Formulary Substitution of Proton Pump Inhibitors Based on Acquisition Price: Changes in Usage and Costs of Acid-Suppressant Therapies

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ABSTRACT

Objective. In addition to indications for proton pump inhibitors (PPIs) outside the intensive-care unit (ICU), these medications are frequently used to manage nonvariceal upper gastrointestinal (GI) hemorrhage and to prevent stress-related mucosal bleeding in ICU patients. In September 2004, the P&T committee at the University of Colorado Health Sciences Center substituted three PPIs for one less expensive, preferred PPI product; all dosage forms were included. Our goal was to determine whether switching these PPIs to the least expensive agent would alter their usage and associated costs in the ICU (48 beds) and in non-ICU sites (325 beds).

Methods. We conducted analyses of hospital databases before the formulary switch of January 1, 2004, to June 30, 2004, and after the formulary switch of January 1, 2005, to June 30, 2005, to compare the usage and associated drug costs of PPIs and histamine-2 receptor antagonists (H2RAs) in non-ICU and ICU sites.

Results. Case-mix indices and length of stay data were similar before and after the switch. The total number of intravenous (IV) and enteral PPI doses charged before and after the switch increased from 1,544 to 4,143 units and from 11,865 units to 17,201 units, respectively. When we adjusted for patient-days, usage patterns of PPIs in non-ICU sites were similar before and after the switch (0.253 and 0.220 units per patient-day, respectively). In contrast, the use of PPIs in the ICU increased after the formulary switch (from 0.942 to 2.056 units per patient-day) as a result of the increased use of both IV PPIs (0.571 to 1.205 units per patient-day) and enteral PPIs (0.371 to 0.852 units per patient-day). Compared with non-ICU usage, the likelihood of PPI use in the ICU was 2.51 times higher after the switch (95% confidence interval [CI], 2.05–3.07; \( P < .0001 \)).

In the ICU, the concomitant use of IV H2RAs decreased from 2,550 to 1,869 units per patient-day. Compared with non-ICU usage, the likelihood of H2RA use in the ICUs was 0.49 times lower (95% CI, 0.39–0.61; \( P < .0001 \)).

Despite increased PPI usage, the cost of acid-suppressant therapy per patient-day in the hospital was similar before and after the switch ($0.65 and $0.59, respectively).

In the ICU, the cost of acid-suppressant therapy per patient-day was reduced from $9.66 to $7.80. Compared with non-ICU sites, the cost of acid-suppressant therapy was reduced by 0.72-fold in the ICU after the switch (95% CI, 0.52–1.00, \( P = .04 \)).

Conclusion. Substituting a less expensive PPI did not alter usage outside the ICU, but it was associated with increased usage in the ICU. Conversely, the use of IV H2RAs decreased in the ICU. Despite substantially more PPI use after the formulary switch, the cost of acid-suppressant therapy was unchanged overall; it was lower in the ICU, probably as a result of the acquisition drug cost savings associated with the switch.

Key words: proton pump inhibitor, acid-suppressant therapy, cost, formulary management, utilization, intensive care, critical care

INTRODUCTION

Proton pump inhibitors (PPIs) are the preferred agents for the management of gastrointestinal (GI) disorders, including Zollinger–Ellison syndrome, nonsteroidal anti-inflammatory drug (NSAID)–induced ulcers, Helicobacter pylori infection, and complicated or refractory gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD).1–11 Intravenous (IV) therapies are infrequently required for these disorders.

The first-line therapy for uncomplicated GERD and peptic ulcer disease involves H2-receptor antagonists (H2RAs), but many clinicians prefer PPIs because of their higher efficacy in reversing symptoms and in promoting tissue healing.12–14 IV H2RAs are the standard of therapy for preventing bleeding from stress-related mucosal disease (SRMD), but some critically ill patients may need to avoid receiving H2RAs, such as patients with associated thrombocytopenia or mental confusion that may be worsened with H2RA administration.15,16

Although limited data are available to support the use of IV PPIs for SRMD, enteral PPIs are noted to be equivalent in efficacy to IV H2RAs for this indication.17,18 Unfortunately, many critically ill patients are unable to receive enteral medications and require IV PPIs. For managing nonvariceal upper GI bleeding, high-dose IV PPIs have been shown to reduce the rates of re-bleeding and red blood cell transfusion and the need for surgery;19–26 these findings have led many clinicians to recommend PPIs before and after endoscopic therapy.27–34

