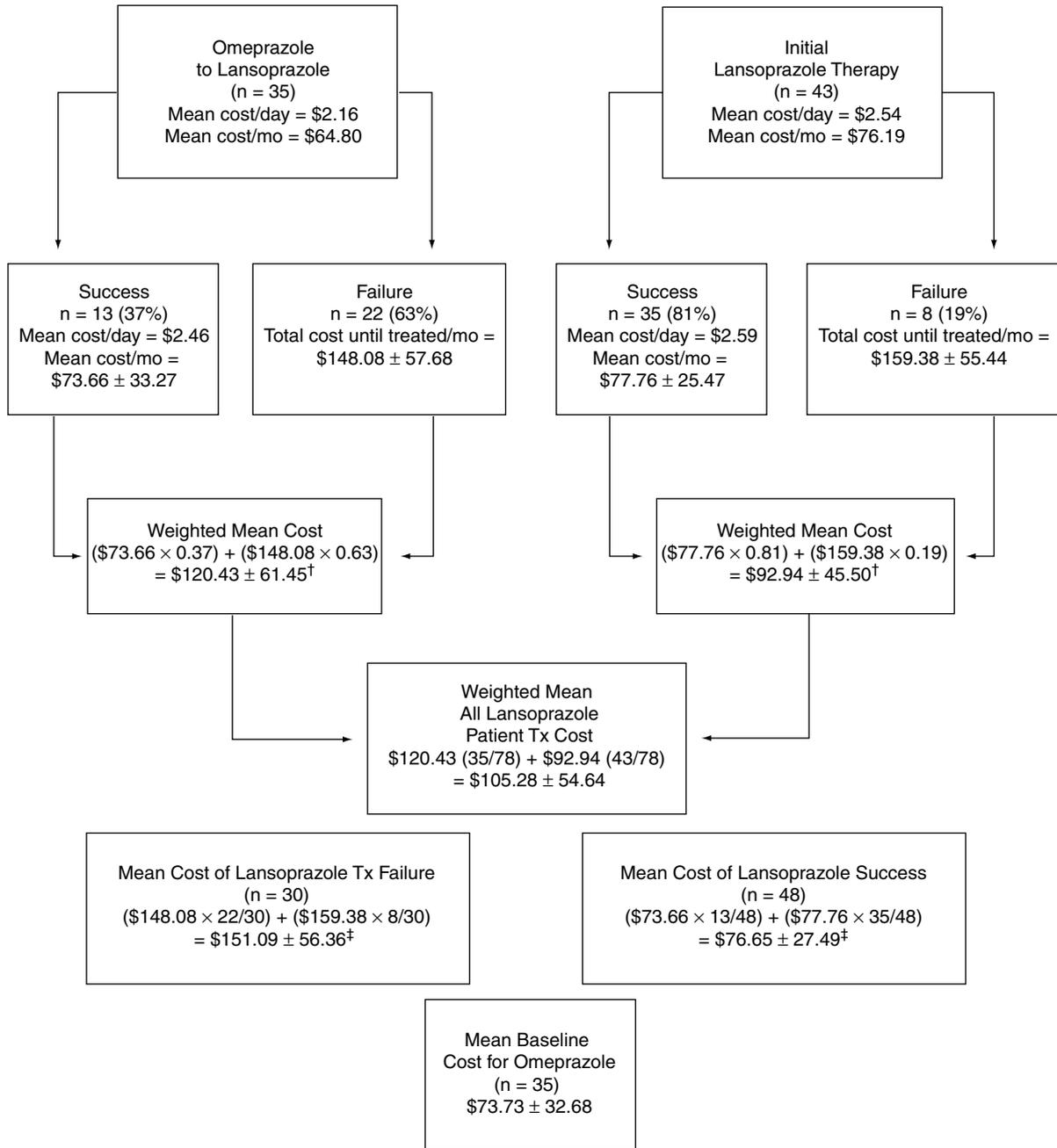
Patients Initially Treated With Lansoprazole

