

InTown Veterinary Group Newsletter

Volume 9, Issue 4
September 2009

InTown Veterinary Group is dedicated to providing referring veterinarians and their clients with an unparalleled range of emergency & specialty services.

Services:

Acupuncture:

Essex Referral, N. Andover, MA
Mass Vet, Woburn, MA

Behavior Services:

Essex Referral, N. Andover, MA
Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

Cardiology:

Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

Dermatology:

Mass Vet, Woburn, MA

Emergency/Critical Care:

Essex Referral, N. Andover, MA
Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

Internal Medicine:

Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

Neurology:

Mass Vet, Woburn, MA

Ophthalmology:

Essex Referral, N. Andover, MA
Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

Physical Therapy & Rehabilitation:

Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

Radiology:

Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

Surgery:

Essex Referral, N. Andover, MA
Mass Vet, Woburn, MA
Port City Vet, Portsmouth, NH

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Upcoming Doctor & Tech Continuing Education Lectures:

Lectures for the year are updated on our website. You can now also register to attend online at your convenience.

Doctor Lectures:

Please refer to www.InTownVet.com for dates, times, locations & to register to attend.

Sept. 3: Treatment of Elbow Osteoarthritis in Dogs, Lauren Blaeser, DVM, DACVS

Sept. 16: Keratoconjunctivitis Sicca (KCS) in Dogs and Cats, Nancy Cottrill, DVM, DACVO

Oct. 13: The Role of Physical Therapy and Rehabilitation in Veterinary Medicine, Charlie Evans, MPT, CCRP

Veterinary Technician Lecture:

Please refer to www.InTownVet.com for dates, times, locations & to register to attend.

Sept. 15, 16, 17: A Primer on Canine Behavior & Body Language, Kati Wrubel, PhD.



New Online Radiology Interpretation Service now Available:

We now provide an online digital radiograph interpretation & data back up service for your hospital. If you already have digital radiography, or are considering upgrading your equipment, this service will be an excellent (and easy to use) addition to your practice. Go to www.InTownOnline.com for more details, a handy how-to guide and pricing information.



Hospital Information:

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No Silver Bullets

John MacGregor, DVM, DACVIM (Cardiology)

Magic doesn't exist. Starting an article like that might make the reader think I don't like Harry Potter books or the tooth fairy. In fact, I do like the Harry Potter books and have nothing particularly against the tooth fairy, the Easter bunny or even Santa Claus (despite the fact that a man sneaking into my house at night wearing red pants is creepy). Medicine is replete with stories about miracle cures for diseases and fabulous tests that will detect disease before it even gets started. However, miracle cures, all knowing tests and magic don't exist in veterinary medicine.

Congestive Heart Failure

Pimobendan is the latest in a long line of medications in veterinary medicine that have been proclaimed to be the "it" drug, (see Enalapril for cardiac drugs, Rimadyl® for pain management, etc). The tendency for any new, useful medication is to use it as initially indicated and then expand that out to patients for whom it was not initially indicated. Eventually, complications and contra-indications become well publicized and the medication falls in amount of use.

Pimobendan is a medication that is newly licensed in the United States for treatment of congestive heart failure in dogs. It is a phosphodiesterase inhibitor that has calcium sensitizing properties and acts as an ion dilator in the canine heart and vasculature. This means that pimobendan increases the strength of contraction in the heart but also causes vasodilation. The vasodilation is a key property of pimobendan as previous studies with inotropic agents such as amrinone and milrinone had almost universally led to early death. It also has antiplatelet properties and decreases white blood cell aggregation.

Pimobendan has proven to be very effective in treating cases of canine congestive heart failure. Numerous studies have proven a survival benefit to Pimobendan in cases of heart failure due to both mitral valve disease and dilated cardiomyopathy. More recently, it has been shown to be beneficial to patients with pulmonary hypertension. This is not a surprise as it is in the same family (phosphodiesterase inhibitor) as the leaves that indigenous people in the Andes chew to combat pulmonary hypertension. It has also been shown to be superior to several angiotensin converting enzyme inhibitors (ACE) inhibitors but the really useful trial comparing effect of pimobendan plus an ACE inhibitor to either one separately has not been done.

