Author's response to reviews

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@shjc.london.on.ca)

Version: 3 Date: 14 Feb 2003

To the Editor, BioMed Central
February 14, 2003

Title: Glucagon-like Peptide 1 Improved Glycemic Control in Type 1 Diabetes
Journal: BMC Endocrine Disorders
Authors: Dr Margaret T Behme (mbehme@uwo.ca)
John Dupre (John.Dupre@lhsc.on.ca)
Thomas J McDonald (tom.mcdonald@shjc.london.on.ca)

Thank you for the reviews of our manuscript. We are submitting a revised manuscript and present a point by point response to the comments of the reviewers.

You noted that John Dupre holds a patent relating to type diabetes and we have added this information to the declaration of competing interests.

We believe we have dealt appropriately with all points raised by the reviewers and that the manuscript now complies with the conditions set by BMC. Please note that the affiliation applies to all authors so that superscripts are not necessary.

We appreciate the reviews, with identification of the referees, and thank you for your consideration of our submission.

Sincerely,
Margaret T. Behme

Response to Reviewer Jens Juul J Holst
Version: 2 Date: 10 Feb 2003

1. Reference to Creutzfeldt et al 1996 has been added [6].
2. The term ED50 has been removed. The dose chosen has been described as that which is sufficient to delay gastric emptying for 30 min but which does not cause abdominal discomfort and nausea.
3. Effects of GLP-1 in figure 1 have been revised as suggested. The effects on glucose AUC were shown in Table 2.
4. Dependency on GLP-1 dose of delay of glucose and HPP responses are consistent with the short half-life of the peptide. The HPP AUC values shown in Table 2 also demonstrate this point. Although the effects of GLP-1 on glucagon may not be obvious from Figure 1, the values shown in Table 2 are valid.
5. Glucose responses from the 8 hour study have been analyzed with two-factor ANOVA as
suggested by Reviewer 2.

6. For 5-day studies, Figure 3 has been revised to show absolute glucose values and the labels for the x-axis have been defined in the figure caption.
7. Single sc injections are rapidly eliminated but are amenable to self-administration by patients and the results of this study show that they have effects in type 1 diabetes.

Specific Points
1) The term "time-averaged" has been retained as an accurate term as defined in the text rather than "time-weighted".
2) The abstract has been shortened to less than 350 words as suggested by the editors.
3) Reliability criteria for the radioimmunoassays have been included.
4) The discussion of the possible direct effects of GLP-1 on tissues or insulin effects has been largely omitted as suggested by the reviewer.

Response to Reviewer Dariush Elahi

Abstract
1. Methods have been placed before results. ED50 has been removed as suggested by reviewer 1. Selection of the dose of 0.63 ug/kg has been clarified.
2. To clarify the AUC values "(delta)" has been added after "incremental" in the results section of the abstract and in Table 2. Errors in the values comparing the effects of GLP-1 and Vehicle have been amended.
3. "Marker of gastric emptying" has not been added because HPP is an indirect indicator of gastric emptying. The phrase "an indicator of gastric emptying" has been added.

Methods
1. The description of the protocol for the dose-finding studies has been revised. Time of day, circumstances, and duration of the studies has been added. The number of volunteers at each dose has been added to Table 2.
2. Table 1 with characteristics of the volunteers has been added as suggested. "the characteristics of the volunteers who participated in the dose finding protocol and in the paired 8 hour or 5-day treatment with GLP-1 are presented in Table 1" has been added to the text.
3. Descriptions of the stability of GLP-1 and validation of home blood glucose values has been amended as suggested.
4. The concentration of GLP-1 after preparation was not assessed. The peptide contents were used in the formulation and the amount absorbed by filtration is not known. The sentence has been added: "The concentration of GLP-1 was based on weight corrected for the peptide content given by the manufacturer.

Results
1. The discrepancies in the number of volunteers has been corrected.
2. Table 2 has been corrected.
3. Figure 2. Paired t-tests for glucose have been replaced with ANOVA for repeated measures for treatment and time treatment effect.
4. Figure 3. (a) "ac" and (b) "hs" have been added to the figure caption.
5. Table 3 has been revised to clarify the tests. The negative values which the reviewer refers to are due to the effects of GLP-1 used in these tests.

Discussion
Discussion has been shortened as suggested by both reviewers.
Rationale for therapy with GLP-1 in patients with good control has been added.
The suggested statement 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" has been
covered by addition to the discussion of "This possibility should be explored in studies of sufficient duration to assess indices of long-term glycemic control".