Testing the Long Term Stability of Vancomycin Ophthalmic Solution

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ABSTRACT
Some patients with a keratoprosthesis (artificial cornea) are required to use prophylactic vancomycin ophthalmic solution daily for life to prevent infection, a regimen which has proven to be highly successful. The objective of this study was to determine whether such vancomycin solutions would remain stable at room temperature for an extended period of time, beyond that suggested by available published stability data and used in current practice. By relaxing the storage requirement and extending the expiration date of this solution, it was hoped that patient adherence and satisfaction would increase. The studied vancomycin ophthalmic solutions were compounded at the Massachusetts Eye and Ear Infirmary, Department of Pharmacy Services, Boston, Massachusetts, and were sent to an outside laboratory for high-performance liquid chromatography potency testing at predefined time points. Vancomycin 14-mg/mL ophthalmic solution compounded with 0.005% benzalkonium retains potency for at least 60 days at room temperature and 6 months frozen. Extending the beyond-use-dating of vancomycin may lead to improved patient adherence by lowering costs and increasing convenience of storage and shipment of the medication.

INTRODUCTION
A keratoprosthesis (KPro) is an "artificial cornea" that can be used in patients with severe corneal opacity in whom standard corneal transplants either have failed or have a high likelihood of failure. Although the KPro has improved patient outcomes by preventing severe corneal blindness, it carries a risk of infection. For patients with autoimmune disease, such as Stevens-Johnson syndrome or pemphigoid, the risk of developing bacterial endophthalmitis leading to blindness is especially high, and these patients are particularly dependent on prophylactic antibiotic use. Immunosuppressed KPro patients are required to use prophylactic antibiotic drops for life to prevent infection.

Recommended antibiotics include a fluoroquinolone ophthalmic solution and a compounded vancomycin 14-mg/mL ophthalmic solution. The use of prophylactic vancomycin virtually eliminates the risk of infection that could lead to endophthalmitis and loss of the eye, and, therefore, has contributed to the success of KPro surgery. While giving vancomycin on a long-term basis contravenes generally accepted prescribing principles, the importance of preventing devastating infections in KPro patients by prophylaxis with vancomycin is overriding. Prophylaxis with vancomycin ophthalmic solution for patients who had undergone KPro was initiated 6 years ago at the Massachusetts Eye and Ear Infirmary (MEEI), Boston, Massachusetts, and to date, there have been no reports of acute bacterial endophthalmitis in compliant patients or of emergence of resistant strains. Vancomycin is prescribed for prophylaxis after the KPro surgery either once or twice daily for life in patients with auto-immune disease.

Since introduction of this prophylactic regimen, however, therapeutic compliance has become a concern of physicians treating these patients. The root of this concern is multiple factors surrounding the drug preparation. First, the solution must be prepared by a pharmacy that specializes in compounding. Second, because of current available stability data and United States Pharmacopeia (USP) Chapter <797> sterile compounding guidelines, the medication may be given only a limited expiration date. The expiration date at MEEI is 45 days frozen or 14 days refrigerated. The implication of this is that patients either have to make numerous and frequent trips to the pharmacy, or must have the drops packed in ice and mailed to their home; either scenario is quite costly and time consuming. Third, since the medication requires refrigeration while in use, an extra burden is created for the patient in providing appropriate storage conditions for this medication at all times. Finally, the need for frequent refills adds to the complexities and cost involved in reimbursement from insurance companies.

The overall goal for this study was to determine if vancomycin 14-mg/mL could be stored at room temperature for an extended period of time. The first objective was to determine if this solution, stored at room temperature for a period of 60 days, would retain potency and remain sterile. It was believed that changing the storage requirement and increasing the expiration period of this solution would lead to increased patient adherence and satisfaction.
One focus of this study was to examine whether extending the expiration date of this preparation would require addition of a preservative. Therefore, we tested a new formulation containing benzalkonium chloride (BAK) 0.005%, a common preservative in many ophthalmic formulations at an average concentration of 0.01% (range, 0.004% to 0.02%). BAK is efficacious against numerous microbes, working by denaturation of proteins and lysis of cytoplasmic membranes. Higher concentrations of BAK can accumulate and remain in ocular tissue for lengthy periods, however, leading to cell death of various types. Thus, the long-term use of ophthalmic preparations containing preservatives has been implicated in negative ocular health effects. For this reason, we also tested a vancomycin ophthalmic solution without BAK to ascertain its room temperature stability at 60 days.

