Cost-effective Selection of H2 Receptor Antagonists for Upper Gastrointestinal Hemorrhage in Japanese Hospital Setting

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The aim of this study was to identify the most favorable H2RA (H2 receptor antagonist) for the treatment of upper gastrointestinal hemorrhage (non-phlebeurysm). A decision tree was constructed to evaluate cost-effectiveness among an existing treatment (control), roxatidine, famotidine and ranitidine from the viewpoints of the payer and the medical facility. Clinical parameters used as transition probabilities were obtained from the results of the domestic RCT (Randomized Controlled Trial) of each drug. The cost items consisted of the direct medical cost, capital cost, and medical staff (doctors and nurses) personnel costs. The time horizon was set at 12.3 days on average and there was therefore no discount. Of the three drugs, at approximately 140,000 yen less than the control, ranitidine was estimated to be most cost-saving for the payer. In percentage terms, ranitidine had the highest earnings rate among the H2RAs of 46.0% and roxatidine had the highest earnings in money terms among the H2RAs of approximately 120,000 yen. A one-way sensitivity analysis used for investigating extra periods of hospitalization showed that this had no impact on the base case. A two-way analysis showed that ranitidine had the highest efficiency of about 55% for the cases analyzed. When a threshold analysis was conducted, it was found that, while there would be no change in the hemostatic rate in substitutive plans, the hemostatic rate of 0.60 for famotidine (ceiling total cost: 375,801 yen) and that of 0.61 for ranitidine (ceiling total cost: 406,271 yen) were the thresholds affecting the results of analysis. It is therefore likely that selecting ranitidine first in preference to roxatidine or famotidine would be more cost-effective.

Key words — H2-blocker, hemorrhage, pharmacoeconomics, decision analysis

Introduction

The importance of evidence-based medicine (EBM) has recently been increasing in the field of healthcare as the quality and cost of medical care is of paramount concern for those being treated. In Japan, under the directions given by the Ministry of Health, Labor and Welfare (MHLW), university and national hospitals have introduced the flat-sum-payment-system (Matsuda S. Executive summary report of research on use of Diagnosis Procedure Combination ; DPC in acute hospital secondary care. March 2003. http://webast.niph.go.jp/) based on the DPC for hospitalized care, in an attempt to standardize healthcare quality and improve transparency.

Asagi et al. and Takahashi et al. reported that upper gastrointestinal hemorrhage is primarily caused by peptic ulcer disease, which accounts for approximately 60% of all patients with the hemorrhage; the second predominant cause is acute gastric mucosal lesion (AGML), accounting for approximately 20% of all cases. The seriousness of upper gastrointestinal bleeding should not be underestimated; particularly in light of the stressful events and experiences that are part of modern life.

In the treatment of upper gastrointestinal hemorrhage, endoscopy is usually performed to confirm bleeding lesions and status so as to determine if the bleeding is related to phlebeurysm or not. Based on the endoscopic findings obtained, a therapeutic strategy is devised. Non-phlebeurysm-related bleedings usually require pharmacotherapy; endoscopic hemostasis using a hemostatic clip or pure ethanol injection is followed by drug treatment. The drugs frequently used are Proton Pump Inhibiters (PPIs) and H2 receptor antagonists (H2-blockers ; H2RAs), and it has been proven that the hemostatic rate achieved three days after the start of drug treatment is approximately 70-90%. One of the PPIs is reported to achieve a hemostatic rate as high as 90%, however its price is up to four times greater than H2RAs,

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which precludes smooth and immediate decision-making to use PPIs. Of the H₂RAs (which have comparable in hemostatic rates) famotidine is widely used in Japan because it is well known. Famotidine costs 403 Japanese Yen (based on the National Health Insurance Price in April 2003) and is the most expensive H₂RA available for the treatment of upper gastrointestinal hemorrhage in Japan. On the other hand cimetidine is a first launched H₂RA in not only Japan but also Worldwide. It was a best alternative as a control for the economic analysis as its brand product is available at the lowest price in H₂RA in Japan.

