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CURRENT AND FUTURE DIRECTIONS IN INSULIN THERAPY

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Overview

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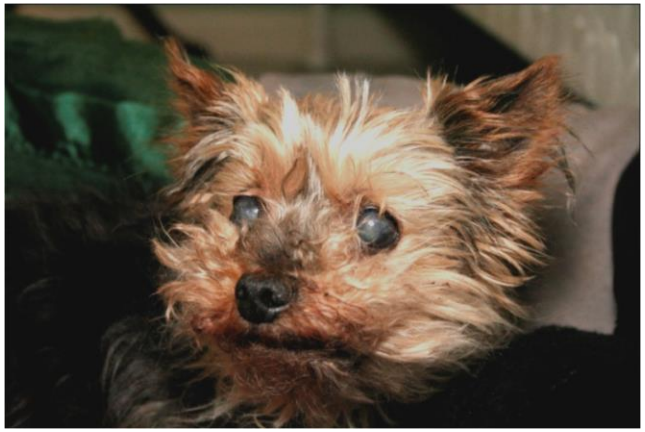

- Pathophysiology
- Insulin Therapy
  - Short acting
  - Intermediate acting
  - Long acting
- Monitoring Diabetic Pets
- Future Directions
  - Implantable and external insulin delivery systems
  - “Artificial pancreas”
  - Stem cell therapy

Pathophysiology

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- Type 1 Diabetes Mellitus (IDDM)
  - Insulin dependent diabetes mellitus
  - Insulin dependence due to ß cell degeneration and/or destruction
  - Most dogs, some cats
- Type 2 Diabetes Mellitus (NIDDM)
  - Non-insulin dependent diabetes mellitus
  - Insulin resistance and ß cell dysfunction
  - Most cats, some dogs

Pathophysiology

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- Insulin is produced by the ß cells within the islets of Langerhans in the pancreas
- Immune-mediated destruction of cells or degeneration of cells results in reduced ability to produce insulin
- Insulin resistance can also result in lack of insulin effectiveness
- Lack of insulin results in the inability to uptake glucose from the blood into cells
- Result is hyperglycemia with glucose-starved cells

Pathophysiology

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- Insulin deficiency results in decreased tissue utilization of glucose, amino acids, fatty acids, accelerated hepatic glycogenolysis and glyconeogenesis, and subsequent hyperglycemia
- Renal tubular threshold for glucose is exceeded, resulting in osmotic diuresis and compensatory polydipsia
- Polyphagia due to starvation of cells and inability of glucose to enter satiety centre

Pathophysiology

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- Histological changes in dogs
  - Reduction in size of pancreatic islets
  - Decreased beta cells within islets
  - Beta cell vacuolation and degeneration
- Congenital form (rare)
  - Pancreatic aplasia
  - Pancreatic hypoplasia
  - Absolute deficiency of beta cells – severe form

Etiology - Dogs

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- Genetics (Australian Terrier, Schnauzer, Bichon, Terriers, Smaller Poodles, Samoyed, Keeshond, Maltese, Lhasa Apso, Spitz, Yorkie)
- Immune-mediated – suspected more in humans than dogs
- Obesity
- Drugs (glucocorticoids, progestagens)
- Infection

Etiology – Dogs continued

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- Concurrent disease (chance of NIDDM)
  - Pancreatitis
  - Hyperadrenocorticism
  - Hypothyroidism
  - Other endocrine disease
  - Diestrus-induced increase in growth hormone
  - Renal insufficiency (?)
  - Cardiac disease
  - Hyperlipidemia (cause or effect)

Etiology - Cats

- Initially impaired insulin action in liver, muscle, fat which is defined as NIDDM (Type 2)
- Genetics suspected but not characterized
- Major risk factors:
  - Increasing age
  - Male gender
  - Neutered status
  - Physical inactivity
  - Glucocorticoid/progestin administration
  - Obesity

Etiology – Cats continued

- Increased insulin secretion required due to insulin resistance, leading to beta cell loss
- Deposition of amyloid in pancreas also suggested to lead to beta cell loss
- Conversion to type 1 (IDDM) once loss of 80-90% of beta cells

Diagnosis

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- Presence of significant hyperglycemia with glucosuria
- Important to document hyperglycemia as glucosuria can occur due to renal disease (Fanconi syndrome)
- DDx for hyperglycemia:
  - Stress, post prandial, hyperadrenocorticism, diestrus, pheochromocytoma, pancreatitis, exocrine pancreatic neoplasia, drug therapy (glucocorticoids, progestagens, thiazide diuretic, dextrose IV fluids), head trauma
- Fructosamine can help diagnose DM

