ABSTRACT

Background: Vitamin K compounded oral solution costs significantly less on a per-milligram basis compared with tablet formulations. Current literature has shown that international normalized ratio (INR) lowering in the reversal of vitamin K antagonists (VKAs) occurs to a similar degree when using vitamin K oral solution compared with tablet formulations. 

Objective: To compare drug spending on vitamin K oral solution versus tablet using a price–performance ratio (PPR).

Methods: A retrospective chart review was conducted at a tertiary care academic medical center to compare INR reversal of VKA-induced coagulopathy on a price basis for vitamin K oral solution versus tablet. The price of the oral solution accounted for supplies and labor. A PPR was calculated based upon the following formula: vitamin K formulation cost divided by the hourly percent change in INR following vitamin K administration. 

Results: The PPR for vitamin K tablets was 27.0 compared with 5.8 for the oral solution (P = 0.006).

Conclusions: Utilization of vitamin K solution resulted in a significantly reduced cost per INR-lowering effect relative to commercially available tablets. Utilization of a compounded vitamin K solution represents an enticing means of cost-savings in the hospital setting.

Keywords: Vitamin K, drug costs, drug compounding

BACKGROUND

Oral vitamin K is an effective and commonly utilized reversal agent for warfarin-induced coagulopathy.1,2 The rising cost of the commercially available vitamin K tablet formulation has prompted interest in cost-saving measures that may reduce hospital drug spending. One option is to use a compounded oral solution that is prepared using the less expensive intravenous formulation of vitamin K. Existing data show that the compounded oral solution possesses increased bioavailability compared with the tablet formulation.3,4 In addition, oral vitamin K solution has been shown to have efficacy similar to oral tablets relative to the reversal of vitamin K antagonists (VKAs) for patients with an elevated international normalized ratio (INR).1,4 Despite these existing data, studies have not directly compared INR values after vitamin K administration between groups. Drug and material costs were estimated based on quotes from our hospital wholesaler. Labor costs were considered negligible for vitamin K tablets. Labor prices were estimated for the oral solution by normalizing our hourly pharmacy technician salary to the 15-minute preparation time. Pharmacists were considered negligible due to their limited time investment for solution preparation. Final estimated drug costs were $11.06 and $2.86 per milligram as described above.

METHODS

This retrospective chart analysis was performed in a single academic medical center. We initiated use of a compounded vitamin K oral solution at our institution in May 2016. This became our formulary agent, and vitamin K tablets were no longer available for use at our institution. Pharmacy technician compounding time, representing preparation of a stock solution from the injectable and staging of individualized oral doses, was assumed to be 15 minutes per dose. The process for compounding the stock solution involves drawing up 3 mL of 10 mg/mL vitamin K injection and diluting it with 27 mL of sterile water. A standard needle, a 5-micron filter needle, and a 3-mL syringe are used in this process. A pharmacist reviews and verifies the compounded batch solution, which is then given a 90-day expiration date based on previously published stability data.5 Individual doses are drawn from the batch solution when required. Adults 18 years of age or older receiving oral vitamin K between March 2016 and September 2016 were identified by query of the electronic medical record. Patients were excluded if they received oral vitamin K for non–warfarin-induced coagulopathy, if oral vitamin K was administered concurrently with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP), or if the INR increased following vitamin K administration. This project met criteria for institutional review board exemption.

A single trained investigator collected all data using a standardized form. A co-author intermittently reviewed collected data for accuracy during the study period. Collected data included age, gender, vitamin K dose, vitamin K formulation, prereversal INR, postreversal INR, time of vitamin K administration, time between prereversal INR and vitamin K administration, and time between vitamin K administration and postreversal INR.

The primary outcome measure, the price–performance ratio (PPR), was estimated by dividing the associated drug cost by the percent hourly change in INR following vitamin K administration. Percent INR change was normalized over time in order to account for potential time differences in measuring INR values after vitamin K administration between groups. Drug and material costs were estimated based on quotes from our hospital wholesaler. Labor costs were considered negligible for vitamin K tablets. Labor prices were estimated for the oral solution by normalizing our hourly pharmacy technician salary to the 15-minute preparation time.

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Price–Performance Ratio Analysis of Enteral Vitamin K Formulations

All data were analyzed using SPSS version 23.0 (IBM North America, New York, New York) and presented descriptively using n (%), median (interquartile range), or mean (standard deviation). Categorical variables were compared using the chi-square test for independence or Fisher’s exact test. Continuous, nonparametric variables were compared using the Mann-Whitney U test. Continuous, parametric variables were compared using the Student’s t-test. All tests were two-tailed and a P value of less than 0.05 was considered statistically significant.

RESULTS

Ninety-six patients were reviewed, and 29 were included in the evaluation. Of these 29 patients, 13 received vitamin K tablets and 16 received vitamin K oral solution. Reasons for exclusion included non–warfarin-induced coagulopathy (n = 48), PCC or FFP administration (n = 16), and INR increase following vitamin K administration (n = 3). All three patients with an increased posttreatment INR received vitamin K tablets.

