INSULIN THERAPY OPTIONS
AND CASE STUDIES OF
DIABETIC CATS AND DOGS

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Overview

- Pathophysiology
- Diagnosis
- Treatment
- Follow-up care, in-clinic & at-home monitoring
- Case examples

Notes available:
www.vetemergency.ca
Pathophysiology

- Insulin is produced by the beta cells within the islets of Langerhans in the pancreas.
- Lack of insulin results in the inability to uptake glucose from the blood into cells.
- Result is hyperglycemia with glucose-starved cells.
- Renal tubular threshold for glucose is exceeded, resulting in polyuria due to glucosuria.
- Polyphagia due to starvation of cells and inability of glucose to enter satiety centre.
Diagnosis

- Presence of significant hyperglycemia with glucosuria

- 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 diabetes mellitus in complicated cases
Therapy
Goals of Therapy

- Reduce or eliminate owner-observed clinical signs
  - Polyuria and polydipsia most obvious change and easy to monitor
  - Polyphagia
- Prevent chronic complications of diabetes mellitus
Diet and Exercise

- Obesity results in insulin resistance
- Weight loss can improve insulin sensitivity
- Essential to
  - Promote weight loss in all obese patients
  - Prevent obesity in patients with ideal body condition
Insulin Therapy
Goals of Insulin Therapy

- Prevent
  - Detrimental effects of hyperglycemia
  - Development of ketoacidosis
  - Hypoglycemia

- In some cases
  - Reversal of diabetic state
  - These cases likely return to a prediabetic state so diabetes mellitus may recur
Treatment Strategies

- 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
Insulin

- Should be started immediately in all dogs and probably all cats
- Almost all dogs and most cats will require twice daily dosing
- Ideal goal - maintain blood glucose as close to physiologic levels as possible
  - Difficult to do, as administered as 1-2 large daily doses, not in response to blood glucose
- Realistic goal = eliminate clinical signs
Insulin Products

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

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

- 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
  - Intermittent IM – 0.1 to 0.2 IU/kg q1-4 hours
  - Intermittent SQ – 0.25 IU/kg q4-6 hours
    - Adjust based on serial measurements of blood glucose concentration
Short Acting Insulin

- 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

- 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

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

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<tr>
<td><strong>Onset of action</strong></td>
<td>½ - 2 hours (dogs)</td>
<td>&lt;1 hour (cats)</td>
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<td><strong>Maximum effect</strong></td>
<td>3 hours (dogs)</td>
<td>3 – 5 hours (cats)</td>
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<td><strong>Duration of action</strong></td>
<td>8 hours (dogs)</td>
<td>8 – 12 hours (cats)</td>
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Caninsulin

- 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

- Able to dilute if needed
- Only available from vet clinics — encourages monitoring
- Previous concern with back-order resolved
Caninsulin - VetPen™

- Only insulin pen designed for pets
- VetPen™ may minimize pet discomfort
  - 42% of cat owners reported that the cat’s response to injections improved after switching to VetPen™
- Some pet owners may find it less intimidating than a conventional insulin syringe
- It is likely to provide more accurate dosing consistently
- Can keep at room temperature for 28 days (vial labeled for 6 weeks)
NPH U-100

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

Onset of action: $\frac{1}{2} - 2$ 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)
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

- 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

- Good first choice in cats
- Glargine not recommended in dogs
  - 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

- **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

- Should not change dose in first week, other than reduction if hypoglycemia.
ProZinc U-40

- 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

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

- No studies evaluating ProZinc insulin in dogs
- Long-acting insulin so not recommended as a first line choice 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
Detemir U-100

- 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 apparently very 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

**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

**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
Degludec – 100 and 200 IU/ml

- Insulin degludec (Tresiba)
  - Similar properties to glargine and detemir
  - Very new insulin, no studies yet in animals
Treat concurrent diseases

- Antibiotics for urinary tract infection
- Therapy for stomatitis (cats)
- Pancreatitis
- Cardiac disease
- Difficulties obtaining definitive diagnosis:
  - Hyperadrenocorticism
  - Renal disease
Monitoring
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

- 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
At Home Monitoring - Curves

- 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 and able to generate accurate at-home serial curves
Glucose Curves

- 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, blood glucose should nadir at 5.5-8.5 mmol/L in dogs & 7-10 mmol/L in cats
- Highest blood 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
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

- Monitoring that can be performed at home
- Should not alter insulin dose based on urine glucose
- Persistent glucosuria indicates the need for further evaluation of blood glucose levels
- High proportion of day with no glucosuria suggests periods of hypoglycemia
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
Complications of Insulin Therapy

- **Hypoglycemia**
  - Complication of insulin therapy
  - Counsel owners on clinical signs, appropriate emergency therapy
  - Reason why we don’t achieve perfect glycemic control

- **Stress hyperglycemia in hospital**
  - Assumption of poor control
  - Inappropriate increase in insulin dose
  - Can lead to Somogyi phenomenon and vicious circle
Switching insulin types

- Start as if newly diagnosed, based on recommended doses listed
- Ensure diet and exercise strategies are adequate
- Need for extra caution if using an insulin prone to cause hypoglycemia (glargine, detemir)
Prognosis