Clinicopathologic changes

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- CBC – usually normal, can see neutrophilia
- Biochemistry – Hyperglycemia, fasting hypercholesterolemia, fasting hyperlipidemia, increased ALT (usually <500 IU/L), increased ALP (usually < 500 IU/L)
- Urinalysis – USG usually >1.025, glucosuria, proteinuria, bactiuria, can have ketonuria

Additional diagnostics

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- Urine culture
- Abdominal ultrasound
- Thoracic radiographs
- fPL or spec cPL

Goals of Therapy

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1. Diet
2. Exercise
3. Insulin therapy (oral hypoglycemic drugs)

- Reduce or eliminate owner-observed clinical signs
  - Polyuria and polydipsia easy to monitor
  - Polyphagia
- Prevent chronic complications of diabetes mellitus
- Obtain remission if possible

Insulin Therapy

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- Started immediately in all dogs and most cats
- Most will need twice daily dosing
- Most effective, fastest means of achieving glycemic control
  - Solid evidence cats started on insulin within first 6 months of diagnosis more likely achieve remission
- Ideal goal - maintain blood glucose concentration as close to physiologic levels as possible
  - Difficult to do, as administered as 1-2 large daily doses, not in response to blood glucose level
- Realistic goal = eliminate or reduce clinical signs

Insulin Products

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- Classified based on
  - Time of onset
  - Duration of action

- Fall into 3 categories
  - Short-acting
  - Intermediate-acting
  - Long-acting

Treatment Strategies

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- Must be flexible
  - Kinetics vary markedly among species & individuals
- Duration of action of most insulins typically shorter in cats than dogs
  - Except short-acting insulin
    - Same duration in both

Short-Acting Insulin

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- Reserved for diabetic ketoacidosis, clinically ill patients and occasionally for combination dosing
- Three methods of administration
  - Low-dose intravenous infusion technique
  - Intermittent intramuscular and subcutaneous technique
- Dosing schemes vary
  - CRI - 1.1 to 2.2 IU/kg/day
  - Intermittently IM - 0.1 to 0.2 IU/kg q1-4 hours
  - Intermittently SQ – 0.25 IU/kg q4-6 hours
    - Adjust based on serial measurements of blood glucose concentration

Short Acting Insulin

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- Regular / Humulin R (U-100) is the short acting insulin of choice

- Lispro / Humalog (U-100) has a similar action to Humulin R
  - No benefit over Humulin R when giving intravenously
  - Less chance of hypoglycemia when given subcutaneously, so may be a better choice in combination with long acting insulin for long term use

Short Acting Insulin

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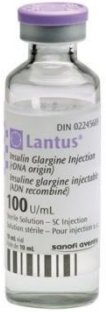
- Glargine insulin
- There are reports of using glargine insulin intravenously or intramuscularly to stabilize a clinically ill patient or a patient with diabetic ketoacidosis (J. Rand, 2012)
- Not reported by other internists or criticalists
- Insufficient data to recommend use, regular insulin should be used



Intermediate Acting Insulins

Caninsulin U-40

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- Good first choice in dogs
- Good second or third choice in cats
- Porcine based

Onset of action	½ - 2 hours (dogs)
	<1 hour (cats)
Maximum effect	3 hours (dogs)
	3 – 5 hours (cats)
Duration of action	8 hours (dogs)
	8 – 12 hours (cats)

Caninsulin

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- Twice-daily administration usually necessary
- Occasionally three times daily dosing required
- **Dogs** starting dose of 0.25-0.5 IU/kg lean weight twice daily
- **Cats** starting dose of 0.25-0.5 IU/kg lean weight usually twice daily
  - Can use pre-treatment blood glucose as a guide, use lower end of dosing if blood glucose is < 20 mmol/L

Caninsulin

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- Able to dilute if needed
- Only available from vet clinics – encourages monitoring
- Previous concern with back-order resolved
- Available in pen form

NPH U-100

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- Good first choice in dogs
- Duration of action usually too short in cats
- Recombinant human insulin

Onset of action	½ - 2 hours (dogs and cats)
Maximum effect	2 - 10 hours (dogs)
	2 - 9 hours (cats)
Duration of action	6 - 18 hours (dogs)
	2 - 9 hours (cats)

NPH

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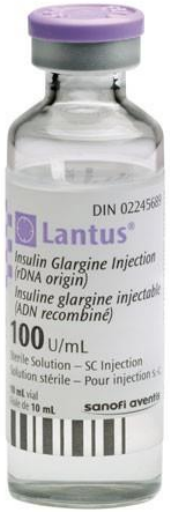
- Twice-daily administration usually necessary
- Starting dose for **dogs:**
  - Some clinicians use starting dose of 0.25 IU/kg
  - Others recommend 0.5 IU/kg if BG >20 mmol/L and 0.25 IU/kg if <20 mmol/L
  - Both are acceptable protocols
  - Always round down to closest unit