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When PPIs were first introduced into the market, the acquisition costs were substantially higher than the costs of H₂RAs, many of which were available as generic formulations. In addition, insufficient data supporting the superiority of PPIs over H₂RAs for many indications prevented them from becoming first-line agents. Similarly, when IV PPIs first became available, their acquisition costs inhibited their routine use and required implementing restrictive guidelines at many institutions.35–37

In the case of enteral PPI formulations, the emergence of additional data and inexpensive generic products secured their presence as first-line therapy options for many indications.38,39 Extrapolation of data from enteral PPI formulations to IV formulations and the emergence of additional IV PPIs enhanced their market presence. The acquisition costs of IV PPIs have steadily declined as their presence in the market has increased.40

At our institution, the implementation of guidelines effectively restricted the use of IV PPIs before the hospital formulary switch to less expensive PPIs.35 Clinical experience suggests that PPI use, especially IV administration, increased after the formulary change.

The objectives of our analysis were to compare usage patterns of PPIs and H₂RAs in the hospital and in the ICU before and after the formulary change and to determine the associated costs.

METHODS

In this study, we analyzed existing hospital databases and compared the usage and acquisition cost of acid-suppressant agents for six-month time periods before (from January 1 to June 30, 2004) and after (from January 1 to June 30, 2005) the formulary switch of PPI products. The institutional review board (IRB) approved the protocol via expedited review prior to data collection. Patient consent and approval of the Health Insurance Portability and Accountability Act (HIPAA) were not required.

The University of Colorado Health Science Center is an academic institution with a 373-bed complement, including 48 ICU beds (medical or coronary, 16 beds; surgical, 16 beds; neurosurgical, eight beds; and burn or trauma, eight beds). The institution does not provide pediatric services. All ICUs have clinical pharmacy services with multidisciplinary patient-care rounds.

In September 2004, the P&T committee approved changes to the formulary, switching from several brands of PPIs to less expensive PPI formulations represented by only one brand. The PPI formulary had been stable for two years before this switch and had consisted of the following:

- esomeprazole capsules 20 and 40 mg (Nexium, AstraZeneca) or lansoprazole capsules 15 and 30 mg (Prevacid, TAP) for patients who could tolerate oral intake
- a simplified lansoprazole suspension that was compounded by the pharmacy department in bulk supply for enteral administration
- IV pantoprazole 40 mg (Protonix, Wyeth Laboratories) for the management of GI bleeding (infusion) or SRMD (bolus administration) when patients were unable to tolerate an enteral PPI or to receive H₂RAs

After the formulary switch, the 15- and 30-mg lansoprazole capsule was the only PPI available for patients tolerating oral intake; the 15- and 30-mg lansoprazole disintegrating tablet replaced the lansoprazole bulk suspension; and IV lansoprazole 30 mg replaced IV pantoprazole.

A guideline directing the appropriate use of IV PPIs was implemented in January 2003 and was continued after the formulary change.35 The adherence rate to the guideline, assessed before the switch, was 64.9%, with nearly all IV doses administered in the ICU or immediately before transfer of the patient to an ICU.

In addition, an algorithm for SRMD promoted H₂RA products, and PPIs were reserved for patients unable to tolerate H₂RA formulations. The H₂RA products on the formulary did not change; these consisted of ranitidine tablets 150 mg (Zantac, GlaxoSmithKline), ranitidine solution 150 mg/ml, and IV famotidine 20 mg (Pepcid, Merck). The daily frequency of administration for PPIs and H₂RAs recommended by the P&T committee, according to the indication of use, was identical for each route of administration before and after the change.

Because of contractual agreements, we cannot share the actual costs of the products; however, nominal pricing for all lansoprazole products was obtained after the formulary switch. IV lansoprazole represented the largest difference in acquisition cost, because it was acquired at approximately a third of the cost of IV pantoprazole.

The cost of IV famotidine was minimally reduced after the formulary switch. The costs of all other PPI and H₂RA formulations were comparable before and after the change. To maintain consistency, we used the cost of each product at the beginning of each time period; costs might have varied slightly over the duration of each time period.

