A cost-utility analysis comparing omeprazole with ranitidine in the maintenance therapy of peptic esophageal stricture

Jeffrey M. Stal MD FRCPC, James C. Gregor MD FRCPC, Harold G. Preiksaitis MD PhD FRCPC, Richard PE Reynolds MD FRCPC

BACKGROUND: Recent studies have suggested that patients receiving omeprazole for prophylaxis against peptic esophageal stricture recurrence have less dysphagia and require fewer repeat dilations than patients receiving ranitidine.

OBJECTIVE: To estimate the incremental utility gain and associated incremental cost of omeprazole compared with those of ranitidine for the maintenance therapy of patients with peptic stricture who required esophageal dilation.

METHODS: Decision analysis using SMLTREE software was used to compare the incremental cost-utility of omeprazole 20 mg once daily with that of ranitidine 150 mg bid for one year. Variables were estimated from the literature, hospital data, and utility analyses involving patients with peptic stricture and health professionals. The primary outcome measure was cost per quality-adjusted life-years (QALYs) gained.

RESULTS: The incremental cost of omeprazole compared with that of ranitidine was $556 per patient treated. The incremental utility gain of omeprazole was 0.0112 QALYs. Overall, the incremental cost/utility ratio of omeprazole in the maintenance therapy of patients with peptic stricture was $49,600 per QALY gained. A sensitivity analysis revealed that the estimates with the greatest impact on the cost/utility ratio were disutility associated with dysphagia and dilation, the probability of requiring redilation and the cost of medications.

CONCLUSIONS: Omeprazole 20 mg once daily is associated with greater utility and higher cost than ranitidine 150 mg bid when used as prophylaxis against stricture recurrence. Omeprazole may be considered clinically and economically sufficient enough to warrant widespread use in this setting.

Key Words: Cost-utility analysis, Omeprazole, Peptic esophageal stricture, Ranitidine

CLINICAL GASTROENTEROLOGY

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Analyse coût-qualité de vie comparant l’oméprazole et la ranitidine dans le traitement d’entretien des strictures œsophagiennes d’origine peptique

DONNÉES DE DÉPART ET BUTS : Selon de récentes études, les patients qui reçoivent de l’oméprazole en prévention des récurrences de strictures œsophagiennes d’origine peptique souffrent moins de dysphagie et sont moins souvent candidats à la dilatation que les patients qui reçoivent de la ranitidine. L’objectif de cette étude était de mesurer, sur les plans de la qualité de vie et des coûts, les avantages de l’oméprazole par rapport à la ranitidine en traitement d’entretien chez les patients qui souffrent de strictures d’origine peptique et qui ont eu besoin de subir une dilatation œsophagienne.

MÉTHODES : L’analyse décisionnelle à l’aide du logiciel SMLTREE a été utilisée pour comparer le rapport coût-qualité de vie associé à l’oméprazole 20 mg une fois par jour à celui de la ranitidine 150 mg deux fois par jour.
Peptic esophageal stricture and dysphagia are serious complications of chronic gastroesophageal reflux disease. Among patients with reflux esophagitis seeking medical attention, the reported prevalence of peptic stricture varies considerably, ranging from 1% to 23% (1). The mainstay of treatment of peptic stricture is esophageal dilation, used most commonly with serial bougienage, which increases the diameter of the narrowed esophageal lumen. While dilation relieves the symptoms of dysphagia, it does not address the underlying pathological reflux, and, therefore, stricture recurrence requiring redilation remains a problem (2). Previous studies that examined the natural history of peptic strictures treated by dilation alone have revealed that nearly half of patients require redilation within one year (2-4).

A logical therapeutic addition to dilation is acid-suppressive pharmacological therapy to control the underlying gastroesophageal reflux. However, previous trials with an H₂-receptor antagonist (H₂RA) as prophylaxis against stricture recurrence have had disappointing results (5,6). Any potential benefit gained from the use of a more potent acid-suppressive medication, such as a proton pump inhibitor (PPI), has to be weighed against the substantial increase in cost.

In a recent study by Smith et al (7), patients with peptic stricture were randomized to receive maintenance therapy with either omeprazole 20 mg once daily or ranitidine 150 mg bid for one year after undergoing esophageal dilation. Significantly fewer patients who received omeprazole therapy complained of dysphagia or required redilation compared with those who received ranitidine. Marks et al (8) compared the cost effectiveness of omeprazole (20 mg once daily) with that of H₂RA (ranitidine 150 mg bid or famotidine 20 mg bid) in the initial treatment of 34 patients with peptic stricture and coexistent erosive esophagitis. Six months after dilation, patients treated with omeprazole required fewer redilations than those treated with H₂RA. Omeprazole therapy was also more cost effective and was associated with a 40% reduction in overall costs to render a patient dysphagia-free.