Long Acting Insulins



Glargine U-100

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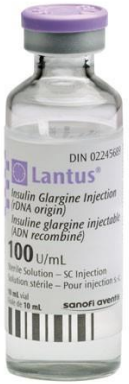
- At acidic pH glargine insulin is in solution
- At the relatively neutral pH of SQ tissues
  - Micro-precipitates form
    - Relatively constant systemic absorption rate
    - Up to 24 hours without significant peak
    - Cannot mix or dilute as micro-precipitates depend on solution's acidity

Onset of action	1 - 2 (cats)
Maximum effect	2 – 9 hours (cats)
Duration of action	8 – 16 hours (cats)



Glargine

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- Good first choice in cats
- Glargine not recommended in dogs
  - Recent published data revealed good glycemic control in only 50% of dogs; concluded that other insulins have a better success rate
- Anecdotal reports claim that glargine seems ineffective in treating diabetic dogs
- Long duration of action could induce hypoglycemia in dogs

Glargine

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- **Cats:** Very conservative starting dose, safer once daily at start however most will require twice daily
- 0.25-0.5 IU/**CAT** either once or twice daily
- More aggressive dosing at some institutions
  - 0.5 IU/**kg** lean weight if blood glucose ≥ 20 mmol/l or 0.25/**kg** if blood glucose is < 20 mmol/l
- Cannot dilute
- Should not change dose in first week, other than reduction if hypoglycemia

Detemir U-100

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- Acylated fatty acid results in reversible binding of insulin to albumin
- Result is slow release of bound fraction, resulting in peakless insulin secretion
- Diluent available from manufacturer, although hard to obtain in North America

Onset of action	~3 hours (cats)
Maximum effect	8 – 12 hours (cats)
Duration of action	10 – 24 hours (cats)

Detemir

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Cats:

- Published abstract (ACVIM 2009) indicated similar action to glargine
- Lower doses needed when compared with glargine
- Potential for hypoglycemia, need to be very conservative with dosing and start once daily
- Reserve for refractory cases
- Starting dose of 0.25 IU/**CAT** once daily, may require twice daily
- More aggressive protocol of 0.25 IU/kg twice daily

Detemir

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Dogs:

- Detemir not recommended in dogs
  - Lack of published data
- Anecdotal reports claim detemir is ineffective in treating diabetic dogs
- Long duration of action and potency could induce hypoglycemia in dogs
- Last resort if all other insulins fail
  - start at very low dose (0.1 IU/kg q24h)
  - gradual, cautious increase
  - may require twice daily dosing

ProZinc U-40

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- Developed to prolong the effects of regular insulin
- Long-acting recombinant human insulin
- Contains insulin, zinc, protamine (fish protein)
- Forms poorly soluble precipitates which extends duration

Onset of action	1 - 4 (cats)
Maximum effect	4 – 12 hours (cats)
Duration of action	12 – 24 hours (cats)

ProZinc

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Cats:

- Starting dose 0.2-0.5 IU/kg once daily
- 25% cats successfully managed with once-daily injections of ProZinc
- Now available in Canada
- Cannot dilute, always round down

ProZinc

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- No studies evaluating ProZinc insulin in dogs
- Long-acting insulin so not recommended as a first line choice insulin in diabetic dogs
  - Duration of action likely too long and risk of causing hypoglycemic episodes
  - The manufacturers of ProZinc report currently investigating its use in dogs
    - May become viable option for management of diabetic dogs in future

Monitoring

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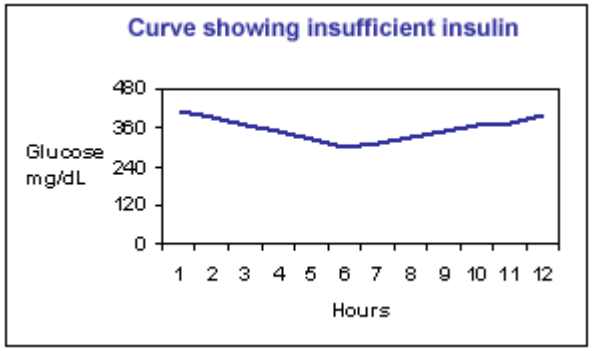
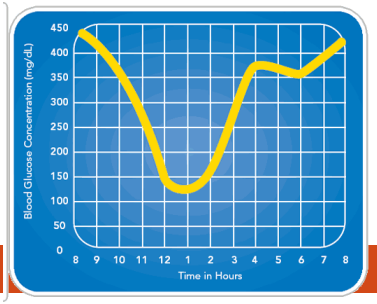