To assess usage, we searched the pharmacy database for all doses of PPI and H₂RA products charged for the six-month periods before and after the formulary switch. We exported these data directly into a Microsoft Excel spreadsheet. We chose the before-and-after time periods of January 1–June 30, 2004 and 2005, respectively, to prevent any potential awareness of an impending formulary switch from altering usage before the change and to provide time for adjustment to the new products after the switch.

Prescribers were notified via newsletters and e-mail of formulary changes, and cost data were provided. The only patient-specific data collected were hospital locations at the end of therapy and the specific route of drug administration. All doses for that regimen were assumed to have been given at the location of therapy completion.

Administration was then categorized for each dosage regimen as “ICU” or “emergency room” versus any other hospital location (non-ICU). The hospital billing database was used to standardize to patient-days, and usage was then categorized as ICU or non-ICU. The hospital billing system applied a case-mix index value to every patient according to billing codes. The index designates the level of care required. We compared the mean case-mix indices for each time period to ensure that patient groups possessed similar acuity levels.

Costs were applied to the cumulative doses of each product formulation and categorized as ICU or non-ICU. Hospital acquisition costs, in U.S. dollars, were used for all products except simplified lansoprazole suspension and lansoprazole disintegrating tablets, including a pharmacist’s time to compound the suspension or a nurse’s time to dissolve the tablets. We assessed these costs before the formulary change so that the continued on page 720
Formulary Substitution of PPIs: Changes in Usage and Cost

The primary outcomes of this assessment were the usage and associated drug costs of PPIs and H₂RAs in non-ICU sites and in the ICU. Data were reported as cumulative totals or aggregate means for each six-month time period. We assessed changes in the route of administration, in ICU and non-ICU usage, and costs in relation to patient-days, and we used odds ratios obtained from 2 x 2 contingency tables. All tests were two-tailed, and odds ratios and 95% confidence intervals (CIs) were reported.

RESULTS

Patient population parameters were similar during the time periods before and after the formulary switch (Table 1). Usage analyses, unadjusted for patient-days, indicated that after the formulary switch (Table 2):

- the number of PPI doses intended for patients tolerating oral intake increased by 31%.
- the number of PPI doses intended for enteral tube administration increased by 192%.
- the number of IV PPI doses increased by 168%.
- the number of enteral H₂RAs doses increased by only 21%.
- the number of IV H₂RAs doses decreased by 7%.

Similar results were obtained when usage was adjusted for patient-days (Table 3):

- The total number of PPI doses increased by 38%.
- The number of enteral PPI doses increased by 25%.
- The number of IV PPI doses increased by 132%.
- The total number of H₂RA doses decreased by 5%.
- The number of enteral H₂RA doses increased by only 5%.
- The number of IV H₂RA doses decreased by 19%.

In relation to non-ICU usage, with adjustments made for patient-days, the likelihood of PPI use in the ICUs was 2.51 times higher after the formulary switch (95% CI, 2.05–3.07; \( P < .0001 \)). This was equally represented by the probability of enteral use increasing by 2.64-fold (95% CI, 2.11–3.30; \( P < .0001 \)) and IV use increasing by 2.11-fold. The CI was nonexistent, because non-ICU usage was negligible before and after the formulary change.

In contrast, the likelihood of H₂RA use in the ICU, in relation to non-ICU use after the formulary switch, decreased by 0.49-fold (95% CI, 0.39–0.61; \( P < .0001 \)), with the probability of enteral use decreasing by 0.24-fold (95% CI, 0.17–0.35; \( P < .0001 \)) and IV use decreasing by 0.73-fold. The CI was nonexistent, because non-ICU usage was negligible before and after formulary change.

Relative to H₂RA use, with adjustments made for patient-days:

- The overall likelihood of using PPIs after the formulary switch increased by 1.46-fold (95% CI, 1.17–1.82; \( P < .0001 \)).
- The probability of use of PPIs in the ICU increased by 3.03-fold (95% CI, 2.75–3.35; \( P < .0001 \)).

