Background and Aim

Basal insulin is given as treatment for patients with Type 2 Diabetes Mellitus (DM) who are failing on oral hypoglycemic therapy. Basal insulin is also a chosen treatment for patients with Type 1 or Type 2 DM who are currently treated with both prandial and basal insulin regimens.

Current basal insulin cannot respond to conditions that affect glucose levels such as exercise, stress, fever etc. Basal insulin dose is often not optimized for changing glycemic conditions that can affect patient’s glucose levels during the day and does not address postprandial (PP) hyperglycemia. In an effort to reduce PP hyperglycemia, basal insulin is often administered at an inappropriately high doses. The Dawn phenomenon, which is an early morning increase in hepatic glucose output, is also not addressed by the current basal insulins and this can lead to either inappropriately high basal doses or exposure to prolonged periods of hyperglycemia. Such high insulin doses result in more hypoglycemic episodes and increased weight gain that further complicates the management of DM. Thus this practice leaves a number of needs unmet that a desirable basal insulin therapy should provide.

The present challenges in basal insulin therapy translate into a need for a self regulated basal insulin formulation that would release insulin in response to the ever-changing needs of the individual patient. The “Smart” Basal insulin formulation would automatically adjust insulin release according to the ambient glucose concentration. The Smart Basal insulin may provide a better overall glucose control. With the recognition of the above unmet needs and benefits that a Smart Basal insulin can offer to patients, a “Smart” Basal insulin formulation called BIOD620 has been developed that has shown to self regulate insulin release in response to changing glucose concentrations. Ingredients in the BIOD620 formulation respond to increased subcutaneous (s.c.) glucose concentration by lowering the pH and increasing solubility of insulin glargine.

Materials and Methods

In vitro insulin release from BIOD620 was tested in the presence of glucose (300mg/dl) and absence of glucose (0mg/dl). A 6-well multwell flat bottom polystyrene plate (receiver well) was filled with 1.0 µm pore transparent polyethylene terephthalate membrane (1.0 µm pore transparent polyethylene terephthalate membrane cell culture insert (donor chamber, BD Falcon). Test set: Donor cell contained 1 ml of BIOD620 formulation with 200µl of phosphate buffer saline (PBS) with glucose. Receiver well contained 1.5ml of 300mg/dl glucose PBS as the release medium. Control set: set was set up as Test set except no glucose was added to it. A 900µl aliquot was sampled at 3h and 6h from each receiver well and replaced by the same volume of the PBS as the release medium. Samples were analyzed by HPLC.

In vivo evaluation, was conducted in 6 diabetic miniature swine that were fasted overnight. Morning Plasma glucose levels (PGL) were high and were used as the starting point for the comparison of the Lantus® (Control) with the BIOD620 formulation (Test). Three swine were tested with each formulation. The dose of 0.25U/Kg was administered s.c. to each pig. Following administration of the formulation, the pigs were monitored and fed 500g of swine food at 360 minutes as the second glucose challenge. PGL were determined every 15 minutes via a commercial glucose strip method (OneTouch® by LifeScan, Inc.

Results

In vitro insulin release studies for BIOD620 demonstrated that insulin release from BIOD620 was dependent upon glucose concentration. Higher glucose concentrations resulted in monotonically increasing insulin concentrations. Figure 1 shows the amount of insulin released from BIOD620 formulations in presence and absence of glucose. The cumulative amounts of insulin released at 6h shows higher insulin release in the test set than control set indicating that insulin release is glucose dependent. (Fig. 1). It was also demonstrated that the amount of insulin released from the BIOD620 formulation was dependent upon the glucose concentration in the environment. Presence of higher glucose concentration, resulted in more insulin release compared to insulin exposed to a lower glucose concentration (Fig. 2).

Pharmacodynamic (PD) response of diabetic swine to BIOD620 was also indicated the self regulated insulin releasing potential of BIOD620. Mean PGL: 2 SEM of 3 swine for test and control formulations are shown in Figure 3. The test group responded rapidly to the elevated glucose levels both initially and upon second feeding, after 360 minutes, than the control group. Figure 3A shows that following s.c. administration, BIOD620 formulation decreased the PGL of the test group faster than basal insulin alone (control group). Even after 360 minutes, the BIOD620 formulation reduced the post meal hyperglycemia that occurred in basal alone (Fig. 3B).

References

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2. www.lantus.com

Acknowledgement

Special thanks to Tim Madsen and the team at Sinclair Research Centre, MO, responsible for diabetic induction, swine maintenance and dose administration.

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