Reviewer's report

Title: Glucagon-like Peptide 1 Improved Glycemic Control in Type 1 Diabetes

Authors:

Dr Margaret T Behme (mbehme@uwo.ca)
John Dupre (john.dupre@lhsc.on.ca)
Thomas J McDonald (tom.mcdonald@sjhc.london.on.ca)

Version: 2 Date: 28 Jan 2003

Reviewer: Dariush Elahi

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after discretionary revisions

Abstract

1. Should the methods be placed before the result section? As it stands now, it is difficult to understand why the dose of 0.63mg/kg was chosen when the ED50 was 0.40mg/kg. At any rate, it may be useful to state that the ED50 dose is a calculated dose.

2. I believe the addition of the symbol D or the word delta in parenthesis before the presentation of the values, would more easily clarify that the values represent the reduction from basal and not the actual levels. Furthermore, I thought GLP-1 reduced glucose and Hpp excretion by 5.4mmol/l and 37pmol/l, as it is stated that "GLP-1 compared to vehicle" and 5.4 is present first. However table 2 shows that it is the other way. Again I am not sure of the values for glucagon are correct. Table 2 indicates that glucagon was reduced by ~4ng/l and increased by 3 for the vehicle and GLP-1. Is this correct? Or is it vice versa? Figure 2 shows a greater reduction with GLP-1.

3. I think the addition of the "marker of gastric emptying" should be added in the result section of the abstract after measurement of PP is introduced.

Methods

1. I do not understand the protocol for administration of the vehicle, 0.32, 0.63, or 1.25mg/kg GLP-1". The next sentence states "for 8-hour studies....either 0.63mg/kg GLP-1, or vehicle,". Please clarify what time of the day and under what circumstances the vehicle and the three doses of GLP-1 were given. For how long were the glycemic and Hpp excursions followed after each dose? Were they performed in random? Did all 15 volunteers participate in every dose? How far apart were each dose employed (x days)? Were the nine volunteers who participated in the 8hour study a subgroup of the original 15 volunteers, or are they different volunteers?

2. I strongly believe that the description of the volunteers for the 3 separate studies would be more easily understood if it were presented in a table as described below. The material on page 5 could then be reduced to 2 or 3 lines, with something like "the patient characteristics of the volunteers who participated in the dose finding protocol and in the paired 8 hr or 5 day treatment with GLP-1 is presented in table 1. In all studies blood samples...and stored at 70degreesC".
Table 1

<table>
<thead>
<tr>
<th></th>
<th>15</th>
<th>9</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>9M/6F</td>
<td>4M/5F</td>
<td>5M/3F</td>
</tr>
<tr>
<td>Age</td>
<td>40+/−</td>
<td>37+/−</td>
<td>34+/−</td>
</tr>
<tr>
<td>BMI</td>
<td>24.6+/−</td>
<td>24.7+/−</td>
<td>25.4+/−</td>
</tr>
<tr>
<td>Duration of DM</td>
<td>16+/−</td>
<td>18+/−</td>
<td>15+/−</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>0.66+/−</td>
<td>0.79+/−</td>
<td>0.73+/−</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>5.9</td>
<td>5.5+/−</td>
<td>6.9+/−</td>
</tr>
<tr>
<td>HbA1C</td>
<td>6.5</td>
<td>6.5+/−</td>
<td>6.5</td>
</tr>
</tbody>
</table>

3. The description of the stability of GLP-1 in the freezer(s) is too long and not warranted. Simply state that "we established that GLP-1 stored in home freezer maintained its biological activity with regards to responses of glucose and Hpp". Again the description of validation of home blood glucose values is too long. Once could simply state that "Capillary blood glucose levels delivered at home correlated with levels determined from the same sample with a R2 value of 0.94."

4. Were any assessments made as for the concentration of GLP-1 after it was dissolved and filtered? Were peptide contents used in the formulation of GLP-1 or actual weight? Did the filter absorb any GLP-1?

Results

1. I am confused. Please clarify the discrepancy for graded doses of GLP-1 between the method section figure1 and table1 in the method section. It is stated that 15 volunteers participated in this phase of the study while the table and figure1 states 12, which is it?

Table2 Please verify the values as described in the abstract section, query (item 2).

Figure2. There are too many paired t-tests perfomed for glucose. I suggest that an ANOVA for repeated measures would clearly provide a statistically significant difference due to treatment effect and probably a time treatment effect (the latter due to delayed gastric emptying).

Figure3. (a) Add "ac" after before meals to the legend of this figure. 
(b) Is the abbreviation for hora somni, "hs" in capital or lower case? Add "hs" or "HS" after night to the legend of this figure.

I think Table3 is confusing. The study was a five day study and it is confusing to use day 0 and day 6. I assume day 0 is before they received any treatment and day 6 is the morning after the 5 days of treatment. I think the confusion can be eliminated by using the words before treatment and after 5 days of treatment. Another concern is the values of Hpp. Since this is "assumed to be a marker of gastric emptying", how does one explain such low or negative values for the 30 minute interval following the meal in the study with vehicle?

I think the discussion can be reduced by at least 20%. It is not clear why a patient receiving intensified insulin therapy, using multiple daily injections, or continuous insulin infusion with very good HbA1C (6.5%) would elect to have a second therapy with GLP-1. This should be a message delivered, i.e., that it is possible that with longer treatment very good glycemic control can be maintained with reduced dose of insulin and less likelihood of hypoglycemia. This I think, should be the focus of the discussion.

Competing interests:

None declared.