- Depends on owner commitment
- Mean survival time from diagnosis in dogs is 2-3 years
- Skewed by older population of pets, often succumb to other diseases
- Higher mortality rate in first 6 months, better longevity if stable after 6 months
- May be closer to mean survival time of 5 years if survive the first 6 months
Cases - Snooky

- 4 yo MN Miniature Poodle
- Diagnosed with DM in October 2010
- Initial diagnostics normal other than hyperglycemia and glucosuria
- Started on Caninsulin 2 units q 12 h
- No change in PU/PD
- Glucose curve revealed hyperglycemia, Caninsulin increased to 3 units q12h
- No change in PU/PD
Cases - Snooky

![Graph showing the number of cases over time from 8:00 AM to 8:00 PM. The graph indicates a peak around 11:00 AM and a decline around 2:00 PM.]
Nadir too high
Duration inappropriate
Options:
- Increase dose
- Give three times daily
- Change insulin

Elected to change insulins given short duration of Caninsulin, started on 3 IU q12h of NPH
Cases - Snooky
Cases - Snooky

- Nadir too high
- Duration appropriate
- Options:
  - Increase dose
- Elected to increase NPH, increased to 5 IU q12h
Cases - Snooky
Cases - Snooky

- Appropriate nadir and duration
- Clinical signs resolved
- Appropriate diet and exercise regime
- Continue to monitor
Cases - Bruno

- 4 yo MN DSH
- Diagnosed with DM in January 2011
- Initial diagnostics normal other than hyperglycemia and glucosuria
- Started on Caninsulin 7 units q 12 h
- Switched to Hill’s w/d diet
- No change in PU/PD
- Regained all weight, now 3 pounds over previous stable weight
Cases - Bruno

- Additional detailed history from owner
- Has 3 other cats, two of which are on free choice food
- Third cat has special diet, however Bruno often chases him away and eats his food
- He is steadily gaining weight
- He used to play all the time, since diagnosis the owner does not play with him due to his disease, tries to keep him quiet
Cases - Bruno

- Additional diagnostic testing
- Repeat blood work (4 months after diagnosis) showed hyperglycemia and glucosuria, remainder normal
- Urine culture negative
- Remainder of diagnostic testing normal
Cases - Bruno

- Potential causes of insulin resistance in Bruno
  - Obesity
  - In appropriate diet and feeding
  - Lack of exercise

- How well is our insulin working currently?
  - Glucose curve
Glucose curve reveals a Somogyi phenomenon

Plan for Bruno

- Reduce insulin by 25%, from 6 IU q12h to 4 IU q12h
- Glucose curve the following day
- Address diet and obesity
- May need a switch in insulin depending on response, next choice would be glargine
Cases - Kirby

- 9 yo MN Bichon Frise
- Diagnosed with DM November 2010
- Initial diagnostics revealed hyperglycemia, lipemic serum, glucosuria
- Started on Caninsulin 3 units q 12 h
- No change in PU/PD
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Switched to Caninsulin 4 units q 12 h
- No change in PU/PD
- Fructosamine 689 umol/L
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Switched NPH 2 units q 12 h
- No change in PU/PD
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Switched NPH 3 units q 12 h
- No change in PU/PD
- Fructosamine 700 umol/L
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Appropriate diet, insulin technique, exercise, no evidence of concurrent disease
- Owners contemplating euthanasia
- Switched to detemir 1 unit q 12 h
- Marked improvement in PU/PD
- Glucose curve:
Cases - Kirby
Cases - Kirby

- Increased detemir to 2 units q 12 h
- Owners very happy with current clinical status
- Fructosamine 467 umol/L
- Glucose curve:
Cases - Kirby

![Graph showing cases over time in Kirby]
Cases - Kirby

- Not perfect control due to hyperglycemia prior to insulin administration
- Reasonable control, especially for a refractory case with no obvious cause for insulin resistance
12 yo 5 kg MN Miniature Poodle

Diagnosed with DM in September 2010

Initial diagnostics revealed hyperglycemia, moderate increase in ALP and ALT, lipemic serum, glucosuria, proteinuria

Started on Caninsulin 1 unit q 12 h

No change in PU/PD

Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 2 units q12h

No change in PU/PD
Cases - Precious

- Increased Caninsulin to 3 units q 12 h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 4 units q12h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 5 units q12h
- No change in PU/PD
Cases - Precious

- Increased Caninsulin to 6 units q 12 h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 7 units q 12 h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 8 units q 12 h
- No change in PU/PD
- Glucose curve revealed persistent hyperglycemia, Caninsulin increased to 9 units q 12 h
- No change in PU/PD
Cases - Precious
Cases - Precious

- Level of insulin would indicate insulin resistance
- Repeat blood work revealed stable elevation in ALP, ALT, proteinuria
- Urine culture negative
- Mild dental disease
- Thoracic radiographs normal
- Abdominal ultrasound:
Cases - Precious
Cases - Precious

- Right adrenal mass present
- Diagnosed as functional adrenal tumour with provocative testing
- Increased glucocorticoid from functional adrenal tumour causing insulin resistance
- Recommended therapy for right adrenal mass
Questions?