PULMONARY ADMINISTRATION OF GLP-1 (GLP-1 TECHNOSPERHE® POWDER) I: KINETICS

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ABSTRACT

Background and Objectives: GLP-1 achieves in vivo effects in glucose regulation and both gastrointestinal and physiological effects in animal studies that rival those of native GLP-1 in terms of efficacy. Inhalation of GLP-1, however, has seen limited success due to biophysical and pharmacokinetic (PK)-related issues. We present herein a novel formulation of GLP-1 (GLP-1 Technosphere® Powder) to produce an inhalable dry powder for pulmonary administration via a MedTone® C inhaler. Five dosage concentrations were achieved at the first post-dose sampling time (3 minutes). Mean peak concentrations of Active GLP-1 following MKC253 inhalation were equivalent to those achieved with intravenous bolus administration. The safety, tolerability, and method could not be validated for adequate dilutions of the samples. The upper limit of quantification for this assay was 130 pmol/L.

The safety, tolerability, and method could not be validated for adequate dilutions of the samples. The upper limit of quantification for this assay was 130 pmol/L. Due to the short half-life, the levels of Active GLP-1 clearly remained above 40 pmol/L for 20 minutes in the 0.75 mg and 1.05 mg dose groups and for more than 30 minutes in the 1.5 mg dose group. This may be important because a recent study observed increased peripheral vascular resistance (PVR) over time that was reported following inhalation of GLP-1. Exposure to MKC253 was similar in both of the 2 highest dose groups with no signs of 'bursting' in the thoracic drug chambers.

The ability to deliver pharmacologically active amounts of GLP-1 via pulmonary administration might reduce the frequency of administration and might also reduce the side effects associated with subcutaneous injection. We also observed that the PK profile of Active GLP-1 was similar to those observed in previous studies in the oral and parenteral routes.

RESULTS

Figure 3. Mean (± SD) Active GLP-1 Cmax Following Inhalation of MKC253 at Different Doses of GLP-1

Table 1. Mean (± SD) Pharmacokinetic Parameters for Active GLP-1 following Inhalation of MKC253 at Different Doses of GLP-1

<table>
<thead>
<tr>
<th>GLP-1 Dose</th>
<th>Cmax (pmol/L)</th>
<th>t1/2 (min)</th>
<th>AUC (pmol/L.min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 mg</td>
<td>2.828</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>0.45 mg</td>
<td>148</td>
<td>24.6</td>
<td>298</td>
</tr>
<tr>
<td>0.75 mg</td>
<td>3.00</td>
<td>3.00</td>
<td>314</td>
</tr>
<tr>
<td>1.05 mg</td>
<td>3.00</td>
<td>3.00</td>
<td>314</td>
</tr>
<tr>
<td>1.5 mg</td>
<td>3.00</td>
<td>3.00</td>
<td>314</td>
</tr>
</tbody>
</table>

REFERENCES