Monitoring



- Marked variation in insulin kinetics, makes monitoring crucial

- Including
  - Assessing clinical signs
  - Serial blood glucose curves
    - Either in hospital or at home
  - Continuous subcutaneous glucose measurements
  - Measuring serum fructosamine concentrations
  - Monitoring presence and degree of glucosuria

Clinical signs

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- Most important monitoring tool
- Remember first goal of insulin therapy is to improve or resolve owner-observed signs
- Best assessment of success of insulin therapy
- If complete resolution of clinical signs, ensure hypoglycemia is not occurring

Glucose Curves

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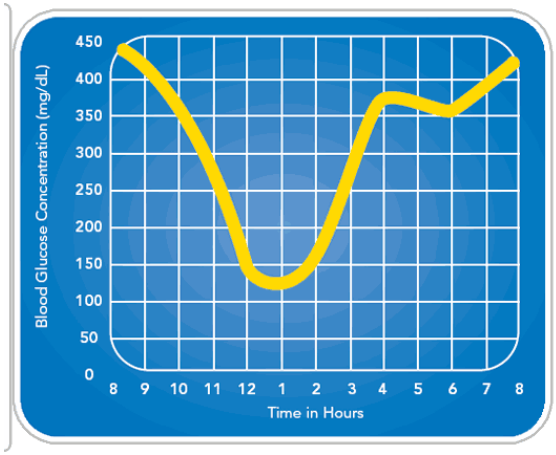
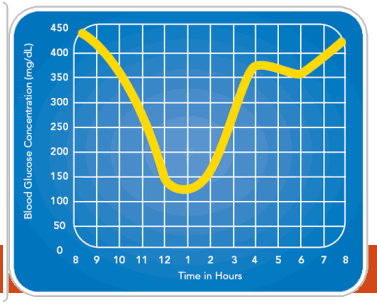
- Long been gold standard
- Glucose curves demonstrate
  - Insulin effectiveness
  - Time to peak effect
  - Duration of effect
  - Blood glucose nadir
  - Degree of blood glucose fluctuation
- Identify Somogyi effect if present
  - Hypoglycemia-induced hyperglycemia

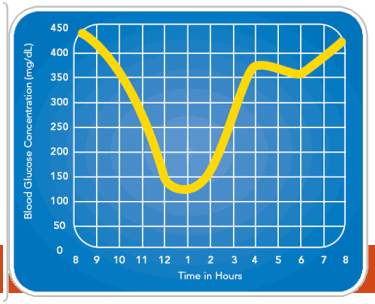


Glucose Curves



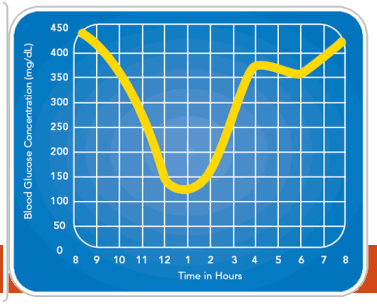
- Maintain normal feeding/insulin schedule
- Ideally, [glucose] should nadir at 5.5-8.5 mmol/L in dogs & 7-10 mmol/L in cats
- Highest [glucose] (peak) < 14 mmol/L in dogs & 17 mmol/L in cats
- Usually require glucose measurements every 2-4 hours, depending on insulin type
  - Every 2 hours for NPH, Caninsulin
  - Every 4 hours for glargine, detemir, ProZinc
- Up to every 30 minutes if looking for Somogyi

Glucose Curves



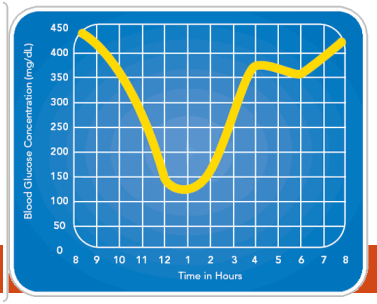
- Ideally 7-10 days after insulin dose change
- Next day if hypoglycemia is a concern
- When you assess BG curve ask three basic questions
  - Has insulin decreased [BG]?
  - If so, what was the nadir?
  - How long has insulin lasted?
- The answers will help you make logical changes in dosing regimen

Glucose Curves



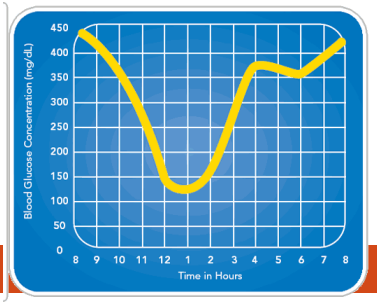
- Measure blood glucose levels for one interval between injections
  - 12 hours if insulin twice daily (some need 24 hr curve)
  - 24 hours if insulin once daily
    - If impossible to obtain 24 hour curve, can start with a 12 hour curve
- If BG <7 mmol/L, measure hourly
- Maintain as normal an insulin and feeding schedule as possible
- If patient does not eat normal amount of usual food at usual time, postpone curve

