The Novel SGLT-2 Inhibitor BI 10773 (Empagliflozin) Prevents Pioglitazone-Induced Weight Gain and Further Improves Glycemic Control in Dietary-Induced Obese Rats

Rolf Grempler1, Leo Thomas1, Achim Sauer1, Michael Mark1, Peter Eickelmann1, Steven Vickers2, Sharon Cheetham2, Thomas Klein1, Robert Jones2

1Boehringer Ingelheim, Biberach, Germany; and 2Reinsci Consulting Ltd, Nottingham, United Kingdom

ABSTRACT

The novel and selective SGLT-2 inhibitor BI 10773 (empagliflozin) in late clinical development for the treatment of type 2 diabetes due to the potential of empagliflozin to reduce or delay the onset of diabetes and to reduce body weight when added to existing therapies is currently being investigated in late clinical development. Here, we investigated whether empagliflozin could attenuate the induced weight gain and improve glycemic control in dietary-induced obese rats. Pioglitazone (Pio) is a well-established anti-diabetic drug with insulin sensitizing properties, but is associated with a weight gain and an increased risk of cardiovascular disease.

INTRODUCTION

Studies in dietary-induced obese rats showed that in addition to its anti-diabetic action, empagliflozin significantly reduced body weight by a selective action on renal glucose excretion.

METHODS

Female Wistar rats (Charles River, 250–300g, n=10 at start) were maintained on a regular powdered diet (420 kJ/day) and reverse-phase lighting (lights out 09:30–17:30) with free access to powdered diet. Rats and food jars were weighed every day at the time of dosing throughout the study. Male rats were dosed with empagliflozin (10 mg/kg po) or vehicle (3 ml/kg po) on Day 0, 15 and 29. On Day 30, animals were placed in metabolic cages for 46 hours to measure glucose and insulin levels. Urinary glucose was measured by standard methods.

RESULTS

Comparisons to vehicle were by the multiple t-test and differences from vehicle are denoted by **p<0.01, *p<0.05. Day 15 and 29 plasma data were analyzed by a general linear model with treatment as a fixed effect. Results are means (adjusted for differences between treatment groups at baseline) ± SEM (calculated from the residuals of the statistical model). Day 0, 15 and 29 blood glucose and urinary glucose excretion were measured by standard methods. Comparisons to vehicle were by the multiple t-test **p<0.01, +p=0.057. Dead bodies were analyzed minus blood, caudate liver lobe, pancreas and both kidneys and the dead body weight excludes these components. Comparisons against vehicle were by the multiple t-test **p<0.01, +p=0.057.

CONCLUSIONS

Empagliflozin significantly reduced body weight and improved glycemic control in dietary-induced obese rats. Further studies are warranted to evaluate the potential of empagliflozin to reduce or delay the onset of diabetes and to reduce body weight when added to existing therapies.

SUPPORTING INFORMATION

Table 1: Body composition after 31 days of treatment with empagliflozin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body weight (g)</th>
<th>Body fat (%)</th>
<th>Lean body mass (g)</th>
<th>Fat mass (g)</th>
<th>Urinary glucose excretion (mg/200 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin 10 mg/kg po</td>
<td>201.5 ± 5.4</td>
<td>21.4 ± 3.2</td>
<td>170.1 ± 5.7</td>
<td>31.4 ± 5.7</td>
<td>30.3 ± 1.4</td>
</tr>
<tr>
<td>Pioglitazone 10 mg/kg po</td>
<td>213.5 ± 4.6</td>
<td>25.3 ± 3.2</td>
<td>160.2 ± 4.6</td>
<td>53.3 ± 3.6</td>
<td>24.3 ± 1.2</td>
</tr>
<tr>
<td>Empagliflozin + Pioglitazone 10 mg/kg po</td>
<td>204.3 ± 5.1</td>
<td>21.1 ± 3.1</td>
<td>173.2 ± 5.5</td>
<td>31.1 ± 5.5</td>
<td>26.3 ± 1.3</td>
</tr>
</tbody>
</table>

REFERENCES