Reviewer's report

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

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Version: 2 Date: 16 Jan 2003

Reviewer: Jens Juul J Holst

Level of interest: A paper of limited interest

Advice on publication: Accept after discretionary revisions

The authors studied the effects of subcutaneous injections of glucagon-like peptide 1 in patients with optimally insulin treated type 1 diabetes and no residual beta cell activity. First, effects of a single injection of escalating doses before a breakfast meal were analysed, and a dose with 50 % effect was selected. Second, the selected dose was applied as premeal injections in 8 hours studies. Finally, a 5 day treatment with premeal injections of GIP-1 or placebo was instituted in 8 type 1 patients. A dose of 0.63 ug/kg was selected for 8-hour and 5 day studies. Incremental areas under glucose and glucagon curves were lowered by GLP-1, and AUCs for glucose were also lowered in the 5 day study. It is concluded that GLP-1 can improve glucose in type 1 diabetes.

Comments: I would agree with the conclusion that GLP-1 could be of value in the treatment of type 1 diabetes. This is still most evident from the original studies of Creutzfeldt et al from 1996 (which are not quoted!). The present study is a bit confusing, and I have problems in finding out what it actually shows. First, the authors define ED50 values for the effects. This is meaningless because a maximum effect is not obtained. The ED50 turns out to be a dose that was pragmatically chosen because it had some efficacy and yet did not elicit nausea. Fair enough, but this has nothing to do with ED50. Secondly, the effect that one can deduce from Fig 1 seems to be exclusively that GLP-1 inhibited gastric emptying. This is most evident from the glucose curves which are postponed by a time interval that is dose-dependent. But I suspect that if the full meal induced glucose excursion had been followed (much like the 8 hour study), then there would not have any effect on the glucose AUC. The dependency of the delay with GLP-1 dose is completely consistent with the short elimination half-life of the peptide. Gastric emptying is inhibited as longs as there is peptide in the body. Precisely the same conclusion can be deduced from the HPP curves. I have a very hard time in seing any effect at all of GLP-1 on the glucagon curves, and I wonder what statistical trics it took to produce the significance.

The glucose curves from the 8 hour study are more interesting in that a real reduction seems to exist at the lunch meal. It isn't large but seems to be consistent.

The results of the 5 day study are difficult to understand. Fig 3 shows only delta values but should show the absolute glucose values. Also, I cannot understand the text on the x-axis (not defined in text or legend).

I am personally inclined to believe that GIP-1 may be useful for treatment of type 1 diabetes, the question really is how to demonstrate this. In my mind, it is close to futile to use single sc injections of this peptide which has an elimination half life of 1-2 minutes (this has turned out to be true for type 2...
diabetes also). Since the patients (and the investigators) were already accustomed to using continuous infusion pumps, then why not try this? Alternatively, one has to wait for one of the analogues with prolonged action to become available. I am sure that some of the companies would be interested in a collaboration.

Specific points:
1) p. 2 and elsewhere: I cannot understand the use of the term "time-averaged"; I assume the authors mean "time-weighted".
2) Why is the abstract so terribly long?
3) I wonder why it has become unfashionable to present reliability criteria for the employed assays. This is particularly relevant for the glucagon assay.
4) The discussion section has a long passage on possible direct effects of GLP-1 on tissues or insulin promoting effects. This discussion is not relevant to the present investigation, and this part of the discussion could be omitted. The manuscript is too long anyway.

Competing interests:
None declared.