The other unknown about pimobedan is its benefit for dogs that are not in heart failure. Here, veterinary medicine should be taking heed of the cautionary tale of Enalapril and other ACE inhibitors. Enalapril had been shown to prolong survival in dogs with congestive heart failure. One study and a case report of two dogs with mitral valve disease demonstrated worsening of regurgitation and another showed no benefit to starting early. However, to date, no studies have been published looking at its use in dogs with dilated cardiomyopathy prior to the onset of congestive heart failure. In human literature, dilated cardiomyopathy is treated with beta blockers instead of alternatives that make the heart beat more vigorously.

Pimobendan is also being used to treat cats in congestive heart failure. This is an off labeled use of Pimobendan (as is its use in canine patients that are not in congestive heart failure) but the rationale for its use is similar to its use in dogs. Cats with reduced systolic function and congestive heart failure (such as cats with restrictive cardiomyopathy, dilated cardiomyopathy and unclassified cardiomyopathy) can benefit from increased contractility and vasodilation. An echocardiogram should always be performed prior to administering it in cats as one of the primary contra-indications for the use of Pimobendan is cardiac hypertrophy or obstructive disease.

To summarize, Pimobendan is a very effective medication for treatment of dogs in congestive heart failure and has utility in patients with pulmonary hypertension. Use of Pimobendan in canine patients that are not in congestive heart failure has not been demonstrated to be beneficial and some studies have suggested that it may be harmful to the patients. While no studies to date have demonstrated its efficacy in cats in congestive heart failure, there are no studies that have demonstrated a negative effect either, so it can be used under the supervision of a cardiologist.

Blood Tests for Heart Disease

The other newest, biggest development in veterinary cardiology is a blood test called NT pro-BNP, that can detect heart disease. (B)rain (N)atriuretic (P)eptide is a hormone that is generally produced by atrial stretch. BNP has physiologic effects including promoting the excretion of sodium, decreasing vasoconstriction and decreasing production of vasoactive substances. Ventricular stretch causes significant upregulation in synthesis and release of BNP and therefore BNP can be a useful test to determine whether significant heart disease is present. BNP is cleared by C-type Natriuretic Peptide Receptor, its relatively short half life makes it difficult to measure. In people it has a half-life of 12 minutes, in dogs it is even shorter at 1.5 minutes. However, BNP starts as a prohormone and breaks down into the active portion (BNP) and the inactive end (The N terminal end) in a 1:1 ratio. The NT end (NT proBNP) is more stable and can be measured. It is cleared by the kidneys and canine and feline studies have focused on NT pro-BNP as a potential test for patients with cardiac disease.

Human studies have shown BNP and NT proBNP to correlate with severity of heart disease and to be predictive of the development of clinical heart disease. It has also been shown to guide therapy and predict mortality. In dogs and cats studies have shown that the level of NT proBNP also correlates to severity of heart disease. The levels are elevated in patients with dilated cardiomyopathy, myxomatous valvular disease and hypertrophic cardiomyopathy. NT proBNP levels also correlate with the New York Heart Association heart failure scores and International Small Animal Cardiac Health Council heart failure scores. In addition, BNP can predict with fairly good sensitivity and specificity whether an animal has respiratory difficulty due to heart disease or respiratory disease.

Another area where the test may prove useful is in screening animals for occult disease. BNP and NT proBNP are elevated in animals with occult disease as well as clinically evident disease. Therefore, if an asymptomatic feline patient shows elevated NT proBNP levels, an echocardiogram could help determine whether occult hypertrophic cardiomyopathy is present. Unfortunately, the test has only reliably detected severe HCM and could not distinguish between normal cats and those with mild or moderate HCM in a recent paper. The test could be similarly used in Doberman Pinschers, however, the reference ranges have not been calibrated for this use yet.

The NT proBNP test should be particularly useful in cats with respiratory difficulty. Cats with respiratory difficulty can be difficult to diagnose with thoracic radiographs and echocardiography is not always readily available. This can lead to difficulty in establishing a cause for the respiratory difficulty and can lead to delays in treatment or even the wrong treatment. This does not apply to cats with pleural effusion as the correct course of treatment is almost always thoracocentesis unless a definitive diagnosis of congestive heart failure has been established. The NT proBNP test was found to be quite specific and sensitive in distinguishing the cause of respiratory difficulty in feline patients with acute dyspnea; sensitivity and specificity were 90% and 88% respectively.



A blood test called NT pro-BNP can detect heart disease.