As the treatment of upper gastrointestinal hemorrhage requires the use of a significant amount of medication at our hospital, we performed an EBM-aided investigation to identify the most favorable H₂RA for the treatment of upper gastrointestinal hemorrhage (non-phlebeurysm) with the aim of reducing these drug costs, both from a payer and institutional perspective.

**Methods**

1. Preparation of a decision tree model

A simple decision tree model was constructed based on the usual treatment offered for upper gastrointestinal hemorrhage in our hospital in order to be employed to evaluate cost-effectiveness among H₂RAs as shown in Fig. 1. The hypothetical 10,000 cohort on the model shows stochastic transitions in the following drug groups: an existing treatment (control) group (cimetidine data were quoted), roxatidine group, famotidine group and ranitidine group. Generally a decision node (box) allows a decision-maker to be administrated four H₂RA therapies. After choosing each of H₂RA

![Decision Tree Model for the Treatment of Acute Upper Gastrointestinal Hemorrhage](image)

Fig. 1. Decision Tree Model for the Treatment of Acute Upper Gastrointestinal Hemorrhage.

A decision node (box) allows a decision-maker to be administrated four H₂RA therapies. After choosing each of H₂RA therapies, the model stochastically transfers health states over time as indicated by chance node (circle). In the analysis, states were divided by the treatment succeeded and one failed. Moreover the successfulness arm (line) were divided by two cases of either recurrence occurring or not.
therapies, the model stochastically transfers health states over time as indicated by chance node (circle). In the analysis, states were divided by the succeeded treatment and failed one. Moreover the successfulness arm (line) were divided by two cases of either recurrence occurring or not. If recurrence occurs all cases automatically switch to PPI therapy and take additional hospital admission. On the other hand, all failure cases automatically switch to PPI therapy as same as cases occurred recurrence.

2. Clinical parameters
To obtain the transition probabilities that are the rate of hemostasis (hemostatic rate) and the recurrence rate for the individual drugs included in the decision model, the hemostatic rate (primary evaluation time point : after 36 hrs) and the recurrence rate (after 72 hrs) for cimetidine were obtained from the results of domestic randomized controlled trials (RCT) which compared each drug with cimetidine (roxatidine from Miyoshi et al.,\textsuperscript{8} famotidine from Kidokoro et al.,\textsuperscript{9} and ranitidine from Kamata et al.\textsuperscript{10}). The formulas used in the calculation of constant hazard hemostasis rates are identical to those used by Goeree and colleagues\textsuperscript{11}.

The cimetidine hemostasis rate at the observation time (36 hrs = 1.5 days) was calculated from the hemostasis rate, using the formula \( (1) \) shown below\textsuperscript{12}.

\[
S(t) = 1 - \exp(-\mu t) \tag{1}
\]

where \( S(t) \) is the probability of hemostasis with cimetidine at time or day \( t \), and \( \mu \) is the constant hazard hemostasis rate.

Assuming that the evaluation measurement index, \( \theta_i \), of a presumed population is constant, the relative risks (RRs) of individual drugs from cimetidine were calculated using the general variance-based method. The hemostasis probabilities in each drug group were estimated by multiplying the RRs of individual drugs by the cimetidine 36-hr hemostasis rate obtained by calculation. When calculating the probability of hemostasis for individual drugs, it was assumed that the RRs of individual drugs to cimetidine were constant at the 36-hour time point using the formula \( (2) \) shown below, as shown at Table 1. The recurrence rates for individual drugs were calculated using the same method, as aforementioned.

\[
P = S(t)^*RR \tag{2}
\]

where \( P \) is the probability of hemostasis with H2RAs other than cimetidine, \( S(t) \) is the probability obtained for, \( RR \) is the relative risk.