Table 1 Hospital Patient Population Parameters for Six-Month Time Periods Before and After a PPI Formulary Switch*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Switch (Jan.–June, 2004)</th>
<th>After Switch (Jan.–June, 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total discharged, all (n)</td>
<td>9,369</td>
<td>10,436</td>
</tr>
<tr>
<td>Non-ICU (n)</td>
<td>8,941</td>
<td>9,951</td>
</tr>
<tr>
<td>ICU (n)</td>
<td>428</td>
<td>485</td>
</tr>
<tr>
<td>Discharged per ICU (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MICU/CCU</td>
<td>216</td>
<td>226</td>
</tr>
<tr>
<td>SICU</td>
<td>53</td>
<td>75</td>
</tr>
<tr>
<td>Burn/trauma ICU</td>
<td>98</td>
<td>91</td>
</tr>
<tr>
<td>NSICU</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>Total patient-days, all (n)</td>
<td>45,720</td>
<td>52,787</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>43,015</td>
<td>49,349</td>
</tr>
<tr>
<td>ICU</td>
<td>2,705</td>
<td>3,438</td>
</tr>
<tr>
<td>Median length of stay</td>
<td>4.9 days</td>
<td>5.1 days</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ICU</td>
<td>4.8 days</td>
<td>5.0 days</td>
</tr>
<tr>
<td>ICU</td>
<td>6.3 days</td>
<td>7.1 days</td>
</tr>
<tr>
<td>Case-mix index, all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ICU</td>
<td>1.3726</td>
<td>1.3523</td>
</tr>
<tr>
<td>ICU</td>
<td>1.3024</td>
<td>1.2729</td>
</tr>
<tr>
<td>Case-mix index, ICU</td>
<td>2.8399</td>
<td>2.9824</td>
</tr>
</tbody>
</table>

* All comparisons are nonsignificant.
CCU = coronary/cardiac care unit; ICU = intensive care unit; MICU = medical intensive care unit; NSICU = neurosurgical intensive care unit.

Table 2 Usage Parameters Unadjusted for Patient-Days before and after a Formulary Switch

<table>
<thead>
<tr>
<th>Units Charged</th>
<th>Before Switch (Jan.–June 2004)</th>
<th>After Switch (Jan.–June 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole capsules*</td>
<td>5,701</td>
<td>0</td>
</tr>
<tr>
<td>20 mg; 40 mg (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole capsules*†</td>
<td>5,161</td>
<td>14,273</td>
</tr>
<tr>
<td>15 mg, 30 mg (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole suspension* (n)</td>
<td>1,004</td>
<td>0</td>
</tr>
<tr>
<td>Lansoprazole disintegrating</td>
<td>0</td>
<td>2,928</td>
</tr>
<tr>
<td>tablets† 15 mg, 30 mg (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole IV*</td>
<td>1,544</td>
<td>0</td>
</tr>
<tr>
<td>40 mg (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole IV†</td>
<td>0</td>
<td>4,143</td>
</tr>
<tr>
<td>30 mg (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine tablet*</td>
<td>8,468</td>
<td>10,514</td>
</tr>
<tr>
<td>150 mg (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine solution*†</td>
<td>393</td>
<td>242</td>
</tr>
<tr>
<td>150 mg/10 ml (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine IV*†</td>
<td>6,898</td>
<td>6,425</td>
</tr>
<tr>
<td>20 mg (n)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Formulary product before the switch.
† Formulary product after the switch.
The probability of use of PPIs in non-ICU sites decreased by 0.59-fold (95% CI, 0.44–0.74; \( P < .0001 \)).

The total cost of PPI therapy adjusted for patient-days was similar before and after the formulary change (see Table 3). Relative to non-ICU PPI costs, the cost of PPIs in the ICU was unaltered after the switch, with an odds ratio of 0.78 (95% CI, 0.54–1.36; \( P = .18 \)). Taking into account H2RA therapy, the overall cost of acid-suppressant therapy was reduced by 0.72-fold in the ICU relative to non-ICU locations (95% CI, 0.52–1.00; \( P = .04 \)).

**DISCUSSION**

The key finding in our analysis was the substantial increase in PPI usage after the hospital formulary was changed to low-cost products. This increased usage was apparent for enteral and IV formulations and evident only in the ICU. Concurrently, the use of H2RA enteral and IV products decreased significantly in the ICU. Despite this change in the use of acid-suppressant therapies in the ICU, the cost of medications per patient-day was reduced.

The use of PPIs in the ICU increased despite the presence of a guideline directing the use of IV PPI therapy and an algorithm for SRMD that promoted H2RA therapy. We did not perform an assessment of adherence to these protocols after the formulary switch, so their effectiveness might have declined with the introduction of less costly PPI therapies. This is partly evident by the diminished use of H2RA products in the ICU, which suggests that PPI formulations were substituted for H2RA therapies.