However, NT proBNP will not take the place of radiographs in dogs and a complete cardiology exam in cats. The cases selected for most of the studies above did not include indications that

would make the data messy. Renal dysfunction can increase levels of NT proBNP (although not in a predictable fashion) and pulmonary hypertension from non cardiac causes can elevate levels as well. In addition, the test is not a bedside test, so its utility is quite limited when you have a severely dyspneic animal on the exam table in front of you as you will not be able to wait 24 hours for test results. In addition, the gold standard for diagnosis of congestive heart failure in the canine patients was radiographic evidence for many cases and this is readily available in most veterinary practices. In feline patients, radiographs are less helpful but the NT proBNP levels were elevated in patients with breathing difficulty due to respiratory disease that had concurrent thyroid or cardiac disease. Additionally, although there is good sensitivity and specificity, in 8-15% of cases, the wrong diagnosis will be reached by relying solely on the NT proBNP test. This is a significant proportion when one considers that the patient in question is dyspneic and the wrong medications could prove lethal. All things considered, the NT proBNP test is useful but its findings need to be verified by radiographs and echocardiography to ensure that the NT proBNP derived diagnosis is accurate.

Therefore, it is with sadness that I must conclude that there are no "magic" therapies for veterinary cardiac patients and no all knowing diagnostic tools either. All medications and tests need to be considered part of the arsenal of diagnostic and therapeutic tools that are invariably best utilized in conjunction with one another. ■

References Available upon Request



An Introduction to New Types of Insulin and Continuous Glucose Monitoring

Marion Haber, DVM, DACVIM

Introduction to New Types of Insulin

Insulin therapy along with dietary management is the most common treatment to establish glycemic control and ideally diabetic remission, in patients with diabetes mellitus. Difficulty in achieving diabetic control has often been due to inconsistent insulin absorption as well as inadequate duration of effect. Choosing the appropriate type of insulin is dictated in part by the species of origin of the insulin itself (feline insulin is most similar to bovine insulin whereas canine insulin is most similar to porcine insulin). However, the availability of animal-derived insulin has recently become another obstacle in the management of diabetic patients. The manufacturer of PZI-VET discontinued production of this insulin due to a lack of readily available animal-derived products and the cost of manufacturing. This insulin is now available only on a limited basis. Human insulin differs from canine insulin by only one amino acid and from feline insulin by four amino acids. Biosynthetic insulins made with human DNA, such as Humulin or Novolin, have been used successfully.

Most recently, insulin analogues have been produced by amino acid alterations to the insulin molecule. This change results in an insulin molecule that allows rapid absorption and faster onset of action. The table below shows an overview of the various intermediate and long-acting insulin preparations by manufacturer, species origin, concentration and cost.

Insulin	Manufacturer	Species Origin	Concentration	Cost (per vial)	Cost (per unit)
Intermediate Acting					
Humulin N-NPH	Eli Lilly	Human	U-100	\$49.29 - 51.49	4.9¢ - 5.1¢
Novolin N-NPH	Novo Nordisk	Human	U-100	\$51.49 - 51.99	5.1¢
Vetsulin/Caninsulin - Lente	Intervet	Porcine	U-40	\$32.00 - 42.50	8¢ - 10¢
PZIR	IDEXX	Human	U-40* 100*	*	*
Long Acting					
Lantus - Glargine	Sanofi-Aventis	Human Analogue	U-100	\$108.99 - 113.99	10¢ - 11¢
Levemir - Detemir	Novo Nordisk	Human Analogue	U-100	\$108.99 - 133.99	10¢ - 13¢

* unknown at this time

NPH – Humulin N, Novolin N

Neutral Protamine Hagedorn (NPH) human analogue insulin contains fish protein protamine and zinc to delay absorption of insulin and thereby prolong the duration of effect. A recent study showed that Humulin N was effective in treating diabetes mellitus in dogs, although postprandial hyperglycemia was commonly noted. Initial dosing for both cats and dogs is 0.25 to 0.5U/kg every 12 hours. In cats, NPH is not commonly used because of its short duration of action. This form of insulin is more commonly used in dogs and has sometimes been chosen as a less expensive alternative, although glycemic regulation is more difficult to achieve with this particular form.

Vetsulin/Caninsulin

This porcine-origin insulin zinc suspension is known in the United States as Vetsulin and in Canada and other countries as Caninsulin. It is a Lente insulin with intermediate duration of action. It is the first FDA-approved veterinary product to treat diabetes mellitus in dogs. Canine and porcine insulin have an identical amino acid sequence making the formation of anti-insulin antibodies less likely. The zinc suspension in this insulin contains 30% amorphous zinc insulin and 70% crystalline zinc insulin. The amorphous portion is rapidly absorbed allowing for faster onset of action with peak activity within 4 hours and lasting up to 8 hours. The crystalline portion is absorbed more slowly and therefore contributes to a longer duration of activity with a peak effect at around 11 hours following injection.

