Background

Tobramycin is a well-known, effective antibiotic for the management of Pseudomonas aeruginosa (P. aeruginosa) and other Gram-negative respiratory tract infections in patients with cystic fibrosis (CF) and is recommended as a component of current treatment guidelines (1). Dry powder inhalers are user friendly and quick in application, but they require sufficient (peak) inspiratory flow and the appropriate breathing technique. Thus, they may not be suitable for every patient, for example young children. Furthermore, not all patients tolerate the inhalation of dry powder, which can cause cough, dysphonia and other airway irritation (2).

Pharmaco has developed a soft mist inhaler TobAir® - a fixed drug-device combination product, providing a liquid formulation for inhalation. Tobramycin as TobAir® is formulated as a 15% solution, administered as 75 mg b.i.d with 10 inhalations per dosing and resulting in a total daily dose of 150 mg.

Pharmaco's new drug-device combination includes a syringe containing 1 mL of a 15% tobramycin solution and utilizes a Podhaler®/PARI LC® PLUS (as an example for a nebulizer) and TobAir® Podhaler™ (as an example for a dry powder inhaler).

Design & Methods

This randomized, cross-over study assessed the aerosol delivery and lung deposition of tobramycin by pharmacokinetic using TobAir® compared to TOBI®/PARI LC® PLUS. Tobramycin plasma levels after using these two devices and after using the TobAir® Podhaler™ were also determined.

During this study, 12 healthy volunteers received three different treatment regimens in a randomized order: A single dose of 75 mg tobamycin radiolabelled with 99mTc delivered by PARI LC® PLUS and utilizing a nebulizer inhalation system designed to emit 20 inhalations which is equivalent to 2 administrations per day (10 actuations per administration) of 75 mg tobramycin (b.i.d.), resulting in a daily dose of 150 mg tobramycin.

TobAir® (tobramycin inhalation spray), is a sterile solution of tobramycin sulfate in Water for Injection (WFI).

The drug-device combination includes a syringe containing 1 mL of a 15% tobramycin solution and utilizes a novel inhalation device designed to emit 20 inhalations which is equivalent to 2 administrations per day (10 actuations per administration) of 75 mg tobramycin (b.i.d.), resulting in a daily dose of 150 mg tobramycin.

Lung Deposition

Representative Images: Images were taken after a single administration of 75 mg tobramycin radiolabelled with 99mTc delivered via TOBI®/PARI LC® PLUS and utilizing a Nebulizer inhalation system designed to emit 20 inhalations, which is equivalent to 2 administrations per day (10 actuations per administration) of 75 mg tobramycin (b.i.d.), resulting in a daily dose of 150 mg tobramycin.

Deposition Pattern (Percent Delivered Dose): Pharmacokinetic data demonstrated that tobramycin lung deposition of 75 mg tobramycin with 10 inhalations via the TobAir® device is higher than that attained with 200 mg tobramycin delivered via TOBI®/PARI LC® PLUS with continuous nebulisation over approximately 20 minutes. These favorable delivery properties of the TobAir® device are also reflected in the deposition pattern, as shown in the table below.

<table>
<thead>
<tr>
<th>Region</th>
<th>TobAir® (b.i.d.)</th>
<th>TOBI®/PARI LC® PLUS (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>36.9 (± 6.5)</td>
<td>26.7 (± 6.5)</td>
</tr>
<tr>
<td>Posterior</td>
<td>61.7 (± 3.8)</td>
<td>30.3 (± 3.5)</td>
</tr>
</tbody>
</table>

PK Data: Plasma tobramycin concentrations were determined after a single dose of 75 mg tobramycin radiolabelled with 99mTc delivered via TOBI®/PARI LC® PLUS and 112 mg tobramycin as dry powder delivered via TOBI® Podhaler™.

PK Parameters: Cmax and AUC (0–24h) were higher in subjects dosed with TobAir® compared to TOBI®/PARI LC® PLUS and lower in subjects dosed with TobAir® and TOBI®/PARI LC® PLUS compared to TobAir® Podhaler™. Tmax and T1/2 were similar for all three devices with a Tmax of 3h for each device and a T1/2 ranging from 3.82h to 3.94h.

Relative Bioavailability (F) denotes that TobAir® is the most effective device with a mean F±SD of 216.0% (± 88.4%) compared to TOBI®/PARI LC® PLUS and 111.1% (± 42.5%) compared to TOBI® Podhaler™ (based on actual dose for TobAir® and TOBI®/PARI LC® PLUS and nominal dose for TobAir® Podhaler™).

Conclusion

In this Phase 1 study, delivery of tobramycin via Pharmaco’s new drug-device combination product was safe and was well-tolerated. TobAir® demonstrated a higher lung deposition and plasma levels with significantly reduced treatment time and burden compared to the delivery via TOBI®/PARI LC® PLUS, as well as a superior relative bioavailability compared to both TOBI®/PARI LC® PLUS and TOBI® Podhaler™. Additional studies are planned to measure if TobAir® may become an efficacious and convenient treatment for CF patients chronically colonized with P. aeruginosa.

References

(3) Pilsbry et al., 2012: Lung penetration profiles: A new method for analysing regional lung deposition data in cinqpharma and respiratory Drug Delivery, 8. 146-149.

Acknowledgement

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