Obstacles diminish in quest for artificial pancreas

DURING AN ORAL PRESENTATIONS session this afternoon, several researchers will detail the latest advancements in designing an automated system that can safely control glucose to near normal levels without any user intervention. The two-hour session, titled *Insulin Delivery Systems*, will begin at 4:30 p.m. in Room 311 at the convention center.

Linda Morrow, MD, Chief Operating Officer at Profil Institute for Clinical Research, Inc., will begin the session with a presentation titled "Human Hyaluronidase Coinjection Accelerates Insulin Pharmacokinetics and Glucodynamics of 3 Rapid Insulin Analogs." Dr. Morrow will present results from a randomized double-blind clinical trial that compared the insulin action and pharmacokinetic profiles of the three marketed rapid-acting mealtime analogs injected alone and with Halozyme's PH20 enzyme, recombinant human hyaluronidase.

"The study was a six-way crossover euglycemic glucose clamp study in 14 healthy volunteers. Each subject received the six treatments in a randomized sequence at the same dose," Dr. Morrow said. "The treatments were Humalog (insulin lispro), NovoLog (insulin aspart), and Apidra (insulin glulisine), with and without PH20."

In the presence of PH20, each analog had comparable profiles that were notably faster than any of the marketed rapid-acting analogs alone.

"PH20 accelerated the absorption of all three rapid-acting insulin analogs, resulting in more physiologic fast-in, fast-out profiles," Dr. Morrow said.

Eyal Dassau, PhD, Senior Investigator and Diabetes Team Research Manager of the Department of Chemical Engineering at the University of California, Santa Barbara, will then present "Clinical Results of Automated Artificial Pancreatic ß-Cell System with Unannounced Meal Using Multi-Parametric MPC and Insulin-on-Board."

"We have developed and clinically evaluated our artificial pancreatic ß-cell system that can safely and effectively regulate glycemia in the face of hyperglycemia and unannounced meal challenges," Dr. Dassau said. "The average percent time in range was 69 percent with no hypoglycemia episodes. All reported results were within the A + B zone of the Control Variability Grid Analysis."

This approach, currently being used by eight clinical research sites around the world, is a fully automated system that uses the Artificial Pancreas System developed at the University of California, Santa Barbara, and Sansum Diabetes Research Institute.

"The artificial pancreas, or artificial ß-cell, will regulate the blood glucose concentrations of people with type 1 diabetes mellitus," Dr. Dassau said. "It may be the next major advancement in the field since the introduction of insulin analogs."

Joseph El Youssef, MBBS, senior fellow at Oregon Health and Science University, will next present "Glucagon at Clinically Relevant Concentrations Is Safe for Seven Days after Reconstitution: Results from Cytotoxicity Studies."

A historically important hormone used for the treatment of hypoglycemia both in the out-patient and hospital setting, glucagon is commercially prepared as a freeze-dried powder intended only for immediate use after reconstitution. When left in solution it has been shown to aggregate and form protein fibrils, and reports of cytotoxicity generated some alarm.

"We now believe that these earlier studies may have come to incorrect conclusions due to use of very high concentrations of glucagon and failure to account for conditions such as pH and osmolarity," Dr. Youssef said. "So we embarked on a series of experiments to discover whether or not glucagon, in clinically relevant concentrations with controlled pH and osmolarity, would aggregate and become cytotoxic."

It now appears that glucagon, when the proper excipients are added and in the absence of extreme acidic conditions, is actually very stable as a water-based solution and does not cause cytotoxicity even at relatively high concentrations for up to seven days after reconstitution.

"Our data from high performance liquid chromatography studies show that under the right conditions glucagon does not form aggregates. Finally, studies in pigs show that even when glucagon does aggregate, it maintains a near-normal ability to break down glycogen and raise serum glucose. These findings suggest that the aggregates may dissociate to monomer form *in vivo* when injected subcutaneously," Dr. Youssef said.

"Our artificial pancreas studies in persons with type 1 diabetes showed that when glucagon is given on an intermittent basis by algorithm, it works much better than a glucagon placebo to avoid hypoglycemia," he added.

Additional presentations will include, "Bi-Hormonal Closed-Loop Blood Glucose Control for Type 1 Diabetes," "Reducing Postprandial Hypoglycemia Using Fuzzy Logic Controller with Insulin Dosing Governor," and "Overnight Closed Loop (CL) Glucose Control Following Consumption of Alcohol in Adults with Type 1 Diabetes (T1D)."

Oral Presentations Preview
Insulin Delivery Systems
4:30 p.m. – 6:30 p.m. Monday
Room 311