A cost effectiveness analysis compares the incremental cost of an intervention with the incremental health effects of that intervention, and the results are expressed as cost per unit of effect. In contrast, a cost-utility analysis compares the incremental cost of an intervention with the incremental health improvement attributable to that intervention, and the health improvement is measured in quality-adjusted life-years (QALYs) gained; results are expressed as cost per QALY gained. By converting the effectiveness data to a common unit of measure, QALYs gained, a cost-utility analysis is able to consider simultaneously the increase in both quantity of life and quality of life (9). This allows an intervention to be compared not only with other treatments for peptic stricture, but also with any health-related treatment strategy.

In this study, a cost-utility analysis was used to compare alternative strategies in the management of patients with peptic esophageal stricture. The goal was to estimate the incremental utility gain and associated incremental cost of omeprazole compared with those of ranitidine for the maintenance therapy of patients with benign peptic stricture who required esophageal dilation.

PATIENTS AND METHODS

The decision analysis was applied to a specific subgroup of patients with benign peptic stricture who had been previously dilated to the point where they were dysphagia-free and had only been dilated as required for recurrent symptoms. In addition, these patients did not have other indications for maintenance therapy with a PPI, such as erosive esophagitis or symptomatic reflux refractory to H₂RAs.

Ten patients with recurrent peptic stricture who met the above criteria were interviewed to obtain utility scores for dysphagia and esophageal dilation. All patients were initially referred to the gastroenterology department at St Joseph’s Health Centre, London, Ontario with a history of dysphagia. Patients’ utility scores were included in the analysis if their esophageal stricture had required at least two previous esophageal dilations. To ensure accurate symptom recall, patients were included only if their most recent dilation was within one year of their utility assessment. Utility scores were also obtained from 20 health professionals working at St Joseph’s Health Centre. These scores reflected their hypothetical disutility for esophageal perforation and for the requirement of having to undergo surgical and non-operative treatment. All participants gave informed written consent under the principles of the second Declaration of Helsinki.
Assessment of dysphagia: Dysphagia severity was determined by the patients’ dysphagia score (Table 1). This score was the sum of the results from both the frequency scale (based on the frequency of dysphagia) and the diet scale (which assessed dysphagia associated with a variety of food types). Scores were obtained from patients’ recall of their symptoms before and after their most recent dilation. The two scales used to generate the dysphagia score were modified from existing dysphagia indexes reported in the literature (8,10,11).

Description of the decision model: Probabilities, outcomes and costs were based on a one-year time span extending from the patient’s most recent dilation. All recurrent episodes of dysphagia requiring redilation and any treatment of potential complications of further dilations over that one year were taken into account. The probability and cost variables were estimated from the literature and hospital data. The decision analysis was performed using a decision tree (12) implemented with SMLTREE computer software (Jim Hollenberg, New York). The structure of the peptic stricture decision tree is summarized in Figure 1. Two alternative maintenance therapeutic options for patients with peptic stricture following esophageal dilation were evaluated: omeprazole 20 mg once daily and ranitidine 150 mg bid. In this model, patients either remained asymptomatic while on one of the two medications or developed recurrent symptoms of dysphagia requiring redilation within one year of their last bougienage. Dilations that were complicated by perforation were treated either surgically or conservatively.

Probabilities: The estimated probabilities of a patient requiring redilation while on omeprazole or ranitidine over a one-year period were calculated using SMLTREE computer software (Jim Hollenberg, New York). The probabilities were based on the literature and hospital data. The decision tree identified the following decision alternatives and their clinical outcomes:

- **ASYMPTOMATIC**
  - **DIE**
  - **SURVIVE**

- **PERFORATION**
  - **CONSERVATIVE**
    - **DIE**
    - **SURVIVE**
  - **SURGICAL**
    - **DIE**
    - **SURVIVE**

**TABLE 1**

<table>
<thead>
<tr>
<th>Score</th>
<th>Frequency scale</th>
<th>Diet scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Less than once per week</td>
<td>Meat</td>
</tr>
<tr>
<td>2</td>
<td>Weekly</td>
<td>Bread</td>
</tr>
<tr>
<td>3</td>
<td>Daily</td>
<td>Apple</td>
</tr>
<tr>
<td>4</td>
<td>Each meal</td>
<td>Banana</td>
</tr>
<tr>
<td>5</td>
<td>Each swallow</td>
<td>Porridge</td>
</tr>
<tr>
<td>6</td>
<td>Cannot eat</td>
<td>Liquids</td>
</tr>
</tbody>
</table>

The dysphagia score is the sum of the scores on the two scales and was recorded as a total score out of 12. *Frequency of dysphagia; †Dysphagia associated with food type.