Glucose Curves



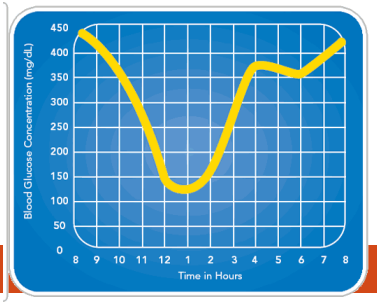
- Perform curves on first day after you initiate or change insulin therapy if you suspect hypoglycemia may occur
- If patient develops hypoglycemia, decrease insulin dose 25%
- Perform another curve following day to check for hypoglycemia
- Do not increase insulin dose based on first day's curve regardless of values

Glucose Curves



- Always interpret results in light of clinical signs
- Curves vary from day to day
  - Stress hyperglycemia can falsely elevate
  - Refusal to eat in hospital can falsely decrease
- If patient not polyphagic, polydipsic, or polyuric & body weight is stable or increasing, you've likely achieved good diabetic control

Glucose Curves



- If no acceptable nadir, adjust insulin dosage
  - Usually dose changes of about 10% are appropriate, more caution with glargine and detemir
- No matter what other [BG], if the nadir <4.5 mmol/L, decrease the dose by 25%
  - When decrease dose because of hypoglycemia, perform a curve the following day
    - Ensure hypoglycemia does not recur
- If hyperglycemia is the issue, repeat curve 7 - 10 days after insulin dose adjustment

BG Curves & Glargine

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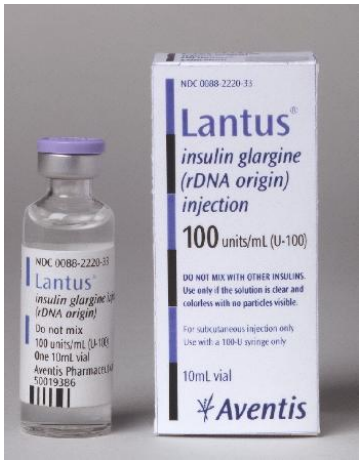
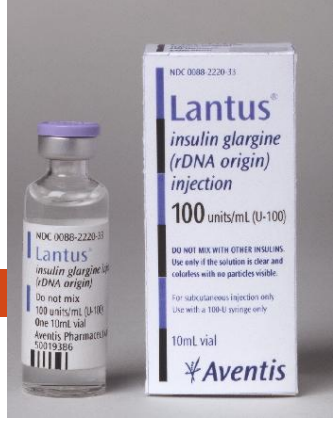
- Interpret blood glucose curves & adjust doses differently than for other insulin types
- Recommendations for dose adjustments are based on pre-insulin blood glucose concentration
  - Compared to other insulins where dose is altered based on the nadir
- Ensures not substantial overlap from the previous injection
  - Minimize the likelihood of causing hypoglycemia



BG Curves & Glargine



- Pre-insulin BG >16 mmol/L
  - Increase glargine dose by 0.25 IU/cat
- Pre-insulin BG 12-16 mmol/L
  - Dose not changed
    - In either of these first 2 scenarios, perform curve to ensure no hypoglycemia
- Pre-insulin BG 4.5-10 mmol/L
  - Dose decrease 0.5 IU/cat
- Biochemical hypoglycemia (BG <4.5 mmol/L) without C/S
  - Dose decrease 1 IU/cat or more

BG Curves & Glargine

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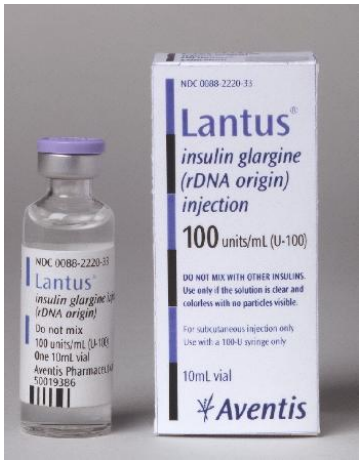
- If clinical signs of hypoglycemia present
  - Dose decrease to 0.25 IU/cat, or at least by 50%
- Do not discontinue within 2 weeks of starting treatment even if normoglycemia present
  - Decrease dose if needed, but do not stop