Forty-three new patients initially received lansoprazole. Slightly more than half of the patients (22/43) were begun on twice-daily dosing regimens. Of those 43 patients, 8 (19%) required a change in drug therapy: 5 because of side effects, one patient due to no response, and 2 with increased dose titration (Table). Five of these patients (4 with side effects and 1 nonresponder) were placed on omeprazole therapy (3 on 20 mg/day and 2 on 40 mg/day), 1 was placed on famotidine, and 2 were placed on higher doses of lansoprazole. The patient placed on famotidine by his primary care provider had a diagnosis of Barrett's esophagus. After review by the Gastroenterology Section, the patient was converted to omeprazole therapy.

Cost of Treatment

A summary of costs associated with failure and success for each group is presented in the Figure. The cost of lansoprazole treatment for all patients who required either a change in dose or a change in agent to achieve successful treatment was calculated. Lansoprazole, regardless of strength (15 mg or 30 mg) or packaging (bulk or unit dose), costs the VA \$1.68 per capsule compared with \$1.87 for omeprazole 20 mg.¹⁰ For all patients, the initial mean monthly cost for lansoprazole treatment was \$105.28, compared with a mean baseline cost of \$73.73 for omeprazole. This figure represents a \$31.55 or 43% increase in drug treatment costs. The weighted mean cost of treating each patient in the original omeprazole group with lansoprazole was \$120.43 per month, compared with the previous omeprazole treatment cost of \$73.73, for an increased cost of \$46.70 or 63%. Within the group of patients initially started on lansoprazole, the weighted mean monthly treatment cost per patient was \$92.94, compared to the treatment cost of \$73.73 for the baseline omeprazole group, for an increased cost of \$19.21 or 26%. The weighted mean treatment cost for patients switched to lansoprazole (\$120.43) compared with the weighted mean cost for patients initially treated with lansoprazole (\$92.94) was sig-

Figure. Medication Cost Comparison*



Tx = treatment.
 *Values ± SD.
 †P = .026.
 ‡P < .001.

nificantly different ($P = .026$). The mean monthly treatment cost for all lansoprazole treatment successes ($n = 48$) was \$76.65, compared with the mean cost of all lansoprazole treatment failures ($n = 30$) at \$151.09 ($P < .001$). The mean cost of therapy for patients initially receiving lansoprazole (\$76.19; $n = 43$) and the mean baseline cost for patients receiving omeprazole (\$73.73; $n = 35$) were significantly different ($P < .0395$).

... DISCUSSION ...

In this small hospital study, the cost increase for a therapeutic interchange program that substituted lansoprazole for omeprazole in patients with acid-peptic disease far exceeded the 12% projected savings that was expected. While possibly understating the cost increase, we designed our study to be conservative by assigning only 1 month of costs for each lansoprazole-associated treatment failure (dose or agent change). In addition, the primary treatment failure rate by definition was 63% in those patients who had previously been stable on omeprazole therapy. Therapeutic failure (eliminating dose increases as a cause of failure) resulted in a 45% failure rate in those patients who previously were stable on omeprazole. Optimizing pharmacotherapy in these previously controlled patients increased the overall treatment cost. Further analysis of the previously controlled group of patients found that of the 16 patients who discontinued lansoprazole therapy, 11 did not respond to the drug and 5 had side effects.

In a recent study evaluating therapeutic substitution of lansoprazole for omeprazole, a greater number of patients reported burning, pain, and acid reflux with lansoprazole than with omeprazole.⁵ The investigators believe that the symptoms, although reported as adverse events, were actually an indication of poor symptom control in their patient population.

