Any insulin for Any Patient? Why not?

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Outline

- Insulin Physiology
- Insulin Pharmacology
- Basal-Bolus Concept
- Clinical Applications

Insulin Protein is Highly Conserved

Insulin is equipotent across species.

Alignments modified from Wallis Lab (http://www.lifesci.sussex.ac.uk/Home/Mike_Wallis/Protein_Hormones/Insulin.html)
Insulin Action on Target Tissues

- Insulin
- Insulin receptors
- GLUT4
- Gene expression & growth regulation
- Glucose utilization
- Glycogen / lipid / protein synthesis

Insulin Pharmacology

- Natural insulin (animal insulin) – isolated from pancreas of cattle and pigs. Only a few products are commercially available (veterinary).
- Recombinant insulin – human insulin produced by genetically altered bacteria. All insulins for humans contain human recombinant insulin.
- Synthetic insulin – insulin chemically altered to achieve a specific pharmacologic action.
- Insulin suspension – complexed insulin is suspended in a vehicle.
- Insulin solution – insulin monomers dissolved in an aqueous vehicle.

Insulins in veterinary medicine

- Human products (U-100)
  - Regular
  - NPH (Neutral Protamine Hagedorn)
  - Synthetic long-acting insulin
  - Synthetic short-acting insulin
- Veterinary products (U-40)
  - PZI
  - Lente

- HUMULIN R®
- HUMULIN N®
- Lantus® – insulin glargine
- Humalog® – lispro insulin
- ProZinc® (human insulin)
- Vetsulin® (porcine insulin)

Insulin Pharmacokinetics

- Aspart, lispro,
- Regular
- NPH
- Detemir
- Glargine

'what the body does to the drug'
Insulin Pharmacodynamics
‘what the drug does to the body’

**Time-Action Profile**

![Glucose Curve Image](http://www.caninsulin.com/)

**Basal-Bolus Concept**

- Insulin always produced.
- Basal insulin modulates HGP
- GLU-INS are closely coupled.
- Bolus insulin released after meals.

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**Ideal insulin therapy replicates the physiologic insulin profile**

Basal insulin to modulate HGP during fasting periods.
Bolus insulin to modulate glucose disposal after meals.

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**No single insulin product replicates the physiologic insulin profile**

Basal-Bolus Optimization = Multiple Insulins

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<th>LEGACY FORMULATIONS</th>
<th>NEWER FORMULATIONS</th>
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<td>BASAL REPLACEMENT</td>
<td>NPH PZI LENTE ULTRALENTE</td>
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BASAL REPLACEMENT

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BOLUS REPLACEMENT

Need for a true basal insulin drove development of long-acting insulin products
- Delayed absorption and prolonged duration of action.

Need for a true bolus insulin drove development of short-acting insulin products
- Rapid onset and short duration of action.

Clinical Applications

- Normal < 150 mg/dl
- Pre-Diabetes 150-220 mg/dl
- Diabetes >220 mg/dl

Then why are there ANY unregulated diabetics?

- Limitations of insulin monotherapy
- Variability
- Reliance on prediction
- Unreliable assessment methods

ANY Insulin ANY Patient
Insulin Monotherapy

- Current recommendations endorse single insulin therapy
- Recommendations broadly based on 24-hr glucose profile.
  - Dog – intermediate-acting insulin administered B.I.D.
  - Cat – long-acting insulin administered daily or B.I.D
- Effective for most patients
  - Improves clinical signs of diabetes
  - Elimination of insulin requirement
- Ineffective for some patients
- Is the basal-bolus concept relevant for dogs and cats?

Species differences and effective insulin monotherapy

**DOGS**
- Insulin dependence at diagnosis.
- Mixed diet composition, inconsistent diet
- Periodic feeding causes postprandial GLU surges.
- Overnight fast

**CATS**
- Insulin reserve may remain at diagnosis.
- Diet typically CHO restricted
- Continuous feeding pattern.
- Nocturnal feeding behavior

Why isn’t Combination Insulin Therapy Used for Canine and Feline Diabetes?

Species differences in ‘normal’.

Recognizing veterinary patients in the pre-diabetic state is difficult.
- Insulin dependent at the time of diagnosis
- Poorly defined metabolic markers for pre-diabetes.
- Available tests are impractical, poorly standardized or both.
- No justification for early identification/intervention of at-risk patients.

Patient/Owner compliance may be a major factor.
- Basal-Bolus requires monitoring and multiple daily injections.
- Scarce evidence for use of multiple insulins in diabetic dogs or cats.

Variability

“What is the reason for the fact that repeated application of an identical insulin dose does not induce an identical metabolic response?”

Lutz Heinemann*

Variability – Differences in the metabolic actions of insulin due to environmental and biologic factors that affect insulin absorption or action.

Clinically relevant variability in the insulin effect

* Heinemann, L, Diab Tech Therap, 2002
Biologic Variability

• Insulin sensitivity is not static
• Variability in insulin action after IV administration to healthy human subjects
• Day-to-day within an individual - 15-25%
• Between individuals - 25-35%

Potential Sources of Variability

- Insulin type and formulation
- Ambient temperature
- Activity level
- Inadvertent IM injection
- Metabolic state (hypoglycemia, ketoacidosis)
- Local factors at injection site

Impact of Variability

• Daily insulin effects are not reproducible.
• Optimal metabolic control is not achieved.
• Concern and anxiety over poor control.
• Frustration for owner and veterinarian.
• Added expense.

Assessment versus Prediction

Current methods are retrospective or temporal
- Clinical history and signs
- Fructosamine Level
- Spot glucose
- Glucose curve

Poor predictors of future glycemic control or insulin needs.
Summary

- Insulin is highly conserved and has similar functions across species.
- Bioactive insulin, regardless of its source or formulation, will exert a glucose-lowering effect in dogs and cats.
- Ideal insulin replacement replicates the basal-bolus pattern of endogenous insulin secretion. No single insulin product is ideal replacement therapy.
- Insulin monotherapy as used in veterinary medicine has efficacy in the majority of patients.
- Variability from numerous sources may influence insulin absorption and action and produce in an apparent lack of efficacy.
- Common monitoring methods, including serial glycemia assessments in the same patient, are poor predictors of a patient’s future glycemic control and insulin requirements.