3. Cost parameters
Table 2 shows these cost items in detail. The cost items included in analysis were: the direct medical costs (e.g. the drug cost of an H2RA, the drip infusion fee, and the medical cost : endoscopic hemostasis fee when recurrence occurred or treatment failed); capital cost (apparatuses for endoscopic hemostasis and ward beds); and medical staff personnel costs (doctors and nurses). Other costs (for example, the capital cost of the life-saving emergency medical center, hospital fee, laboratory test fee, processing fee, and the cost of other drugs) were assumed to be similar in all drug groups and not included in the analysis. Costs on hospitalization and endoscopic hemostasis were searched at St Luke’s International Hospital based on medical fee receipts. For more information ethic aspect has been taken into account when searching the receipts. The relationship among decision model, hospitalization and endoscopy costs as shown at Fig. 2. Medication costs on H2RAs and a PPI were derived from the national health insurance price as of April 2003 and incorporated into the decision model.

Doctors and nurses’ personnel expenses were individually calculated by using the following equation. Statistics required for calculation were taken from Survey on wage structure and labor of Japan issued by MHLW.

Personnel expense = practical time (sec) \times wage (yen/sec)

For more information time to perform endoscopy by a doctor was set to be 1,800 sec (30 min), and one to provide daily care to 1.7 patients was set to be 86,400 sec (24 hours).

Capital costs for equipment such as an endoscopy and a ward bed were computed by equivalent annual cost as Drummond et al\textsuperscript{13} stated. Its equation is as follow:

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Hemostatic rate (95% CI)</th>
<th>Recurrence rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing therapy (control)</td>
<td>0.436 (0.433 - 0.440)</td>
<td>0.101 (0.096 - 0.106)</td>
</tr>
<tr>
<td>Roxatidine</td>
<td>0.465 (0.346 - 0.627)</td>
<td>0.123 (0.063 - 0.238)</td>
</tr>
<tr>
<td>Famotidine</td>
<td>0.556 (0.355 - 0.868)</td>
<td>0.080 (0.068 - 0.159)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>0.658 (0.425 - 1.020)</td>
<td>0.122 (0.067 - 0.224)</td>
</tr>
</tbody>
</table>

CI: confidence interval
Moreover equivalent annual cost was converted to net present value (NPV) of the equipment based on the following equation.

\[ \text{NPV} = E \times \text{AF}_{5,4\%} \]

(\(\text{AF}_{5,4\%}\) is the annuity factor for 5 years at an interest rate of 4 percentage)

For more information upon calculation of NPV of an endoscopy equipment, a new article price was set at 15 million yen and a resale price, at 900,000 yen based on catalogues of OLYMPUS CORPORATION. On the other hand upon calculation of NPV of a bed, a new article price was set at 268,000 yen and a resale price, at zero yen, based on catalogues of Komatsu Ika Kogyo Co., Ltd.

### 4. Setting of other conditions

As showed at Fig. 2 the time horizon of the present analysis was set to be 12.7 days on average including additional hospitalization, therefore no discount was made. In
addition, the present analysis was performed from the viewpoints of the payer and the medical facility.

The analysis software used was DATA 3.5 (Tree Age Software, Inc., Williamstown, MA) and Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA).

5. Sensitivity analysis (Confirmation of robustness)

Generally, sensitivity analyses should be undertaken for testing over the range of variables of plausible values in order to gain robustness of the base case result. There are many different ways of testing variables in a sensitivity analysis.

Upon performing the sensitivity analysis, the variables requiring the sensitivity analysis were identified by drawing a tornado diagram, called a tornado analysis. Because the book by Muenning P14) stated a tornado analysis is a handy way of determining how much influence each of the variables has on the overall model as the overall influence of the variables on the cost or effectiveness of a particular strategy is not easy to predict. It also stated the extent to which a variable can influence the dominance of each strategy in a decision analysis model is determined by: 1) the overall magnitude of the variable, 2) uncertainty associated with the baseline value of the variable, 3) the relative position of the variable in a decision arm, and 4) the number of decision arms in which the variable appears.