Recently published data report an emerging trend of patient dissatisfaction and treatment failures caused by lack of response or adverse effects in patients on lansoprazole in the VA medical setting.^{4,6-9} Further study of the effectiveness of lansoprazole in other populations may be warranted. If possible, it would be useful to characterize patients who may be less likely to succeed with lansoprazole so that they could be stabilized sooner, which would result in cost savings. In our patients we found no significant differences between failure and success

with lansoprazole in terms of age and number or type of diagnoses reported.

In the group of 43 patients initially placed on lansoprazole, 8 were considered to have primary treatment failure. Six patients had therapeutic failure: 5 because of side effects and one because of lack of efficacy. This failure rate is less than that encountered with the group initially treated with omeprazole. We cannot explain the variance. Perhaps the number of lansoprazole failures would increase as time passed and additional followup occurred. Despite the greater apparent efficacy noted in this group compared with the patients who were converted from omeprazole to lansoprazole, the cost of therapy was still higher than that for the baseline omeprazole-treated group. The higher treatment cost may be explained by the fact that only 21 of 43 patients (49%) in the lansoprazole group were dosed once daily compared with 27 of 35 patients (77%) in the baseline omeprazole group.

In a large study, diarrhea was the most frequently reported side effect associated with lansoprazole therapy, with an incidence of 4.1%.¹¹ Recently, 2 reports were published indicating non-drug-class-type diarrhea associated with lansoprazole. In one case report, the authors concluded that the severe secretory diarrhea was likely related to lansoprazole and not a gastrinoma or other cause.¹² In the second report, 3 patients who had not experienced diarrhea on omeprazole were changed to lansoprazole therapy and developed severe diarrhea necessitating discontinuation of the drug and a change back to omeprazole.¹³ Two of the three patients became symptomatic when rechallenged with lansoprazole, and the third improved on concurrent sulfasalazine therapy but was diarrhea free only when lansoprazole was replaced with omeprazole. The author was unable to explain why diarrhea occurred in patients on lansoprazole but not in patients on omeprazole. In our study, 9 of 10 patients requiring discontinuation of lansoprazole therapy because of side effects had drug-associated diarrhea. A recently published abstract confirms this finding.⁷ In a published study of therapeutic substitution of lansoprazole for omeprazole, fewer adverse events were reported with omeprazole, and diarrhea was reported in 15 lansoprazole-treated patients compared with 1 omeprazole-treated patient ($P < .01$).⁵ Microscopic colitis recently was reported in six patients suffering from lansoprazole-induced diarrhea.¹⁴ Several VA patients who were switched from omeprazole to lansoprazole therapy developed chronic diarrhea (3-10 loose, nonbloody bowel movements per day).

Colonoscopy and flexible sigmoidoscopy examination of 6 patients revealed microscopic colitis that resolved within 4 to 10 days after discontinuation of lansoprazole therapy. Follow-up biopsy demonstrated normalization of colonic histology.^{8,9} The 12% incidence of diarrhea in our study is at least 3 times greater than that reported in the literature reviewed here and in the patient package insert (3.6%) for lansoprazole.¹⁵

Lansoprazole failure also may be associated with the observed lack of dose response. In our study, 13 patients required upward dose titrations with lansoprazole. Five of these patients were eventually switched back to omeprazole therapy. Damman et al found that lansoprazole did not show a dose-related increase in effectiveness over time with pH levels of >4 after intake of 60 mg versus 30 mg of lansoprazole.¹⁶ The median duration of time with gastric pH levels of >4 was virtually identical with the 30-mg and 60-mg lansoprazole regimens. This may be due to the great intraindividual and interindividual variability of lansoprazole absorption. Greater variation in intragastric pH values was found in the group receiving 60 mg compared with the group receiving 30 mg.

