INSULIN OVERVIEW

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Commercial Nomenclature

$ Iletin - Manufactured by Lilly

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$ Iletin Regular, "NPH", etc.

$ Derived from beef/pork

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$ Humulin - Manufactured by Lilly

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$ Human derived (recombinant DNA)

US Manufacturers

1. Eli Lilly (Iletin, Humulin)
2. Novo Nordisk (prev. Squibb)
3. Aventis (insulin glargine)
4. IDEXX (PZI) – no longer available
5. Intervet (Vetsulin)
6. Novo Nordisk (Insulin aspart)
7. Eli Lilly (Insulin lispro)

History

$ Discovered by FG Banting and CH Best in JJR Macleod's lab in Toronto in 1921.

$ 1923 - Eli Lilly Company made first commercially available insulin.

Unit of Insulin

- Standard to assure uniformity
- Present standard is 24 units per mg
- Originally standard based on hypoglycemic activity in rabbits
- Now based on absolute weight of insulin prepared from recrystallized composite sample.

Factors Affecting Absorption

1. pH (stable at 7.4)
2. Crystal size
3. Zinc binding
4. Protein (protamine) binding

Humulin - Manufactured by Lilly Company

Derived by:

- *E. coli* recombinant DNA; rDNA or
- Enzymatic conversion of pork insulin at the B-30 terminal amino acid - to human insulin

Purified Insulins

- Some insulin preparations contain small amounts of proinsulin and other related molecules
- Contaminants → allergic reactions, lipodystrophy, etc.
- "Purified" and "single peak" contain minimal amounts

Insulin Activity After SQ Administration to the Dog and Cat

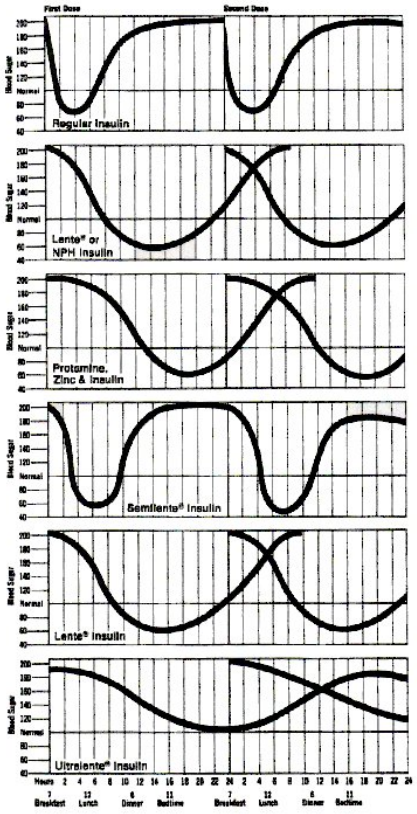
Type	Action	Peak Activity hrs	Duration hrs	Added Protein	Route
Regular	Rapid	1-5	4-10	None	IV, IM, SQ
NPH	Intermediate	2-10	4-12	Protamine	SQ
Lente - Vetsulin	Intermediate	2-6	6-10	None - acetate buffer	SQ
PZI	Prolonged	4-10	12-30	Protamine	SQ
(*)Aspart	Short	0.1-3	3-5	Shorter acting than regular	SQ
(*)Lispro	Short	0.5-1½	< 6	Shorter acting than regular	SQ
(*)Glargine	Long	No true peak-very gradual onset	24 15 (in the cat)	Recombinant human analog	SQ

(*)Information derived from humans. Used to prevent postprandial hyperglycemia.

Requires a longer acting insulin to be used simultaneously.

<u>Comparative Time Activities</u>

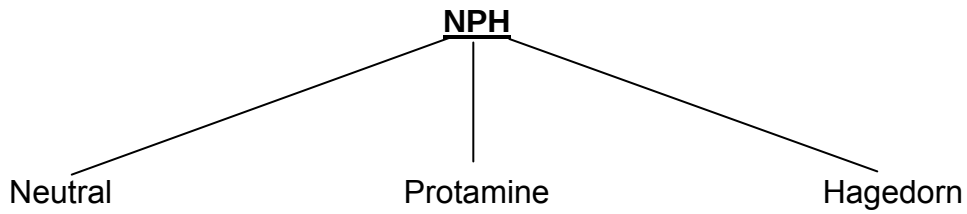
<u>of the Various Insulins</u>



Factors Affecting Time of Absorption

1. Volume
   - 1 ml (40 units) of U-40 absorbed more quickly than 0.4 ml of U-100.
2. Unit Dosage
   - As unit dosage increases rate of absorption decreases .
3. Site of Injection
   - An injection site consisting of a moving body part allows for faster absorption.
4. Condition of Skin
   - Scars delay.

