Common Cardiac Drugs – How they work!

Terri DeFrancesco, DVM, DACVIM (Cardiology), DACVECC
North Carolina State University
College of Veterinary Medicine
Raleigh, NC
Teresa_defrancesco@ncsu.edu

Discussion Agenda

• Heart failure medications
  – Diuretics
    • Furosemide, Spironolactone
  – Vasodilators
    • Enalapril, Benazepril, Amlodipine, Sildenafil
  – Inotropes
    • Pimobendan, Digoxin
• Anti-arrhythmic medications
  – Diltiazem, Atenolol
  – Lidocaine, Sotalol

Sam

Presenting Complaint: Dyspnea

History:
Dyspnea and wheezing for 1 day.
Murmur for years.

Heart Failure Physiology

• How do we diagnose heart failure?
  – No single test
  – Response to therapy can be diagnostic

Discussion

• NCSU Physical examination:
  T= 100.2 F, HR – 180, RR – 140, mm – pale pink, CRT – 1.5 sec, Grade 4/6 systolic murmur PMI left apex. Loud breath sounds diffusely and dyspnea. BP – 130/83 (99)

• Diagnostic evaluation: Thoracic Radiographs, Chemistry panel
Cardiac output = HR x stroke volume

The 3 most common causes of heart disease in small animal veterinary medicine:
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Valvular regurgitation

Furosemide (Lasix®, Salix®)
- Onset of action and peak
  - IV: 5 min and 30 min
  - PO: <1 hour and ~2 hours
- 1-4 mg/kg q 24 hrs – TID (max 12 mg/kg/d)
- Can give as continuous rate infusion:
  - 0.25-0.5 mg/kg/hr x 2-4 hr IV
- ACUTE TX - Relief of symptoms
- CHRONIC TX - Lowest effective dose
- Adverse Effects
  - Hypovolemia, hypokalemia, hyponatremia
  - Azotemia, dehydration

Diuretics
- Preload reduction
- NEVER increases cardiac output
- Inhibits Na⁺ or Cl⁻ resorption in the renal tubules
- Loss of H₂O and solute into the urine
- Mainstay in acute therapy of heart failure

FONSP
- Furosemide
- Oxygen
- Nitroglycerin
- Sedation
- Pimobendan (Dog, some cats)
Preload and Cardiac Performance

Cardiac Output

Preload

Not congested

congested

Furosemide

- Long term – lowest effective dose
- Home monitoring of resting RR and cough frequency
- Flex dose
- In severe end stage HF
  - Increase frequency
  - Periodic SQ injections (RHF)
- Max – 12 mg/kg/day

Additional Diuretics

- Sequential Nephron Blockade
  - Loop diuretics: furosemide
  - Thiazides and Spironolactone: distal tubules
  - Improved survival
  - Anti-aldosterone – Neurohumoral benefit
  - Weak and possibly questionable diuretic
- Spironolactone/hydrochlorothiazide (Aldactazide®)
  - Will add in with end-stage refractory HF

Spironolactone (Aldactone®)

- Competitive antagonist of aldosterone
- Potassium sparing diuretic
  - Multiple canine studies show no diuretic effect in normal dogs
- Weak diuretic, synergism with furosemide
- Slow onset of action, peak in 48 - 72 hours
- Dose?: 0.3 - 2 mg/kg/day
  - (sub diuretic dose v. diuretic dose)
- Adverse effect: Azotemia, hyperkalemia

Thiazide Diuretics

- Can be a potent additional diuretic used in dogs with refractory edema and “normal” renal function.
- Potassium wasting diuretic
- Often use a combination product – Aldactizide – Spironolactone and hydrochlorothiazide
- Typical HF dog that may go on all 3 diuretics is the Cavalier King Charles Spaniel
Vasodilators

- Reduce Preload
  - Nitroglycerin (ER treatment of HF)
- Reduce Afterload
  - Amlodipine (Systemic + Pulmonary hypertension, Refractory CHF)
  - Sildenafil (Viagra) (Systemic + Pulmonary hypertension, Refractory CHF)
- Mixed Vasodilators
  - ACE- Inhibitors (Enalapril, Benazepril) (chronic tx HF)
  - Nitroprusside (ER treatment of HF)
  - Pimobendan (Systemic + Pulmonary hypertension)

Nitroglycerin 2% ointment

- Venodilator (primarily abdominal veins)
- Transdermal ointment applied to ear pinna
- Develops a tolerance
- Useful in first 24 hrs
- WEAR GLOVES

ENALAPRIL, BENAZAPRIL
Angiotensin Converting Enzyme Inhibitors

- Inhibits synthesis of Angiotensin II
  - Ag II hemodynamic effects
  - Ag II local myocardial effects
    - increases collagen
    - growth factor
- Inhibits breakdown of Bradykinin (endogenous vasodilator)
- Balanced vasodilator
- Main adverse effect: azotemia, hypotension,