MATERIALS AND METHODS
All preparations of sterile vancomycin ophthalmic solution were compounded at MEEI, Department of Pharmacy Services, under sterile conditions, using defined recipes that were developed and reviewed by the Pharmacy Department (MEEI Department of Pharmacy Compounding Records). All compounded medications at the MEEI are prepared in accordance with USP Chapter <797> guidelines and MEEI Pharmacy Services policies and procedures. All supplies used for the final compounded preparation (bottles, caps, tips) were sterilized via ethylene oxide at the Infirmary's central storeroom prior to use.

The vancomycin ophthalmic solution was prepared by reconstituting one vancomycin 500-mg vial for injection with 10 mL of 0.9% sodium chloride for injection. The diluted solution was then drawn into a 60-mL syringe and a sufficient quantity of 0.9% sodium chloride for injection was added for a final volume of 35.7 mL, and a final concentration of 14 mg/mL. This solution was then passed through an appropriate 0.22-micron filter before being repackaged into sterile ophthalmic bottles.

The vancomycin 14-mg/mL solution with 0.005% BAK was prepared by diluting a 500-mg vial of vancomycin powder for injection with 10 mL of 0.9% sodium chloride. This solution was then mixed with 1.35 mL of BAK (1.33 mg/mL). A sufficient quantity of 0.9% sodium chloride

### TABLE 1. Results for Vancomycin 14-mg/mL Solution (Unpreserved).

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Time of Testing</th>
<th>Assayed Concentration of Vancomycin</th>
<th>Endotoxin</th>
<th>Sterile</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Time 0</td>
<td>15.04</td>
<td>None</td>
<td>Yes</td>
<td>RT</td>
</tr>
<tr>
<td>2</td>
<td>Time 0</td>
<td>15.03</td>
<td>None</td>
<td>Yes</td>
<td>RT</td>
</tr>
<tr>
<td>3</td>
<td>14 days</td>
<td>15.6</td>
<td>111.4</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>4</td>
<td>14 days</td>
<td>15.3</td>
<td>109.3</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>5</td>
<td>14 days</td>
<td>15.1</td>
<td>100.7</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>6</td>
<td>30 days</td>
<td>15.1</td>
<td>100.7</td>
<td>Yes</td>
<td>RT</td>
</tr>
<tr>
<td>7</td>
<td>30 days</td>
<td>15.3</td>
<td>109.9</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>8</td>
<td>30 days</td>
<td>15.4</td>
<td>110.0</td>
<td>Yes</td>
<td>RT</td>
</tr>
<tr>
<td>9</td>
<td>60 days</td>
<td>15.3</td>
<td>109.6</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>10</td>
<td>60 days</td>
<td>15.4</td>
<td>110.0</td>
<td>Yes</td>
<td>RT</td>
</tr>
</tbody>
</table>

*Initial concentration target was 14 mg/mL.

### TABLE 2. Results for Vancomycin 14-mg/mL with Benzalkonium 0.005%.

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Time of Testing</th>
<th>Assayed Concentration of Vancomycin</th>
<th>Endotoxin</th>
<th>Sterile</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Time 0</td>
<td>18.3</td>
<td>None</td>
<td>Yes</td>
<td>RT</td>
</tr>
<tr>
<td>2</td>
<td>14 days</td>
<td>14</td>
<td>100.00</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>3</td>
<td>30 days</td>
<td>14.6</td>
<td>104.3</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>4</td>
<td>30 days</td>
<td>15.7</td>
<td>112.1</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>5</td>
<td>60 days</td>
<td>14.6</td>
<td>104.3</td>
<td>No</td>
<td>RT</td>
</tr>
<tr>
<td>6</td>
<td>60 days</td>
<td>18.7</td>
<td>133.6</td>
<td>Yes</td>
<td>Frozen</td>
</tr>
<tr>
<td>7</td>
<td>6 months</td>
<td>15.6</td>
<td>133.6</td>
<td>Yes</td>
<td>Frozen</td>
</tr>
<tr>
<td>8</td>
<td>6 months</td>
<td>15.3</td>
<td>109.8</td>
<td>Yes</td>
<td>Frozen</td>
</tr>
</tbody>
</table>

*Initial concentration target was 14 mg/mL.