Figure 1) Decision tree for maintenance therapy of patients with peptic stricture who required esophageal dilation. The decision tree identifies decision alternatives and their clinical outcomes. The possible outcomes are represented by chance nodes (○). □ Decision node; Δ Terminal node.
was incorporated into the decision tree model. An average disutility score for esophageal dilation was generated using the TTO technique. This value was added to the disutility score for dysphagia. Disutility scores for esophageal perforation, and surgical and nonoperative treatment were obtained from 20 health professionals by using the TTO approach. The average of these scores was included in the decision model. Disutility of death from esophageal perforation was obtained by using the mean age of the patients in Smith and co-workers’ (7) peptic stricture study, 71 years, and calculating life expectancy from Canada life tables (23).

**Sensitivity analysis:** A one-way sensitivity analysis was performed on all of the input variables across their clinically plausible ranges to determine the impact of each variable on the overall costutility ratio.

**Statistics:** For statistical analysis, Student’s t test for paired data was used. Differences were considered significant at P<0.05. Data were averaged and expressed as the mean ± SE.

**RESULTS**

**Utility scores:** The average age of the patients who underwent a utility assessment was 64.4±4.3 years (range four to 82) with an equal male:female ratio. Of the 10 patients studied, seven were receiving a PPI, two were using an H2RA and one was not taking any medication. The mean cumulative number of dilations that these patients underwent was 7.7±1.5 (range two to 14). The mean time between their last dilation and the utility assessment was 56.5±20.5 days (range one to 201). Four of 10 patients complained of heartburn. Dysphagia and utility scores of these patients are summarized in Table 3. All 10 patients experienced symptomatic improvement following dilation, reflected by a decrease in their dysphagia scores and an increase in their utility values. Although the improvement in the dysphagia scores following dilation was relatively large compared with the increase in the utility scores for dysphagia, all differences were statistically significant. Only one patient complained of any residual dysphagia following dilation.

The incremental cost of omeprazole compared with ranitidine in this decision analysis was $556 per patient treated. The incremental utility gain of omeprazole was 0.0112 QALYs (the equivalent of four days). Overall, the incre-

<p>| TABLE 2 | Summary of the estimated costs used in the decision analysis |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 20 mg daily (one-year supply)</td>
<td>931</td>
</tr>
<tr>
<td>Ranitidine 150 mg bid (one-year supply)</td>
<td>358</td>
</tr>
<tr>
<td>Esophageal dilation</td>
<td>101</td>
</tr>
<tr>
<td>Surgical treatment of esophageal perforation, and 14 day in-patient hospital stay</td>
<td>7,576</td>
</tr>
<tr>
<td>Conservative (nonoperative) treatment of esophageal perforation, and 14-day in-patient hospital stay</td>
<td>4,166</td>
</tr>
</tbody>
</table>

| TABLE 3 | Summary of patients’ symptoms and utilities for dysphagia |
|----------|---------|--------|-----|
|          | Before dilation | After dilation | P |
| Mean dysphagia score (mean ± SE) | 6.4±0.9 | 0.7±0.7 | 0.00004 |
| Mean utility score (TTO method) | 0.950±0.019 | 0.998±0.002 | 0.02 |
| Mean utility score (SG method) | 0.900±0.041 | 0.994±0.004 | 0.03 |

Dysphagia score reflects the sum of results from the frequency and diet scales described in Table 1. SG Standard gamble; TTO Time trade-off
Maintenance therapy of peptic stricture

mental cost:utility ratio of omeprazole in the maintenance therapy of patients with peptic esophageal stricture was $49,600 per QALY gained.

**Sensitivity analysis:** A sensitivity analysis was done to evaluate the effects of the variation of all of the independent costs, probabilities and utility assumptions used in the decision model. The baseline estimates and results of the sensitivity analysis are summarized in Table 4. Disutility associated with dysphagia and dilation had the greatest impact on the overall cost:utility ratio, reflected by the huge variation in the cost:utility ratio of $1.85 million to $11,800 per QALY. The highest individual disutility score for dysphagia and dilation among the 10 patients (0.32 QALYs) was used as the upper limit of the range in variation. The other estimated disutility scores had a small impact on the cost:utility ratio.