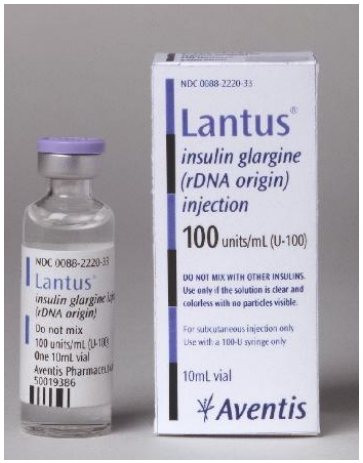


BG Curves & higher dose Glargine

- Perform 12-hour blood glucose curves for the first 3 days after initiating insulin treatment unless starting at very low dose (0.25-0.5 IU/cat)
  - Detect hypoglycemia, if present
    - Decrease dose as needed
  - Many cats require dose reduction within the first three days of glargine treatment
- After first three days, discharge & have return for BG curve in 7 days
- Perform subsequent BG curves at one, two, and four weeks, then PRN to monitor control

BG Curves & low dose Glargine

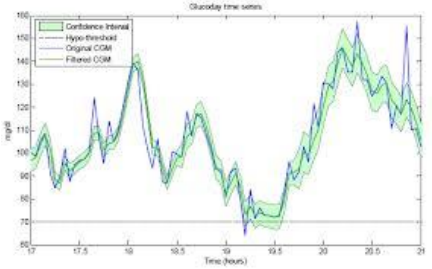
- First glucose curve at 7-10 days
- Follow recommendations for typical monitoring
- Counsel owners about clinical signs of hypoglycemia



At Home Monitoring - Curves

- Allows you to maintain diabetic control
- At-home-generated glucose curves could help avoid some problems associated with in-clinic curves
  - Stress-induced hyperglycemia
  - Patients not eating
- Venous blood not necessary
  - Capillary blood is suitable
- Many studies show owners willing, able generate accurate at-home serial curves

Continuous SQ glucose curve



- Small electrode inserted in SQ, measures interstitial glucose concentrations which correlates closely to blood glucose
- Reading every 5 minutes sent to wireless monitor (must be within 2 metres of animal)
  - Attached to animal with jacket
  - Hung on cage door in hospital
- New models display results in real time on monitor
- Provides an on-going picture of glucose levels
- Currently use not permitted in pets in Canada

Fructosamine

- Glycated proteins synthesized from irreversible binding of glucose
- Reflects mean glucose concentration in past 1-2 weeks
- Good for long term monitoring once stable
- Not affected by acute stress hyperglycemia
  - 360-450 umol/L good control
  - 450-550 umol/L moderate control
  - >600 umol/L poor control
- Hypoproteinemia and hyperthyroidism can lower fructosamine levels

Urine glucose sticks

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- Monitoring that can be performed at home
- Should not alter insulin dose based on urine glucose
- Persistent glucouria indicates the need for further evaluation of blood glucose levels

Typical Monitoring Regime

- Evaluate at one week
  - Feed animal at home then bring immediately to clinic
  - Discuss history, resolution of clinical signs
  - Blood glucose curve, measure BG every 1-2 hours
  - Fructosamine level can also be performed
  - Adjust insulin by 0.5-1 IU if required, adjust by 0.25 IU if glargine
  - Adjust frequency if necessary

Typical Monitoring Regime

- Re-evaluate at 3 weeks
  - Vital signs, weight, glucose curve
  - Discuss at home monitoring
- Re-evaluate at 6-8 weeks
  - Vital signs, weight, glucose curve
  - May not need glucose curve if clinical signs indicate control
  - Otherwise aim for pre-insulin BG of 10-15 mmol/L and fructosamine of 350-450 umol/L
- Re-evaluate at 10-12 weeks, base monitoring on response to therapy
- Re-evaluate every 4 months

Goals

- Marked improvement of, or resolution of, PU/PD and polyphagia
  - Ensure no hypoglycemia if complete resolution
- Normalization of body weight
- BG between 15 mmol/L pre insulin to 5 mmol/L at nadir
  - Do not adjust insulin if these BG targets are not met but the animal is clinically doing well
- Fructosamine between 350-450 umol/L

Reasons for poor control

1. Technical problems
   a. Errors in handling, shaking, diluting, freezing, heating, outdated insulin, drawing up air, poor injection technique, wrong syringe
2. Insulin underdose
   a. Consider if insulin dose ≤ I IU/kg unless glargine
3. Insulin overdose and possible Somogyi Phenomenon
   a. Suspicious if owners report days that seem well controlled then days that are poorly controlled
   b. Suspect if higher dose insulin with persistently elevated glucose levels (> 1.5 IU/kg q12h)