Based on the results of the tornado analysis, first a one-way sensitivity analysis was performed when varying the extra period of hospitalization with the range from 3.40 to 15.20 days. Secondly a two-way sensitivity analysis was carried out because the hemostatic rates of famotidine and ranitidine were varied individually within the range of the confidence interval (0.335 to 0.868 for famotidine, and 0.425 to 1.000 for ranitidine). In addition, a threshold analysis was also performed in order to estimate optimized point on cost-effectiveness of either famotidine or ranitidine when varying variables in either group. For more information generally the threshold values for each of famotidine and ranitidine were automatically calculated by DATA 3.5. The total costs for each group were linearly varied, depending upon varying the hemostatic rates for each group. The cross point indicates the threshold values.

Results

1. Cost analysis (base case)

A result of a cost analysis for the base case was shown at Table 3.

Ranitidine was estimated to save costs most for the three cost components (total cost, medical earnings and medical practice cost), compared with existing therapies. However, when the relationship between earnings and costs was studied, cimetidine (existing therapy) was most profitable of 141,582 yen (reduction rate : 27.8 %). Of the three other drugs evaluated, roxatidine was estimated to be the most profitable of 117,983 yen and famotidine was least profitable of 101,600 yen. Furthermore, as shown at Table 3, when earnings rate in each of H2RAs was computed ranitidine had the highest rate of 46.0% and roxatidine, the lowest one of 39.0 % in H2RAs. In arguing on balance of reduction rate between medical practice earnings and its costs, the cost re-
duction of 26.3% in ranitidine was smaller than the earnings' one of 30.5%, whereas the costs' reductions, larger than the earnings' one in both roxatidine and famotidine.

2. Sensitivity analysis

As shown the results of the tornado diagram for the total cost at Fig. 3 in order to discuss the overall influence of variables on costs or outcomes, the hemostatic rates for the most influential drugs, famotidine and ranitidine, and extra period of hospitalization were identified influence on the base case as confounding factors. Therefore the one-way sensitivity analysis in which the extra hospitalization (mean : 9.3 days) was made to vary within the range of the confidence interval (3.4-15.2 days) resulted in no impact on the base case result i.e. ranitidine produced the greatest total cost reduction among the H2RAs, as shown at Fig. 4. The result of the two-way sensitivity analysis was shown at Fig. 5. It was found that famotidine, ranitidine and roxatidine may show high efficiency in approximately 40%, 55% and 5% of the cases analyzed, respectively. For more information the aforementioned percentages indicate areas occupied on the figure. Wider is an area of the treatment group ; more cost-effective is the group.

In addition, the threshold analysis showed at Table 4 that, where there would be no change in the homeostatic rate in substitutive plans, the homeostatic rate of 0.61 for ranitidine were the thresholds affecting the results of analysis. The aforementioned result was interpreted that if the hemostatic rate for famotidine was constantly gained less than 0.60, ratididine was cost-effectively dominant to famotidine. For more information the cross point of cost for famotidine was 375,801 yen, one for ranitidine 406,271 yen.

Discussion

In Japan, the EBM-Based Guideline for Treatment of Gastric Ulcer Disease (developed as part of the MHLW's total program on scientific research promotion and healthcare technology evaluation) has recently been published as a guiding principle for the treatment of gastric ulcer disease. The Guideline recommends PPIs as the first line of drug therapy ; and since 90% of patients with gastric ulcer disease are infected with Helicobacter pylori, a PPI-based combination regimen with two antibiotics (AMOX and CAM) is recommended for eradication of H. pylori. A meta-analysis performed by DiMario et al15) proved a significant advantage for a PPI (omeprazole) over H2RAs (odds ratio = 2.00, 95% confidence interval : 1.57-2.55). For H2RAs, the Guideline clearly states that "if PPIs cannot be used, then H2RAs which are next to the PPIs in efficacy will be used." Accordingly, PPIs (note that in Japan, only omeprazole has ob-

Table 3. Estimation of the Relationship between Medical Practice Earnings and Costs.