Absorption	SQ
Regular -	Rapid - prepared at neutral pH in U.S.
Regular + Protamine -	Delayed
Regular + Protamine + Zinc -	Further prolonged



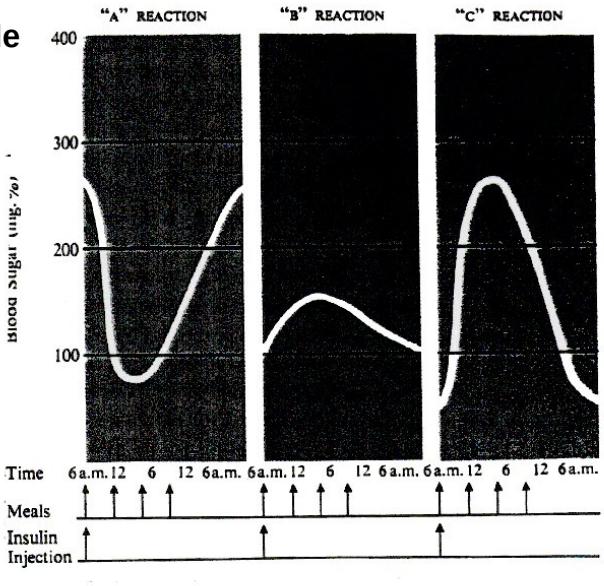
NPH = Iletin® = isophane

ISO = equal, phase = appearance

$ NPH is a crystalline form containing regular and protamine zinc in stoichiometric proportion - leaving no residue.

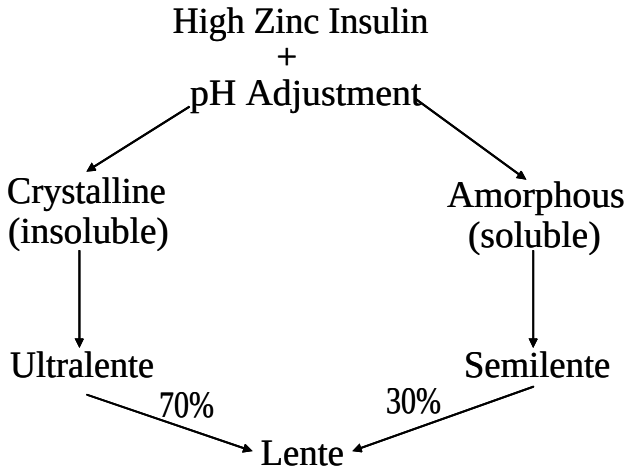
$ Effects comparable to mixture of 2 to 3 hours regular to one part protamine zinc.

Types of Response to a Single Daily Dose of NPH Insulin



Lente (VETSULIN) - "Slow Action"

- Intermediate acting
- The result of formulating a relatively insoluble insulin without the need for a modifying protein
- Insulin + zinc □ soluble zinc insulin
- Insulin + (10 X) zinc + acetate buffer = insoluble insulin at pH 7.4



Note that Vetsulin has amorphous insulin that causes an early onset effect.

Drug Interactions

Decrease hypoglycemic effects:

- Corticosteroids
- Contraceptives
- Diltiazem
- Dobutamine
- Thiazides

Increase hypoglycemic effects:

- Alcohol
- Anabolic steroids
- □-blockers
- Salicylates
- Tetracyclines

Insulin Mixtures

NPH + regular

- Can be purchased commercially in 70/30 proportions

Insulin Syringes

- Must match the insulin
- U-100 syringes available in
  - 0.3

- $ 0.5
- $ 1.0 ml capacities
- $ U-40 – for PZI and Vetsulin

Insulin Glargine for the Compensated Feline Diabetic

A long-acting insulin derived from recombinant DNA technology for human diabetics. It is a no peak insulin that provides 24-hour coverage. In veterinary medicine, it has been found to be very effective for maintenance treatment for the feline diabetic. It is calibrated at 100 units/1 ml. **This insulin cannot be refrigerated nor can it be mixed with any diluent.** Best to use with U-100 insulin syringes that are available at a 0-30 unit dose scale. Insulin glargine works very similar to PZI. Insulin glargine is given SQ only at a preferred dose of 0.25 U/kg divided bid or 0.5 U/kg sid and titrated to effect.

Treatment of Insulin Overdose

- Karo syrup - 1.0 ml/kg (% ml/lb) orally if conscious
- Glucagon injection - 0.03 mg/kg (0.015 mg/lb) given intramuscularly

Insulin Availability After January 2006

Eli Lilly will cease producing the following insulin products:

- Regular Iletin Pork
- NPH Iletin Pork

Human Products Available

- Humulin Regular
- Humulin NPH
- Insulin Glargine can be used in cats

Veterinary Products Available

- PZI (compounded) for cats – best to give divided Bid
- Intervet - Vetsulin for Dogs and Cats - best to give divided Bid; company's recommendation of once a day dosing predisposes to too many episodes of hypoglycemia. Best to avoid by beginning as BID.