A twice daily dose is most commonly necessary, but because of the duration of effect, once daily dosing may be possible in some animals. Dosing in dogs is recommended to start at 0.5 IU/kg once to twice daily.

Porcine insulin differs from feline insulin by three amino acids, however vetsulin can be used in cats. Peak effect appears to be an average of four hours after administration with the duration of effect between 8-12 hours. This duration of effect is shorter than what is seen with Glargine. Because of the early peak effect and potent action, this insulin may predispose cats to counter-regulatory hormone responses even if cats are not in a hypoglycemic range. This resulting Somogyi phenomenon would make it difficult to regulate diabetic cats clinically. The recommended starting dose is 0.25-0.5U/kg with a maximum of 2U per injection, twice daily.

PZIR

PZIR is a new protamine zinc recombinant human insulin preparation that should soon be available on the market. A recent study (Nelson et al. *JVIM* 2009) evaluated the efficacy of this insulin in controlling hyperglycemia in newly diagnosed diabetic cats as well previously poorly controlled diabetic cats. Of the 133 cats that were treated with this new insulin, 75% of owners noted an improvement in polydipsia, and 79% of owners noted an improvement in polyuria. There was also a significant increase in mean body weight. Ultimately, 85% attained good diabetic control by day 45 of the study. The study found that the effects of this insulin were comparable to the previously used PZI-VET insulin that now only has limited commercial availability. Mean time to blood glucose was between 5 and 7 hours and most cats had increasing blood glucose concentrations by 9 hours after administration. The starting dose for this insulin in this study was 0.25U/kg twice daily. This insulin has not been evaluated for use in dogs.

Glargine

Glargine is a long-acting insulin and the first choice of insulin for cats. It is formulated with a low pH of 4 and therefore is poorly soluble at physiologic pH. It forms microprecipitates when it is injected into the subcutaneous tissue; therefore, the insulin is slowly released in a delayed, prolonged, and relatively constant absorption from the site. Glargine should not be diluted as this would change the pH and therefore affect the formation of the microprecipitates as well as the absorption. It has been noted that given intramuscularly, Glargine may act more like a short-acting insulin and could therefore be used in patients with diabetic ketoacidosis, however this has not been studied. Glargine has been very successful in achieving diabetic remission when given twice daily along with an appropriate low carbohydrate, high protein diet. Glargine

should be started at twice daily dosing for at least the first four months, but then may be reduced to once daily. While hypoglycemia may occur, it is less likely that actual clinical signs are noted as compared to other insulins. It is recommended that serial/daily blood glucose curves should be obtained for three consecutive days after starting this insulin. Dosing should be started at 0.5U/kg subcutaneously twice daily. It is most beneficial to evaluate the pre-insulin blood glucose concentrations along with the nadir blood glucose concentration when adjusting insulin dosing. Almost all cats will have their initial dose reduced within two weeks and many will achieve remission in 4 weeks. Amount of water consumption as well as urine glucose quantification can be obtained and applied in adjusting insulin dosage. For further information, please refer to this website: www.uq.edu.au/ccah.

In dogs, Glargine has resulted in unpredictable serum insulin concentration response. In some dogs it has failed to cause a significant glucose lowering effect. There are some anecdotal reports of the use of this insulin in dogs, but currently there are no canine studies demonstrating its use and adequate efficacy.



Commonly used insulins in veterinary medicine.

Detemir/Levemir

Detemir is a newer synthetic insulin analogue with a long duration of action similar to Glargine. The information that follows is a summary from an abstract and proceedings presented at ACVIM 2009. This insulin molecule is modified by the addition of an acylated fatty acid chain that enables reversible binding to plasma proteins, especially albumin. This insulin molecule is then slowly released into plasma. This slow release, as well as its prolonged absorption, may result in a longer duration of action than what is seen with Glargine. Use of this insulin resulted in similar remission rates than seen with Glargine. Recommended starting dose for this insulin is 0.5U/kg twice daily. Detemir has not been studied for use in dogs.