Among the estimated probabilities used in the decision model, varying the risk of requiring redilation while taking either omeprazole or ranitidine brought about the most significant change in the cost:utility ratio. Adjusting the risk of perforation from dilation over a wide range of probabilities resulted in an intermediate change in the cost:utility ratio. The upper limit of the range in the probability of perforation was obtained from a study that evaluated patients undergoing dilation for peptic stricture in which the perforation rate (0.013) was much higher than that reported by most studies (4). Adjusting either the estimated probability of requiring surgery for perforation or the associated mortality rate had little effect on the cost:utility ratio.

Varying the cost of either omeprazole or ranitidine had a large impact on the cost:utility ratio. The upper limit of the range in variation surrounding the estimated cost of omeprazole reflects the cost of doubling the dose. Regarding the sensitivity analysis of the cost of ranitidine, the range limits of $180 and $709 reflect the costs of other equivalent H2RAs available in the Canadian market. Variations in the other estimated costs resulted in a small change in the range of cost:utilities.

**Threshold analysis:** A summary of the threshold cost and probability values necessary to equalize the total costs of omeprazole and ranitidine is provided in Table 5. Threshold analysis revealed that the cost of omeprazole would have to be decreased by at least 60% (to less than $375) to equalize the costs of the two medications. The probability of perforation resulting from dilation would have to be greater than 51% to render the costs of the medications equal. The analysis was unable to generate threshold values for the probability of either requiring redilation (regardless of medication) or requiring surgery from perforation because there was no possible variation in probability that would equalize the total costs of omeprazole and ranitidine.

**DISCUSSION**

Both chronic dysphagia and the need for esophageal redilation contribute to the high morbidity of recurrent peptic stricture. Strictures are thought to recur as a result of ongoing gastroesophageal reflux, independent of coexisting heartburn or erosive esophagitis (2). PPIs, such as omeprazole, are the most potent acid-suppressive pharmacological agents currently available for controlling gastroesophageal reflux (24). Recent studies have demonstrated that omeprazole is
superior to ranitidine as maintenance therapy in the prevention of recurrent strictures (7,8). The high daily cost of omeprazole must be weighed against the end result of fewer dilations (and decreased costs associated with less frequent dilations) and the associated increased utility.

This decision model revealed that the incremental cost/utility ratio of omeprazole in the maintenance therapy of patients with peptic esophageal stricture was $49,600 per QALY gained. Although omeprazole clearly provides this patient population with increased utility compared with ranitidine, this improvement in utility is not without substantial financial cost. Whether the cost/utility ratio of omeprazole is clinically and economically attractive enough to recommend widespread use in this clinical setting is unclear.

A recent review by Laupacis et al (25) provided tentative guidelines for using clinical and economic evaluations of medical strategies. Technologies or therapies that were both more effective and more expensive were placed into one of three categories. Therapies that cost less than $20,000 per QALY gained are almost universally accepted. In contrast, the authors do not recommend therapies that cost more than $100,000 per QALY gained. The cost/utility ratio of omeprazole in our study was $49,600 per QALY gained. Laupacis et al (25) suggested that there is moderate evidence to support the use of treatments costing between $20,000 and $100,000 per QALY gained. The cost/utility ratio of omeprazole compared with ranitidine, omeprazole may still be considered a reasonable strategy given the economic guidelines described above.

Sensitivity analysis revealed that among the cost, probability and utility assumptions used in the decision analysis, the estimates that had the greatest impact on the overall cost/utility ratio were disutility associated with dysphagia and dilation, probability of requiring redilation, and cost of the medications. Disutility scores for dysphagia and dilation were accurately obtained in this study from the mean scores of 10 patients by using accepted methods of utility calculation. The costs of the medications used in the analysis reflect current market prices in Canada. The estimated probabilities of requiring redilation while on omeprazole or ranitidine are likely to be accurate because they were based on the published results of a large, well designed study that specifically compared the two medications in the prevention of stricture recurrence (7). Although the decision analysis was limited to one year, a recent study by Agnew et al (26) demonstrated that the frequency of dilations in the first year of treatment is predictive of the frequency in subsequent years. Variations in the other utility, probability and cost estimates resulted in only minor changes in the cost/utility ratio because the risk of perforation associated with dilation was so low. Similarly, the unrealistically high threshold costs associated with dilation and either surgical or conservative treatment of perforation reflect the lack of impact that these variables had on the cost/utility ratio.

CONCLUSIONS

Omeprazole 20 mg once daily is associated with greater utility than ranitidine 150 mg bid when used as prophylaxis against peptic esophageal stricture recurrence. This increased utility is at the expense of substantial financial cost. Nevertheless, omeprazole may be considered clinically and economically attractive enough to warrant widespread use in this setting. The cost/utility ratio in this model is significantly influenced not only by the cost of the medication, but also by the patients’ perception of their state of health, as reflected by the disutility scores for dysphagia and esophageal dilation.

REFERENCES

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