<table>
<thead>
<tr>
<th></th>
<th>Total cost*</th>
<th>Medical practice earnings</th>
<th>Medical practice costs</th>
<th>Difference (Yen)</th>
<th>Earnings rate** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Yen)</td>
<td>(Yen)</td>
<td>(Yen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Existing therapy</td>
<td>520,848</td>
<td>331,215</td>
<td>189,633</td>
<td>141,582</td>
<td></td>
</tr>
<tr>
<td>(control)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>42.7</td>
</tr>
<tr>
<td>Roxatidine</td>
<td>478,053</td>
<td>302,518</td>
<td>184,535</td>
<td>117,983</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42,795(8.2%)</td>
<td>28,697(8.7%)</td>
<td>5,098(2.7%)</td>
<td></td>
<td>39.0</td>
</tr>
<tr>
<td>Famotidine</td>
<td>406,271</td>
<td>253,935</td>
<td>152,335</td>
<td>101,600</td>
<td></td>
</tr>
<tr>
<td></td>
<td>114,577(22.0%)</td>
<td>77,280(23.3%)</td>
<td>37,298(19.7%)</td>
<td></td>
<td>40.0</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>375,801</td>
<td>244,112</td>
<td>131,689</td>
<td>112,423</td>
<td></td>
</tr>
<tr>
<td></td>
<td>145,047(27.8%)</td>
<td>87,103(26.3%)</td>
<td>57,944(30.5%)</td>
<td></td>
<td>46.0</td>
</tr>
</tbody>
</table>

*Upper values indicate total costs and lower values indicate incremental costs (%reduction rate)

which is difference between a total cost in existing therapy and each of ones in other H2RA agents.

**Earnings rate = Difference (= medical practice earnings - costs) / earnings
Fig. 4. One-way Sensitivity Analysis on Extra Period of Hospital Admission.

Longer is extra period of hospital admission, more expensive are expected costs in all drugs group. However within the range of 3.4 to 15.2 days there are not any cross points of lines for roxatidine, famotidine, and ranitidine with a line for existing therapy. JPY: Japanese Yen

Fig. 3. Tornado Analysis for Upper Gastrointestinal Bleeding.

A long bar indicates that confounding factors impact in the base case. Otherwise a short bar indicates they don’t impact on the base case. JPY: Japanese Yen

Obtained an official approval for an injection formulation) would normally be selected. However, since PPIs are 1.7 to 4 times higher in price than H2RAs, it is not an easy decision to use PPIs when considering the consumption of healthcare resources. In this study, we first investigated cost-effectiveness of H2RAs and then linked the investigation to evaluation of PPIs and H2RAs.

A PubMed (in English) and Japan Centra Revno Medicina (for medical journals written in Japanese) search was performed to identify clinical parameters for H2RAs which were required for analyses. In overseas, a large number of RCTs of ranitidine were found, whereas RCTs of famotidine and roxatidine were rarely found. In Japan, head-to-head RCTs among H2RAs were not frequently carried out. We therefore decided to identify clinical parameters specific to Japan, and while utilizing a random effect model, a frequently used model in meta-analyses, we only used the domestic RCT results to try to estimate clinical parameters to be incorporated into a decision tree model. This estimation revealed no significant differences in hemostatic rates among cimetidine, ranitidine, famotidine and roxatidine, and suggested no differences in clinical efficacy among the H2RAs. The meta-analysis performed by Di Mario et al. indicated that when the endpoint was a healing rate of peptic ulcer disease 4-6 weeks after the start of treatment, no significant differences were noted among H2RAs (cimetidine, ranitidine and famotidine) in the endpoint.