Baseline characteristics, including pre-reversal INR, are represented in Table 1. All characteristics were similar between groups. Table 2 describes the characteristics of warfarin reversal, which were also similar between groups. Outcomes of INR reversal and the calculated PPR for each formulation are represented in Table 3. The oral solution had a significantly lower median INR, which was driven largely by drug-spend differential between tablet and oral solution. Median percent change in INR per hour was similar following administration of vitamin K tablets and oral solution.

Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th>Vitamin K Formulation</th>
<th>Tablet (n = 13)</th>
<th>Oral Solution (n = 16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>7 (53.8)</td>
<td>13 (81.3)</td>
<td>0.226</td>
</tr>
<tr>
<td>Median age in years (IQR)</td>
<td>76 (67–85)</td>
<td>70 (62–73)</td>
<td>0.232</td>
</tr>
<tr>
<td>Mean prereversal INR (SD)</td>
<td>4.28 (1.84)</td>
<td>3.84 (1.46)</td>
<td>0.493</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; IQR = interquartile range; SD = standard deviation.

Table 2 Characteristics of Vitamin K Administration

<table>
<thead>
<tr>
<th>Vitamin K Formulation</th>
<th>Tablet (n = 13)</th>
<th>Oral Solution (n = 16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median vitamin K dose, mg (IQR)</td>
<td>5.0 (5.0–10.0)</td>
<td>5.0 (3.0–10.0)</td>
<td>0.503</td>
</tr>
<tr>
<td>Median time in hours between prereversal INR and vitamin K administration (IQR)</td>
<td>6.3 (3.3–11.3)</td>
<td>4.8 (2.1–11.9)</td>
<td>0.714</td>
</tr>
<tr>
<td>Median time in hours between vitamin K administration and postreversal INR (IQR)</td>
<td>18.3 (13.0–20.9)</td>
<td>13.0 (10.3–17.5)</td>
<td>0.132</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; IQR = interquartile range.

Table 3 Price Performance Results

<table>
<thead>
<tr>
<th>Vitamin K Formulation</th>
<th>Tablet (n = 13)</th>
<th>Oral Solution (n = 16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PPR, USD/percent change in INR per hour following vitamin K administration (IQR)</td>
<td>27.0 (18.2–38.7)</td>
<td>5.8 (3.0–14.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Median cost per vitamin K dose, USD (IQR)</td>
<td>$55.30 (55.30–110.60)</td>
<td>$15.00 (9.00–30.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median percent change in INR per hour following vitamin K administration (IQR)</td>
<td>2.60 (1.72–3.44)</td>
<td>2.48 (0.97–3.53)</td>
<td>0.948</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; IQR = interquartile range; PPR = price–performance ratio; USD = United States dollars.

DISCUSSION

Vitamin K oral solution provides a significantly reduced PPR compared with vitamin K tablets in this small subset of patients with warfarin-induced coagulopathy. Adoption of the oral vitamin K solution therefore provides equivalent efficacy at a reduced drug spend.

When the PPR is compared, there is a direct correlation with the tablet formulation of vitamin K being 4.66 times more costly than that of compounded oral solution. The decreases in INR in both groups occurred over a similar time period and were not significantly different for either formulation. In addition, the time to lower the INR was similar between both groups.

This study had several limitations. We did not examine adverse events with vitamin K administration. In addition, vitamin K efficacy was only examined in regard to VKA-induced coagulopathy and without emergent reversal via PCC or FFP.

We selected a PPR for purposes of analysis instead of a more complex cost-effectiveness analysis. Finally, our sample size was small, limiting the generalizability of our results.

Previous studies have shown that vitamin K oral solution may have increased bioavailability compared with the tablet formulation and may lead to overcorrection of INR, causing some potential for resistance.3,6 However, others have shown that vitamin K oral solution may be dosed effectively to bring the INR into the therapeutic range without VKA resistance being of particular concern.7 Further research will need to look at the percentage of patients achieving goal INR and the percentage of patients who were overcorrected.

This study is unique in that a PPR analysis of vitamin K oral solution versus tablet has not been performed before.
Though price–performance analyses are not regularly performed in pharmacy, they are performed regularly in business and determine the cost associated per unit of production. Businesses will commonly use this approach when comparing two similar products produced by competing manufacturers. As we expected similar efficacy, we felt that it was appropriate to compare the two medication formulations using this approach because it would be able to quantify the cost-savings more fully while confirming our expectation of equal efficacy. Alternative approaches, such as a cost-effectiveness analysis, are more complex and beyond the expertise of our group. If we had been uncertain whether the two formulations would have had similar efficacy, we would not have used this approach, nor would we advocate its use.

The matter of commercial availability of oral liquid formulations for certain medications has been discussed recently. While commercially prepared dosage forms are preferred for their ready availability, rigorous manufacturing processes, and product consistency, the disproportionate cost of vitamin K tablets compared with an extemporaneously prepared liquid formulation may lead some health systems to adopt the compounded liquid formulation. Our findings provide evidence to support such an approach.

CONCLUSION

This retrospective study shows that a compounded oral vitamin K solution confers a significant price advantage for similar effect compared with the commercially available tablet formulation. This study further justifies the use of oral vitamin K solution as an effective cost-saving measure for hospital drug spend.

REFERENCES