The History and Future of Insulin Formulations

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Presentation Objectives

To share the history of development of insulin products as a possible basis for predicting the future directions with protein therapeutics.
Outline

- History of insulin
- Formulations and products
- The birth of the recombinant era
- Future possibilities
- Summary
Early History of Diabetes

- 1552 BC – earliest known record of diabetes
- 1st century AD – diabetes described as “melting down of the flesh and limbs into urine”
- 16th century – Paracelsus identified diabetes as a serious general disorder
- 1870s – Bouchardat noted disappearance of glycosuria in diabetes patients during rationing of food in Paris
- 1869 – Langerhans announces that pancreas has two systems of cells
- 1889 – Minkowski and von Mering first study effect of removal of pancreas in dogs
- 1908 – Zuelzer develops first injectable pancreatic extract but severe side effects
- 1919-20 Frederick Allen establishes first treatment center in the US
History of Insulin

- Frederick Banting’s initial idea: “Ligate pancreatic ducts of dogs. Wait 6-8 weeks for degeneration. Remove the residue and extract.”
- Requested access to dogs from J.J.R. Macleod in Toronto and worked with the assistance of Charles Best
- Announced results from early experiments on December 26, 1921 at American Physiological Society meeting at Yale, along with intent to conduct human studies with extract
- First human study on January 11, 1922 with a critically ill 14 year old
History of Insulin

George Clowes, Eli Lilly and Company, attended the Yale meeting and suggested Lilly could provide resources to produce the extract in quantity.

May 1922 an agreement was signed between the University of Toronto and Lilly.

Lilly committed $250,000 to the joint effort.
History of Insulin

- Potency of extract diminished as process was scaled up
- Walden, at Lilly, recognized that a precipitate that was discarded was where the potent material was
- Led to process of isoelectric precipitation with standardized purity and potency
- First US physician to use Lilly insulin was Elliot Joslin
- Lilly’s Iletin® marketed in October 1923 after being tested with 7000 doctors and their patients
- By 1975 Lilly was processing 1 ton of pancreas per hour to keep up with demand
Insulin Hexamer
Recombinant Insulin

- Genentech rDNA human insulin obtained on 24 August, 1978 from combination of A and B chains individually expressed in E. coli
- Key technologies included
  - Rapid chemical synthesis of DNA
  - Use of RP-HPLC for purification of DNA fragments and detection and characterization of expressed proteins
Recombinant Insulin timeline

- 24 August 1978: first rDNA insulin (approx. 20 ng.)
- 25 August 1978: Lilly and Genentech sign development agreement (announced September 6)
- 5 October 1979: Lilly gets permission for 150L fermentation
- 7 October 1979: Zinc insulin crystals from first significant batch
- 15 July 1980: first human studies with BHI at Guy’s Hospital in London
- 9 July 1981: first 40,000L fermentation
- 26 August 1982: Approval to market BHI in UK
- 10 April 1986: Approval to market BHI derived from human proinsulin
Rationale for recombinant human insulin

- Limited supply of animal pancreas to support increasing incidence of diabetes
- Continuing possibility of allergic reactions to animal insulin
- Logic of use of human protein if available
- Because it was possible!
Tests Used to Evaluate BHI

- Rabbit hypoglycemia assay
- Insulin radioreceptor assay
- Amino acid composition
- Amino acid sequence
- Gel electrophoresis
- FAB mass spectrometry
- Disulfide bond verification
- HPLC
- Peptide mapping
- Zinc crystallization
- X-ray structure
- 2D NMR
- Limulus assay for endotoxins
- Insulin receptor assay
- USP rabbit pyrogen test
- BP proteolytic activity assay
- Proinsulin RIA
- C-Peptide RIA
- E. coli peptide RIA
Insulin Physiology

- Normal physiology of basal concentrations supplemented by large prandial insulin spikes
- Target for therapy is to provide formulations or systems that mimic normal physiology
- Goal to maintain hA1Cs in patients with diabetes at less than 7.0
History of insulin formulations

• Regular animal sourced insulin 1920’s
• NPH insulin 1940’s
• Lente and Ultralente insulins – longer acting formulations – 1953
• Human rDNA insulin 1980’s
• Insulin lispro – genetically modified short acting insulin 1990’s
• Insulin glargine – genetically modified long acting insulin 2000’s
• Non-injectable insulin formulations
Insulin product profiles
NPH Insulin

- 1936 protamine zinc insulin described
- 1946 Neutral Protamine Hagedorn (NPH) introduced by Nordisk
- Neutral insulin with prolonged action
- Could be mixed with regular insulin
Lente Insulins

- 1953 Ultralente, Lente, and Semilente formulations made available
- Zinc used as delaying agent
Modified Insulins

Lispro insulin (Humalog® - Lilly)
- Onset in 10-15 minutes
- Avoids need to carefully plan time of injection prior to meal
- Peak at 30-90 minutes with duration of 3-5 hours

Insulin glargine (Lantus® - Aventis)
- Acidic solution
- Microprecipitates after s.c. injection
- Crystals dissolve slowly to release insulin glargine with full activity after 4-5 hours and sustained to 24 hours
- No significant peak
Modified Insulins

Insulin detemir (Levemir® - Novo Nordisk)
- Basal insulin analog
- Covalent link to a fatty acid that enhances binding to albumin
- Detemir released at a constant rate over 24 hours
- Data suggests improved and more predictable control
History of pump development – exemplified by MiniMed story

- 1979 - Al Mann CEO of PaceSetter Systems became interested in insulin pumps
- 1983 - MiniMed 502 introduced
- 1985 - MiniMed spun out
- 1986 - MiniMed introduced “insulin friendly tubing”
- 1992 - Launch of the MiniMed 506
- 1996 - Launch of 507C
- 1999 - Model 508
- 2001 - MiniMed acquired by Medtronic
Pump Insulins

- Limitation of aggregation of insulin in lines
  - Buffered insulin formulations
  - New tubing materials
  - Less aggregating insulin (e.g. lispro)
Alternatives to injection of insulin

- Inhaled insulin
  - Insulin is absorbed through the lung alveoli
  - Extensive studies have shown a similar kinetic profile to fast acting injected insulin
  - Exubera® - Pfizer, expected to be available shortly

- Buccal insulin (Oralin®- Generex)
  - Uses RapidMist™ technology to deliver insulin to buccal mucosa
  - Mixture of insulin, surfactants and lipids
  - Approved in 2005 in Ecuador
Alternatives to insulin injections

- **Oral insulin**
  - Emisphere Technologies
    - Eligen® technology
    - Carrier facilitates transport across membranes
    - Suggests modification of parent molecule conformation
    - Insulin dissociates from complex after transport
  - Nobex
    - Hexyl insulin monoconjugate 2 (HIM2)
    - Covalent modification of insulin with oligomers at select sites
    - Facilitates transport across membranes
Future projections

- Islet replacement for Type I disease
- Gene replacement for Type I disease
- Closed loop feedback pumps
- Improved delivery devices to improve compliance
- Better control of obesity in the developed world beginning to lessen incidence of Type II disease