INTRODUCTION

• Pneumococcal meningococcal infections represent a significant treatment challenge.1
• Liposomal amikacin for inhalation (LAI) is novel, once-daily formulation of amikacin in development for the treatment of meningococcal infections.2
• LAI is composed of charge-neutral, highly biocompatible liposomes (0.3 μm) that encapsulate multicationic amikacin (Figure 1), which are delivered via a nebulizer. These liposomes are mostly taken up by pulmonary macrophages in vitro.3

METHODS

LAI was prepared by Inhaled Incorporated using a proprietary manufacturing process.32 Stills, Sprague-Dawley rats were randomized into 3 groups: group 1 (n = 24) was exposed to an aerosolized solution of amikacin sulfate at a targeted amikacin dose of 90 mg/kg; group 2 (n = 24) was exposed to LAI at a targeted amikacin dose of 90 mg/kg, and group 3 consisted of 8 rats that were used as controls, receiving no inhalation treatment. Rats were exposed to nebulized drugs over a period of 70-90 min using a PARI LC Plus nebulizer (80% of nebulized solution delivered to the lungs). Groups 1 and 2 were euthanized at 24 h, 7 days, and 14 days after dosing. Group 3 was euthanized immediately after dosing and at 7 days, 3 days, 7 days, 14 days, or 21 days after dosing. Control rats were euthanized immediately after dosing and at 1 hour, 4 hours, 24 hours, 3 days, 7 days, 14 days, and 21 days after dosing. Control rats were euthanized immediately after dosing and at 1 hour, 4 hours, 24 hours, 3 days, 7 days, 14 days, or 21 days after dosing. Control rats were euthanized immediately after dosing and at 1 hour, 4 hours, 24 hours, 3 days, 7 days, 14 days, or 21 days after dosing. Dosing was conducted by asphyxiation immediately after dosing (t = 0) and at 1 hour, 4 hours, or 24 hours after dosing, as shown. The animals treated with LAI were examined with a Nikon Eclipse Ti fluorescence microscope (Nikon Instrument Inc, Melville, NY) at 510-560 nm (excitation) and ≥590 nm (emission) for fluorescently stained amikacin.4

RESULTS

The distribution and elimination of amikacin remaining in the lungs following a single 90 mg/kg dose of LAI or inhaled amikacin sulfate solution were consistent throughout different lung lobes/sections.

CONCLUSIONS

• LAI-treated rats exhibited a 2-fold increase in the concentration of amikacin remaining in the lungs (AUC; Figure 2) and AUC₀₋₂₄ h and approximately a 2-fold increase in elimination half-life (t₁/₂) compared with rats receiving amikacin sulfate solution. Almost double of the initial amikacin measured in the lungs (31%) of LAI-treated rats remained in the lungs 24 hours after dosing compared with 18% for amikacin sulfate solution–treated rats.

Macrophages loaded with amikacin were localized primarily in the lumen of small airways (yellow arrows) during the first 24 hours after LAI administration. After 3 days, most of the fluorescent macrophages in the airways disappeared, with a concomitant increase in the number of fluorescent macrophages in interstitial lung tissue.5

REFERENCES


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DISCLOSURES

All authors are employees of Inhaled Incorporated.

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Biodistribution and Clearance of Liposomal Amikacin for Inhalation and Free Amikacin After a Single-Dose Inhalation in Rats

Lungs of LAI-treated rats released diffuse staining immediately after dosing and increased intracellular (macrophage) staining over time; lungs of amikacin sulfate solution–treated rats showed a very diffuse staining pattern immediately after dosing, which disappeared after 1 hour.

Graphical representation of LAI liposomes encapsulating amikacin

Figure 1. Red and green immunofluorescent staining of caudal lobe tissue sections in rats following a single 90 mg/kg dose of inhaled LAI (purple and green, respectively) or amikacin sulfate solution (red and green, respectively). Images correspond to lung samples taken immediately post-dosing (IPD) at 1 hour, 4 hours, or 24 hours after dosing, as shown. The stained sections were examined with a Nikon Eclipse Ti fluorescence microscope (Nikon Instrument Inc, Melville, NY) at 510-560 nm (excitation) and ≥590 nm (emission) for fluorescently stained amikacin.

Table 1. Lung and Serum Amikacin Concentrations in Rats Following a Single Exposure (90 mg/kg) to LAI or Amikacin Sulfate Inhalation

<table>
<thead>
<tr>
<th>Property</th>
<th>Treatment</th>
<th>Lung</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋₂₄ h (μg/ml)</td>
<td>LAI</td>
<td>12067</td>
<td>466</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>5916</td>
<td>96</td>
</tr>
<tr>
<td>AUC₀₋₂₄ h (μg/ml)</td>
<td>LAI</td>
<td>12065</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>4240</td>
<td>1628</td>
</tr>
<tr>
<td>C₀ (μg/mL) at sacrifice</td>
<td>LAI</td>
<td>1159</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>460</td>
<td>312</td>
</tr>
<tr>
<td>C₀ (μg/mL or ml of sample)</td>
<td>LAI</td>
<td>132</td>
<td>3</td>
</tr>
</tbody>
</table>

| 1/2 τₘ (min) | LAI        | 0.36   | 3       |

AUC₀₋₂₄ h, area under the curve from 0 to 24 hours; C₀, concentration; τₘ, half-life; ISD, insufficient data to calculate the parameter; LAI, liposomal amikacin for inhalation; t₀₋₅₀₄, trough concentration; IPD, immediately post-dosing; LAI, liposomal amikacin for inhalation.

Figure 2. Comparison of pulmonary amikacin concentrations in the lungs of rats after a single administration of LAI and inhaled amikacin sulfate solution at a targeted dose of 90 mg/kg. Rats were exposed to nebulized drugs via a mouse-only inhalation system.