For both Glargine and Detemir, remission rates are higher if good glycemic control is achieved within the first 6 months of diagnosis. Achieving good glycemic control will help reverse glucose toxicity in the B-cells of the pancreas, thereby facilitating insulin production and therefore reducing exogenous insulin requirement. It is important to note that a low carbohydrate-high protein diet is an essential component to attaining diabetic remission.

A Brief Introduction to Continuous Glucose Monitoring

Serial glucose curves are the gold standard for monitoring patients receiving insulin for diabetes mellitus to assess both efficacy and duration of action of the insulin. This can at times be accomplished at home, but in-hospital glucose curves are common as well. A glucose curve will disrupt a

patient's normal at home routine and eating habits with varying severity. It also increases handling and stress which can ultimately lead to inaccurate glucose readings. Continuous glucose monitoring systems (CGMS) have been utilized in human medicine since 2000. The system is equipped with a sensor that is inserted into the subcutaneous space. This sensor contains a patented semi-



Glucose Sensor: *The sensor is inserted under the skin using an autoinsertion device that comes with the system.*

permeable membrane that allows glucose to enter and interact with glucose oxidase to form hydrogen peroxide. The oxidized Hydrogen peroxide releases a charge that is detected by an electrode within the sensor. The sensor is calibrated with blood glucose levels to produce the interstitial glucose

readings based on the reaction intensity. Interstitial glucose measurements are obtained every 10 seconds with an average value recorded every 5 minutes. The sensor can remain in place for up to 3 days and the working range is set at 40-400mg/dl.

There are several types of devices that are currently available. The CGMS® IPro™ Recorder available through Medtronic is an at home monitoring system where a

transmitter is attached to the sensor obtaining blood glucose readings over a period of 3 days. During this period of time, owners should be keeping a log of their pet's activities and meal times, to help with analyzing the data that is produced. The blood glucose readings are downloaded after three days and adjustments in insulin dosage and home routines can be addressed. The Guardian® REAL-Time unit is also available through Medtronic for in-hospital use. A similar transmitter is applied to the sensor and actively transmits the glucose concentration to a small monitor which displays the current glucose reading. The monitor has to be within 6 feet of the patient. Readings can be obtained from every 30 minutes to every two hours. This monitoring unit is most useful in those patients where repeated glucose readings are necessary, including patients with diabetic ketoacidosis, pediatric patients, patients with insulin secreting neoplasia and critical care patients. This unit may also be used intra-operatively for insulinoma or other hypoglycemic conditions. Twice daily blood glucose calibrations at home or at the hospital are necessary for accurate measurements with both of these units. CGMS can be used to help reduce stress to the patient, reduce the risk of anemia from continued venous sampling, and improve the number of reliable readings especially in patients where venous access is limited. ■

References Available upon Request

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New Offering! Continuous Glucose Monitoring

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Dear Colleagues,

We are excited to inform you that Massachusetts Veterinary Referral Hospital now carries continuous glucose monitoring (CGM) equipment. This new monitoring technology will be available both on an outpatient basis to patients being cared for by our Internal Medicine Service and to patients in our intensive care unit.

Continuous glucose monitoring allows for accurate blood glucose measurements to be obtained for up to three days by a sensor that is inserted in the subcutaneous space. The CGM units will be used on an outpatient basis, greatly aiding our ability to monitor and regulate our canine and feline patients with diabetes mellitus.

Reduced Stress, Improved Data:

Using CGM as a tool will enable us to gather more accurate and timely blood glucose information while reducing the risk of anemia and stress through reduced handling and fewer blood samplings.

There are multiple applications for CGM technology in the intensive care unit, including:

- Patients with diabetes mellitus/diabetic ketoacidosis
- Patients with neoplasia producing insulin-like substances (e.g. insulinoma, leiomyoma/leiomyosarcoma, etc.)
- Critical Care patients(e.g. sepsis)
- Patients receiving parenteral nutrition
- Pediatric patients
- Pre-, intra- and post-operative surgical patients requiring close glucose monitoring

We are excited to make this new diagnostic option available to your patients that are referred to both Massachusetts Veterinary Referral Hospital in Woburn, MA and Port City Veterinary Referral Hospital in Portsmouth, NH. Thank you for your continued support and please don't hesitate to contact us with any questions regarding the CGM system, or with any other questions about the services available at Massachusetts Veterinary Referral Hospital.

Best Wishes,

Patrick M. Welch, DVM, DACVO
Medical Director,
Massachusetts Veterinary Referral Hospital