ELUTION AND BIOACTIVITY OF VANCOMYCIN AND TOBRAMYCIN INCORPORATED WITHIN CALCIUM SULFATE

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SUMMARY:
In the treatment of osteomyelitis, high local concentrations and minimal systemic concentrations of antibiotics are most desirable for effective infection abatement and low frequency of treatment side effects. Calcium sulfate pellets can be manufactured as a bone void filler with various antibiotic agents for use against specific bacteria in infected bone voids. In bone infections caused by Methicillin Resistant Staph Aureus (MRSA), in-vitro testing has indicated that vancomycin eluting from calcium sulfate pellets can be highly effective in eradicating the MRSA.

INTRODUCTION:
Calcium sulfate is a proven bone graft substitute into which antibiotics can be incorporated, providing an effective treatment against osteomyelitis. When antibiotics are incorporated into calcium sulfate, animal studies have shown that local levels of antibiotics are high, while systemic levels are low. This local treatment of infection encourages new bone formation and minimal systemic side effects. Tobramycin has been incorporated into calcium sulfate and is highly effective against many types of bacteria, but is not effective against MRSA. In this study, vancomycin was incorporated into calcium sulfate pellets, and the elution characteristics and biological activity of vancomycin were evaluated against MRSA.

METHODS:
Alpha-hemihydrate calcium sulfate (OSTEOSET®, Wright Medical Technology) was fabricated into 4.8 mm diameter pellets with the incorporation of: 1) 4% Vancomycin (Vancocin®, Eli Lily), and 2) 4% Tobramycin Sulfate (Nebcin®, Eli Lily). To determine the elution characteristics of both types of pellets, eight pellets (approximately 850 mg) were immersed in 20 ml of phosphate buffered saline (PBS) and the eluant was measured daily using a fluorescence polarization immunoassay (TDx, Abbott Laboratories). The biological activity of this eluant was also measured daily using a fluorescence polarization immunoassay (TDx, Abbott Laboratories). The detection limit of the biological assay is 15 ug/ml. The biological activity of this eluant was also measured daily using a fluorescence polarization immunoassay (TDx, Abbott Laboratories). The biological activity of this eluant was also measured daily using a fluorescence polarization immunoassay (TDx, Abbott Laboratories).

RESULTS:
Figure 1 shows the elution performance of pellets loaded with 4% vancomycin and pellets loaded with 4% tobramycin. The elution profile for the tobramycin is similar to the local in-vivo elution profile found in animal studies. The elution profile of the vancomycin is extended when compared to the tobramycin eluant. Zones of inhibition were measured for both the tobramycin and the vancomycin eluants at days 1, 3, and 7 against S. Aureus (ATCC #29213) and MRSA (ATCC # 33591). For each bacterial strain evaluated, a standard curve must be constructed which relates the zones of inhibition to a concentration of antibiotic in ug/ml for the specific antibiotic. In these in-vitro assays, vancomycin has an extended release profile compared to tobramycin sulfate in the calcium sulfate pellets. In calcium sulfate pellets, vancomycin eluting from the pellets is highly effective against MRSA.

CONCLUSIONS:
Antibiotic eluates from calcium sulfate for varying amounts of time and at varying concentrations, depending upon the loading and the specific antibiotic. In these in-vitro assays, vancomycin has an extended release profile when compared to tobramycin sulfate in the calcium sulfate pellets. In calcium sulfate pellets, vancomycin eluting from the pellets is highly effective against MRSA.

**REFERENCES:**

**Table 1:** Zones of Inhibition

<table>
<thead>
<tr>
<th>Eluant</th>
<th>Vancomycin vs SA 29213</th>
<th>Tobramycin vs SA 29213</th>
<th>Vancomycin vs MRSA</th>
<th>Tobramycin vs MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>18 mm (667 ug/ml)</td>
<td>17 mm (&gt;1000 ug/ml)</td>
<td>0 mm</td>
<td>17 mm (750 ug/ml)</td>
</tr>
<tr>
<td>Day 3</td>
<td>5 mm (15.6 ug/ml)</td>
<td>14 mm (250 ug/ml)</td>
<td>0 mm</td>
<td>14 mm (187.5 ug/ml)</td>
</tr>
<tr>
<td>Day 7</td>
<td>0 mm</td>
<td>14 mm (250 ug/ml)</td>
<td>0 mm</td>
<td>11 mm (62.5 ug/ml)</td>
</tr>
</tbody>
</table>

**Figure 1:**

- **X-axis:** 0 to 1000 μg/ml
- **Y-axis:** 0 to 18 mm
- **Legend:**
  - Vancomycin Sulfate
  - Tobramycin Sulfate

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