Additionally, Robinson and colleagues reported that 30 mg of lansoprazole was not significantly better than 15 mg of lansoprazole in maintaining healing of erosive esophagitis.¹⁷ Avner et al showed that 15 mg of lansoprazole was as effective as 30 mg or 60 mg of lansoprazole in healing duodenal ulcers.¹⁸ Two studies recently demonstrated that increasing the dose of lansoprazole from 30 mg to 60 mg provided no additional benefit in healing erosive esophagitis.^{19,20}

In contrast, omeprazole has a well-established dose response. Increasing the standard dose of 20 mg of omeprazole causes dose-related stronger acid suppression.²¹⁻²³ In patients with severe esophagitis refractory to 20 mg of omeprazole, dose titration resulted in healing of esophagitis as assessed by symptom scoring and endoscopy.²⁴ In another study Lind et al demonstrated that omeprazole produced dose-dependent inhibition of acid secretion.²⁵ Klinkenberg-Knol and coworkers recently reported that progressive dosing with omeprazole was able to successfully heal erosive esophagitis and maintain the healing over 11 years.^{26,27}

Jaspersen et al reported a prospective, randomized trial of omeprazole (40mg/day), lansoprazole (60mg/day), and pantoprazole (80mg/day) for maintenance therapy in patients with stricture whose esophagitis was healed with omeprazole 40 mg/day.²⁸

After 4 weeks of treatment, the proportion of patients remaining in remission (no esophagitis or stricture and symptom free) was 90% in the omeprazole group, 20% in the lansoprazole group ($P < .01$), and 30% in the pantoprazole group ($P < .01$). Omeprazole was superior to lansoprazole and pantoprazole in patients requiring omeprazole 40 mg/day for healing.

These observations are consistent with those of Koop et al, who reported that doses of pantoprazole exceeding 40 mg did not induce a further progressive increase in intragastric pH.²⁹ The half-lives of omeprazole and pantoprazole at pH 3 to 4 are 4 minutes and 9 minutes, respectively, and the absolute concentrations of both drugs for equipotent inhibition of H⁺/K⁺ ATPase activity are different, with higher reactivity of omeprazole in inhibition of H⁺/K⁺ ATPase. These effects might explain why no dose-related acid suppression was observed with pantoprazole. Recent reports indicate a similar lack of dose response for rabeprazole as determined by pH assessments or healing.^{30,31} Patients in the present study who failed to respond to lansoprazole may have proton pump inhibitor requirements beyond the lansoprazole peak response. This effect may have been at least partially responsible for the results in our patient population.

Potential limitations to interpreting data in our study include the small sample size, lack of power analysis, and retrospective design. Statistical interpretation of the differences between groups and the power of statistical tests are influenced by the sample size. Although retrospective studies can evaluate what characteristics are associated with the effect of a particular drug, causal relationships are more difficult to establish with this type of design compared with other prospective research designs.

Initiation of any therapeutic interchange program—whether local, regional, or national—should be accompanied by an appropriate educational intervention program to preclude placing patients on suboptimal therapy, such as prescribing ranitidine to treat Barrett's esophagus.³²⁻³⁵ Appropriate implementation of educational intervention programs has been described previously.³⁵ Suboptimal therapy can result in avoidable increases in morbidity and expense.

...CONCLUSION...

Although the findings in this study are preliminary and the statistics are observational in nature,

important lessons can be learned. Projected savings from a therapeutic interchange program of lansoprazole for omeprazole may not be realized. In our study, all-cause failure rates for lansoprazole appeared to drive the institutional cost above that for omeprazole. Persistent diarrhea, occurring in 9 of the 78 lansoprazole-treated patients (12%) and none of the omeprazole-treated patients, was higher than what has been reported in the literature. Furthermore, it appeared to be drug rather than drug-class specific.

Our findings suggest that therapeutic interchange of lansoprazole for omeprazole for the treatment of acid-peptic disease is less effective and more costly. We await the publication of the complete results from two recently published abstracts that evaluate costs and clinical and humanistic outcomes in VA patients after the conversion program.^{2,36} The reproducibility of these preliminary results in other institutions is unknown but certainly warrants further consideration and additional studies, including those evaluating comparative efficacy, requirements for dosing frequency, side effects, and pharmacoeconomics.

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