In the present study, a simulation analysis was performed...
using a decision model into which the following parameters were incorporated: hemostatic rate (a surrogate endpoint); recurrence rate (a true endpoint); and cost parameters. Although no statistically significant differences were noted in the hemostatic rate among the four drugs evaluated, including the existing therapy (cimetidine), each of the four drugs seemed to have its own properties in terms of therapeutic efficacy for upper gastrointestinal hemorrhage. Specifically, ranitidine was less costly in all three cost components evaluated (total cost, medical earnings and medical practice costs) than the existing therapy, whereas the difference between earnings and costs from the viewpoint of a medical institution was slightly smaller for ranitidine than roxatidine. On the other hand, roxatidine was also the least costly, although to a smaller extent, in all three cost components evaluated when compared to the existing therapy, whereas the difference between earnings and costs was greater. Famotidine was located between ranitidine and roxatidine. The cost reduction produced by the three drugs when compared to the existing therapy was primarily attributable to the smaller number of extended hospitalizations required for symptom aggravation and/or additional endoscopy. Finally ranitidine had the highest earnings rate in H2RAs from the institutional viewpoint. Because earnings' reduction was larger than cost reduction in ranitidine, whereas the earnings' reductions, smaller than the costs' reductions in both roxatidine and famotidine.

A tornado diagram was drawn to identify confounding factors that substantially affect analysis results, and by varying the confounding factors a sensitivity analysis was carried out. For extra hospitalization, no impact was found on the base case result. A two-way sensitivity analysis in which the hemostatic rates of ranitidine and famotidine were made to vary simultaneously revealed that the hemostatic rate of an H2RA substantially affected the result. It was considered, however, to be more likely that ranitidine would be more cost-effective than famotidine. It was therefore expected that the present analysis might provide a basis for decision-making for selecting drugs. All patients do not always follow the simulation model evaluated in this study, and the analysis used in this study has limitations from the viewpoint of individual patients. It may be required to compare the analysis results against clinical practices at our hospitals to evaluate transferability and generalizability of the analysis results, and in addition, to investigate the cost-effectiveness of H2RAs and PPIs in the treatment of upper gastrointestinal hemorrhage.

In the future, as pharmacists put EBM into practice, it is expected that they will not only explore evidence available through publication, but also create their own new evidence using information surrounding them in order to resolve problems confronting them.

In conclusion, as described above we take into consideration that the present analysis is a proper method of evaluating the three drugs. It is likely that selecting ranitidine first

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**Table 4. One-way Threshold Analysis on the Hemostatic Rate: Famotidine vs. Ranitidine.**

<table>
<thead>
<tr>
<th></th>
<th>Famotidine predominant</th>
<th>Ranitidine predominant</th>
<th>Threshold (Yen)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Famotidine</strong></td>
<td>0.60-0.87</td>
<td>0.35-0.60</td>
<td>375,801.5</td>
</tr>
<tr>
<td><strong>Ranitidine</strong></td>
<td>0.42-0.61</td>
<td>0.61-1.00</td>
<td>406,271.0</td>
</tr>
</tbody>
</table>

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**Fig. 5. Two-way Sensitivity Analysis on the Healing Rate: Famotidine vs. Ranitidine.**

Each area indicates the least costly therapy. If probability on the treatment succeeded by ranitidine is higher at 0.86 or over and one in famotidine ranges from 0.35 to 0.74 ranitidine is constantly the best choice to treat for upper gastrointestinal hemorrhage. Otherwise if probability on the treatment succeeded by famotidine is higher at 0.74 or over and one in ranitidine ranges from 0.42 to approximately 0.8 famotidine is constantly the best choice to do.
will provide a more cost-effective outcome than selecting the other two drugs.

References

3) Package insert of cimetidine® injection 200 mg (Sumitomo Pharmaceuticals).
4) Package insert of roxatidine® injection 75 (Teikoku zoki).
5) Package insert of famotidine® injection 10 mg, 20 mg (Yamanouchi Pharmaceuticals).
6) Package insert of ranitidine® injection (Glaxo SmithKline).