*Lot 2074327, Vancomycin 500 mg (Hospira, Lake Forest, Illinois), Lot 24-382-DK, 0.9% Sodium Chloride Injection (Hospira)*

*Lot 2074327, Vancomycin 500 mg (Hospira), Lot 24-382-DK, 0.9% Sodium Chloride Injection (Hospira)*

*RT = room temperature

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FIGURE 1. Boston Keratoprosthesis, Type I (left) and Type II (right). The devices are made of PMMA and have the shape of a collar button, with a front plate and a separate back plate. They are placed in a corneal graft so that the plates clamp the tissue. The graft-keratoprosthesis combination is then sutured into the patient’s cornea like a standard corneal graft. The Type II device is used in end-stage dry eyes where the anterior nub is allowed to protrude through the lid skin.

BAK stored at room temperature also retained potency on days 14, 30, and 60. Samples of vancomycin with BAK that were kept frozen for 6 months retained potency. Four of the samples of vancomycin with BAK in one of the lots tested had higher than expected concentrations (range, 111.5% to 130.7%).

Sterility
All of the samples tested for antimicrobial growth remained sterile and had no endotoxin growth during the study period. At day 63 (i.e., beyond the last testing date), however, one of the samples without BAK had suspected fungal growth (not verified by culture). This same sample at day 60 was reported as having no growth.

pH Testing
The pH testing of vancomycin ophthalmic solution samples stored at room temperature was 3.49 on day zero and 3.71 at day 60. The pH of vancomycin ophthalmic solution with BAK samples stored at room temperature was 3.59 at time zero and 3.79 at day 60.

DISCUSSION
Pharmacists who compound must either use published literature sources or rely on direct testing methods to establish expiration dates. When determining an expiration date, the pharmacist must be able to say that the quality and the integrity of the compound are maintained for the entire labeled life of the preparation. A survey in 1989 of hospital pharmacists reported the need for stability and other information on extemporaneous drug formulations.8 In 1991, guidelines for the preparation of sterile ophthalmic preparations were published, followed by a Handbook of Extemporaneous Ophthalmic Preparations and an American Society of Health-System Pharmacists Technical Assistance Bulletin, both in 1993.9-11 In recent years, however, published information with extended stability data for compounded antibiotic ophthalmic solutions has been lacking.

Literature searches have produced limited data on extended stability of vancomycin ophthalmic solution. One study of vancomycin in artificial tears recommended storage times of 45 days at -10°C, 10 days at 4°C, and 7 days at 25°C.12 A second study of vancomycin stability did not recommend a storage time due to the drop in pH after 7 days to a level less than 3.5.13

A telephone survey performed by one of the authors (CLM) in 2005 found the price of vancomycin ophthalmic solution to vary among compounding pharmacies, from $25 to $120. Some pharmacies added the preservative BAK to the preparation, others did not. The objective of the present study was to provide new data regarding the storage duration and potency of vancomycin ophthalmic solution stored at room temperature that could be applied to practice. USP Chapter <797> requires that the concentration of the final preparation be within 10% of the labeled amount for the shelf-life of the preparation. With the results of this study, the authors have concluded that it is feasible to maintain vancomycin 14-mg/mL with BAK 0.005% at ambient room temperature (20°C to 25°C) for a period of 60 days. During this period, this solution maintained a pH that is just within the acceptable range for the eye and developed no bacterial growth in any of the samples. Because of the potential fungal contamination found in one of the samples
without BAK beyond the 2-month storage period, the authors are recommending against storage at room temperature of preparations of vancomycin that do not contain BAK.

A 4-mL quantity of vancomycin with BAK, when prescribed at a dosage of one drop either once daily or twice daily, could potentially last for 30 to 60 days. The new data indicate that this preparation can be used for a time period two to four times as long as that recommended for the preparation formerly dispensed by the Infirmary's pharmacy. Switching patients to the new formulation for maintenance prophylaxis therapy has the potential for significant cost savings to patients, at least 50% (potentially as much as 75%), and requires fewer trips to the pharmacy for refills. Storage of the medication at room temperature also eases the burden of having to keep the medication refrigerated, and the preparation does not require shipment on ice.

CONCLUSION

The results of this study have implications not only for the practitioners who prescribe vancomycin ophthalmic solutions and for the pharmacists who compound them, but also for the patients who use them every day. Knowing the stability of these preparations gives the practitioner greater clinical flexibility. For pharmacists, these results show the promise of an alternative formulation of vancomycin that can be given an extended expiration date, allowing fewer refills (and thus fewer patient trips to the pharmacy), lower cost, and simpler shipping and storage requirements. By reducing barriers to compliance, we hope to improve patient adherence and thus outcomes.

REFERENCES


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