Reasons for poor control

3. Short duration of insulin effect
    a. Can be seen with twice daily insulin therapy, especially in cats with Caninsulin
    b. Perform glucose curve to evaluate
    c. Fructosamine usually moderately to severely elevated
4. Prolonged duration of insulin effect
    a. Not usually an issue with NPH or Caninsulin
    b. Can be seen in glargine used twice daily
5. Impaired absorption of insulin
    a. Rarely occurs, avoid by rotating sites (thickened skin)
    b. Consider if dehydrated, poor circulation

Reasons for poor control

6. Binding of insulin by antibodies
    a. Amino acid sequence differs from human, porcine and bovine insulin
    b. Can result in production of anti-insulin antibodies
    c. Requirement for insulin extremely high
    d. If insulin dissociates from antibody, result in erratic insulin need
    e. Present in 14-37% of cats, but no correlation to glycemic control
    f. Likely not a factor in almost all cases
    g. Potentially more of a concern in dogs receiving beef source insulin

Reasons for poor control

7. Concurrent disorders
   a. Result is insulin resistance (>1.5 IU/kg unless glargine/detemir)
   b. Inflammatory, neoplastic, endocrine, drug use, infectious
      - Obesity
      - Chronic renal failure
      - Pancreatitis
      - Stomatitis, urinary tract infection
      - Hyperadrenocorticism
      - Hyperlipidemia
      - Acromegaly in cats
      - Inflammatory bowel disease
      - Hyperthyroidism/hypothyroidism

Stepwise work up – poor control

1. Review previous work up and therapy
2. Determine whether insulin is outdated, has been shaken, diluted, frozen, heated;
3. Review that correct syringes are being used
4. Assess owner's method of drawing up insulin
5. Review diet and exercise regime
6. Increase insulin dosage every 5-7 days until 1 IU/kg q12h
7. Generate glucose curves to assess for Somogyi phenomenon
8. Diagnostic work up for diseases causing insulin resistance
9. Switch insulin type

Switching insulin types

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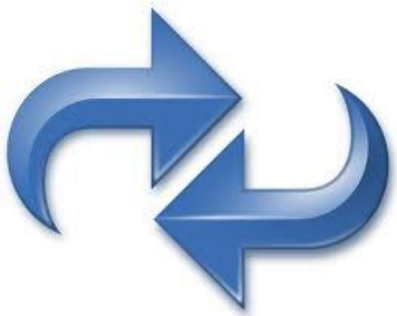
- Start as if newly diagnosed, based on recommended doses listed
- Ensure diet and exercise strategies are adequate
- If transitioning due to inability to obtain current insulin type (for example Caninsulin backorder), dose of new insulin should be 75% of current insulin dose
- Need to reduce further if using an insulin prone to cause hypoglycemia (glargine, detemir)



Diabetic remission

- Resolution of clinical signs, normalization of blood glucose levels and fructosamine without therapy for one month
- Most likely to occur if rapid therapy for DM started early on, to reduce length of glucotoxicity and lipotoxicity
  - Damaging effect of chronic hyperglycemia on beta cells, and effect of increased use of fatty acids by beta cells
- Usually occurs within first 3 months of starting therapy
- Occasionally seen after more than a year
- Viability of beta cells may not fully recover, number of beta cells likely also permanently reduced
  - Pre-diabetic state
- Counsel owners to watch for recurrence of clinical signs

Diabetic remission

- Positive predictors of diabetic remission
  - Strict glycemic control
  - Administration of corticosteriods prior to diagnosis
  - Absence of polyneuropathy
  - Older age
  - Use of glargine
- Negative predictors of diabetic remission
  - Elevated cholesterol
  - Elevated urea and bilirubin
  - Anemia

Diabetic remission

- Predictors not related to remission
  - Glucose concentration
  - Fructosamine concentration
  - Serum concentrations of insulin, glucagon, insulin growth factor-1
  - Age
  - Sex
  - Body weight
  - Renal failure
  - Hyperthyroidism
  - Ketoacidosis
  - Presence of concurrent diseases

Future Directions

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- **External continuous insulin delivery systems** have been used in human diabetic patients
- A recent review did not find strong evidence that this system was superior to multiple daily injections
- Benefits – more discreet, less labour intensive
- Disadvantages – increased cost, malfunction leading to DKA, scarring at injection site, have to avoid water activities, still requires blood glucose monitoring and uploading information, security flaw noted (can wirelessly hack into system and change insulin delivery dosage)

Future Directions

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The "Artificial Pancreas":

- **Implantable continuous insulin delivery systems** that deliver insulin based on an internal glucose monitoring system
- **Bio-artificial pancreas** consisting of a sheet of encapsulated ß cells that when surgically implanted, exist as an endocrine pancreas
- Introducing a **genetically engineered virus** which causes a DNA change of intestinal cells to become insulin-producing cells