Although we did not assess specific indications, we do not believe that PPI use in the ICU increased as a result of patient characteristics or disease states that necessitated PPI therapy per the P&T committee guidelines. PPI therapy for GI bleeding was considered appropriate before and after formulary change. Therefore, the amplified use was most likely a result of therapy for SRMD.

We believe that the primary driver of the increased use of PPIs in the ICU was the reduced cost of these products after the formulary switch, which probably resulted in less concern for whether other acid-suppressant therapies were warranted and lack of guideline adherence. The addition of low-cost formulary alternatives has been shown to enhance utilization, especially if cost is dependent on incentives for usage.41,42

Other potential influences of PPI use in our study included:43

- enhanced promotion of the local product by the drug company after the switch to one PPI brand.
- the increased use of PPIs in the community setting, resulting in the continuation of therapy upon admission to the ICU.
- enhanced acceptability of the appropriateness of PPI therapy.
- the possible influence of literature supporting the use of PPIs for SRMD therapy that was published after the initial assessment period.

The use of PPIs outside the ICU did not increase in relation to H2RA therapy. This is not surprising, because the costs of oral PPI formulations were essentially unchanged after the formulary switch. Whether this finding represents effective management of appropriate prescribing after the change, or whether it indicates uncontrolled use prior to the formulary change, is unknown.

It is interesting that the increased use of PPIs in the ICU did not confer their additional use outside the ICU, as would be expected when patients are transferred. This finding supports the notion that enhanced ICU use was probably attributable to SRMD therapy, because PPI regimens would be discontinued as risk factors for bleeding subsided, whereas patients requir-

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**Table 3 Usage and Cost Parameters of PPIs and H2RAs Adjusted for Patient-Days and Hospital Location before and after a Formulary Switch**

*Comparisons using odds ratios obtained from 2 x 2 contingency tables are presented in the text.*

- ICU = intensive care unit; PPI = proton pump inhibitor; H2RA = histamine2-receptor antagonist. Key: — = negligible.
Formulary Substitution of PPIs: Changes in Usage and Cost

ing PPI therapy for GI bleeding would require long-term oral PPI therapy.

Appropriate discontinuation of PPI therapies at our institution has been reassuring, because some institutions report that 50% of their patients are discharged home with unnecessary acid-suppressant therapies.44 Because we work in an academic institution, this is a concern; prescribing practices at teaching hospitals influence prescribing practices at local community institutions and among general practitioners.45

Several evaluations have been conducted to assess the financial impact of restricting PPI use. The results show that practices such as establishing guidelines directing appropriate use, therapeutic interchange, step-down therapy, and prior authorization limit the use of PPIs and reduce associated costs.35-37,46-48 Our analysis indicated that although PPI use increased in the ICU, the cost of acid-suppressant therapy per patient-day was reduced. Therefore, restricting the use of PPIs based upon cost is not warranted.

The findings of two retrospective analyses showed that cost savings associated with the formulary switch to less expensive PPIs were negated by increased failure rates.89,90 Therefore, PPI therapy should be determined by clinical indications and patient characteristics rather than by cost.

STUDY LIMITATIONS

Our assessment is not without limitations. Because we did not determine patient-specific variables, the comparison before and after the switch might have been influenced by differences in patient characteristics or practice changes. Moreover, we were unable to assess the clinical appropriateness of prescribing practices.

Our assessments were based on database analyses at a single institution. Whereas the databases were not modified over the assessment period, it is possible that data entry and extraction might have varied. Similar results at other institutions would validate our data; at present, however, our results might not be representative of, or might not be directly applicable to, those of other institutions.

We assumed that patients received all doses of a specific regimen at the hospital location where the therapy was discontinued, and we applied product costs at the beginning of each time period rather than real-time costs—which might have changed slightly.

CONCLUSION

Changing the formulary PPIs to low-cost products was associated with a substantially increased use of PPIs, a decreased use of H2RAs, and reduced costs of acid-suppressant therapies in the ICU. No changes in use or in associated costs were observed outside the ICU.

REFERENCES


administering intravenous proton pump inhibitors to all patients presenting to the emergency department with peptic ulcer bleeding. *Value Health* 2003;6:457–464.


