Technosphere® Inhaled Human Insulin has a More Rapid Onset of Action Than Subcutaneous Insulins

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ABSTRACT

Inhaled Technosphere® Insulin (TI) Afrezza® is characterized by fast absorption and short half-life. It was previously reported that TI insulin has a similar onset of action as subcutaneous (SC) insulin in Linopin despite its faster absorption, based on 12 patients from study MKC-TI-177. We aim to verify whether pharmacokinetic (PK) properties of TI translate into a faster onset of action compared to SC regimens. Data from 3 eglycemic clamp studies were analyzed using WinNonlin Phoenix software. 1) MKC-TI-176 in 32 healthy volunteers at TI doses of 10, 30, 60, and 80 U versus SC RHI at 15 U; 2) MKC-TI-177 in 12 type 1 diabetes mellitus (T1DM) patients at TI 20 U versus SC insulin Linopin at 8 U; 3) MKC-TI-116 in 25 type 1 diabetes mellitus at TI 30 U versus SC insulin Linopin at 10 U. Area under glucose infusion rate (GIR) from time 0 to 240 min (GIRAUC0-240) and time (T) to reach partial areas (10 and 50% GIRAUC0-240) were estimated using the linear trapezoidal rule. GIR profiles were fitted to first order input and first order output mathematical models to estimate time to maximum GIR (T-GIRmax) and time to 20 and 50% GIRAUC0-240. Parameters of insulin were determined using non-compartmental methods. The conclusion on onset of action of TI insulin from data of MKC-TI-177 study seems to be inconsistent with results of the pooled analysis using larger sample sizes. This pooled analysis demonstrated a faster onset of action for TI than SC insulins based on all derived GIRmax and GIRAUC0-240 parameters. Time to 20% GIRAUC0-240 ranged from 2.5 to 18 min for TI and from 53 to 60 min for SC insulin. The faster onset of action of TI compared to SC insulin can be relevant for optimal dosing of TI with respect to meals.

RESULTS

Table 1. Onset of action parameters of TI versus SC insulins

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose TI</th>
<th>Dose SC</th>
<th>T-aTmax</th>
<th>T-10%</th>
<th>T-50%</th>
<th>aCmax</th>
<th>aTmax</th>
<th>GIRmax</th>
<th>GIRmax (min)</th>
<th>aTmax (min)</th>
<th>GIRmax (min)</th>
<th>GIRmax (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKC-TI-176</td>
<td>10 U</td>
<td>8 U</td>
<td>36</td>
<td>111</td>
<td>135</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>53</td>
</tr>
<tr>
<td>MKC-TI-177</td>
<td>20 U</td>
<td>10 U</td>
<td>57</td>
<td>34</td>
<td>47</td>
<td>3.4</td>
<td>7.7</td>
<td>41</td>
<td>30</td>
<td>112</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>MKC-TI-116</td>
<td>30 U</td>
<td>30 U</td>
<td>60</td>
<td>57</td>
<td>60</td>
<td>10</td>
<td>111</td>
<td>55</td>
<td>132</td>
<td>109</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

INTRODUCTION

Afrezza (Technosphere Insulin, TI)

-Recently approved by FDA to control high blood sugar in adults with type 1 and type 2 diabetes mellitus.
-Characterized by fast absorption with a peak serum concentration at Tmax = 15 min and return to near-baseline in about 3 hours [1].

Pharmacodynamics for TI (Table 1)

- Mean glucose infusion rate (GIR) profiles were smoothed and corrected for baseline.
- GIRmax, calculated by linear trapezoidal integration.
- T-GIRmax was estimated from the cumulative GIRmax over time.
- T-GIRmax and aCmax were estimated from exponential fit to smoothed GIR.
- In study MKC-TI-116, GIRmax from TI was extrapolated from GIRmax.

CONCLUSIONS

The meta analysis demonstrated a faster onset of action for TI than SC insulins based on all derived GIRmax and GIRAUC0-240 parameters.

- Time to 20% GIRAUC0-240 ranged from 2.5 to 18 min for TI and from 13 to 34 min for SC insulin across studies.
- Time to 50% GIRAUC0-240 ranged from 7.7 to 16 min for TI and from 41 to 47 min for SC insulin across studies.
- Time to 10% GIRmax ranged from 25 to 34 min for TI and from 53 to 60 min for SC insulin across studies.
- Study MKC-TI-177 showed an outlier GIR profile after TI administration.

The faster onset of action of TI compared to SC insulin is relevant for optimal dosing of TI.

REFERENCES


American Diabetes Association • 76th Scientific Sessions • June 10 - 14, 2016, New Orleans, Louisiana