Future Directions

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Implantable closed loop continuous insulin delivery

- Medtronic has a promising system in development
- An implanted sensor in the jugular vein transmits blood glucose levels to an implanted insulin pump
- The system improved the amount of time blood glucose levels were normal, and reduced hypoglycemic events
- The insulin pumps last for an average of eight years
- The sensors last for an average of nine months

Future Directions

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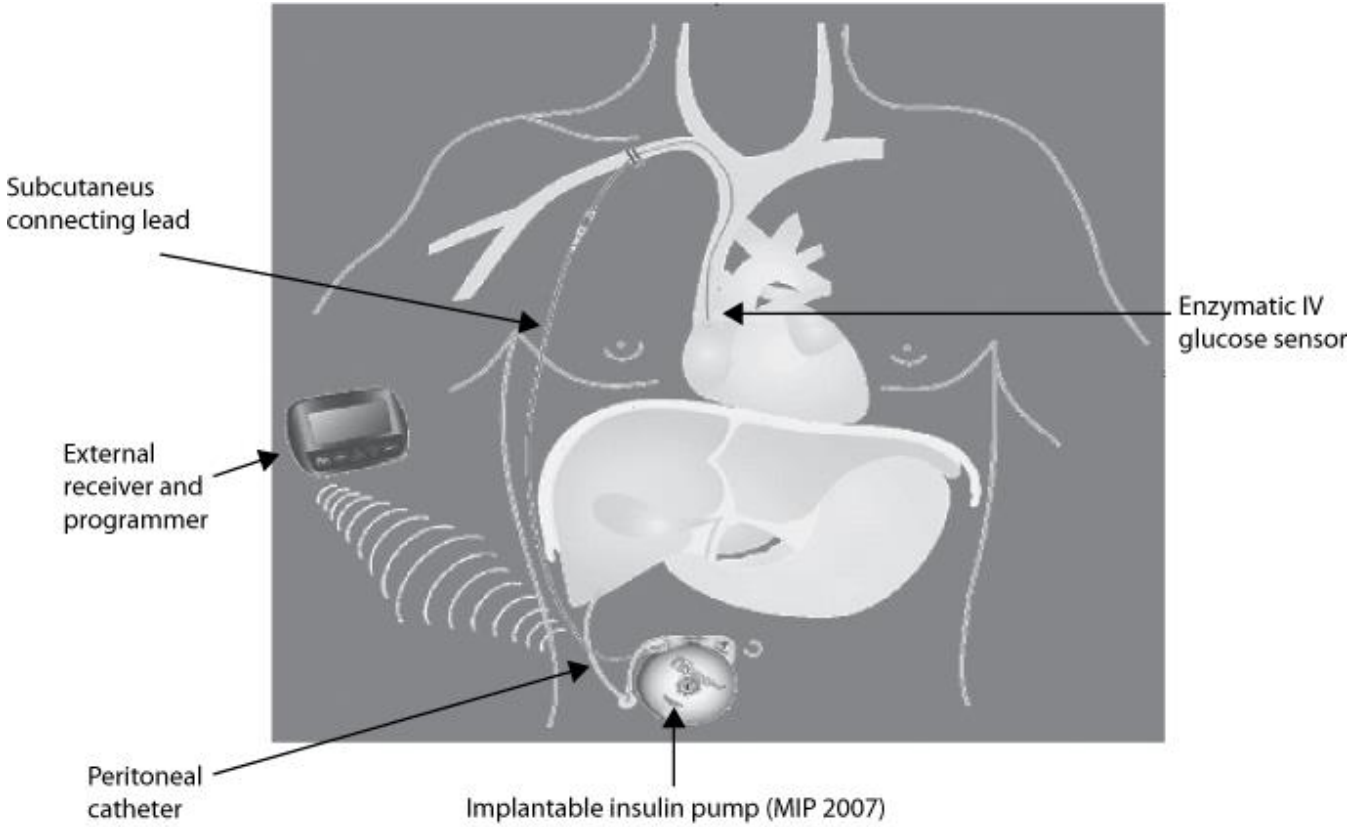

Figure 1. Scheme of human implantation of the Long-Term Sensor System® (LTSS, Medtronic-MiniMed), a prototype of implantable artificial beta-cell.

http://www.aidia.cz/tag/minimed/

Future Directions

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Stem cell therapy

- Use of stem cells to produce new pancreatic cells that are capable of producing insulin
- Need to also stop destruction of new pancreatic cells, therefore suppression of immune system required in patients where immune-mediated destruction is suspected
- Promising results in early studies

Questions?

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