AMLODIPINE (Norvasc - Pfizer)

- Calcium channel blocker with primary effect of vasodilation (minimal cardiac effects)
- Indicated for treatment of clinical hypertension in both cats and dogs
- Also indicated for adjunctive treatment of advanced CHF in dogs
- Adverse effects - hypotension

Sildenafil (Viagra, Revatio – Pfizer)

- Phosphodiesterase V inhibitor that causes nitric oxide induced vasodilation
- Proposed vascular bed selectivity
- Used to treat pulmonary hypertension in people
- Preliminary use in dogs with pulmonary hypertension with favorable outcomes
- Very Expensive
- Well tolerated – hypotension is main adverse effect
Heart rate
- Beta Blockers
- Ca++ Ch. Blockers
- Lidocaine
- Sotalol

Preload
- Diuretics
- Venodilators (Nitro)
- Mixed Vasodilators
- NaCl restriction

Cardiac Output
- Afterload
- Arterial Vasodilator
- Amlodipine
- Sildenafil
- Mixed Vasodilator
- ACE-Inhibitors

Contrastility
- Calcium sensitizer
- Lidocaine
- Pimobendan
- Digoxin

Afterload
- Calcium sensitizer
- Venodilators (Nitro)
- Diuretics
- Mixed Vasodilator

Vetmedin® (pimobendan)
Dual Mode of Action
- "Inodilation"
- "Myocardial output"

Direct heart muscle action
- Calcium sensitizer
- Promotes efficient use of existing calcium
- Increases force of contraction
- Does not increase myocardial energy requirements

Balanced vasodilation
- Selective peripheral phosphodiesterase III inhibitor
- Dilates both arterial and venous vessels
- Reduces preload and afterload
- Improves cardiac function

Vetmedin®
Pharmacokinetics and Pharmacodynamics
- Rapid absorption
  - Mean peak plasma levels achieved 0.5-1.0 hour after administration of a single oral dose
- Pimobendan is demethylated to an active metabolite (UD-CG 212)
  - UD-CG 212 has the same pharmacodynamic profile as pimobendan
- Elimination half-life
  - Pimobendan: 0.5 hours
  - UD-CG 212: 2.0 hours
- Prolonged pharmacodynamic effect (>8h)
- Routes of excretion
  - Feces: 95%
  - Kidneys: 5%

Digoxin: When to use in CHF?
- Congestive HF in DCM (together with pimo)
- Supraventricular arrhythmia (A. Fib, SVT) in MR or DCM
- Owner compliance and ability to do therapeutic monitoring
  - Digoxin is inexpensive; digoxin level = $40

Vetmedin®
Labeling
- Indications
  - Management of the signs of mild, moderate, or severe (modified NYHA Class II, III, or IV) CHF in dogs due to Valvular Insufficiency (MVD) and Dilated Cardiomyopathy (DCM)
  - Use with concurrent therapy for congestive heart failure (eg, furosemide, etc) as appropriate on a case-by-case basis
- Dose rate
  - 0.33 mg/lb (0.5 mg/kg) per day, in two divided doses that are not necessarily equal
  - Chewable 1.25 and 5 mg scored tablets
  - $55
- Adverse effects
  - Well tolerated drug. Concerns about tachyarrhythmia and sudden death in humans. (Not FDA approved for use in humans)

Digoxin: pharmacokinetics
- NaK-ATPase inhibitor and centrally mediated increased parasympathetic tone

- Oral absorption
  - tablet 50-70 %
  - elixir 75-90 %
- Elimination
  - renal
- Half - life
  - 20 - 40 hours
- Adverse effects
  - Anorexia, Vomit, Diarrhea
  - Arrhythmias
    - AV Block
    - Ventricular arrhythmias
- Reduce dose
  - Elixir
  - Renal disease
  - poor renal perfusion (Dobe DCM)
  - Obesity / cachexia
  - Hypokalemia
  - Old age
  - Shetie/Collie (MDR1 mutation)
- Start low titrate dose
  - Serum concentration at steady state (~ 5 days)
    - 8 hrs post - pill
    - 0.5 – 0.9 mg/ml therapeutic conc.
Treatment

**Initial treatment**
- Furosemide
- Oxygen
- Nitroglycerin
- Butorphenol

**After able to take PO meds**
- Pimobendan

**Sent home 3 d later**
- Enalapril 0.5 mg/kg BID
- Amlodipine 0.075 mg/kg BID
- Pimobendan 0.2 mg/kg BID
- Furosemide 2 mg/kg BID

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**DIXIE- 6 yo FS Boxer**
- Presents for collapse (probably syncope)
- Has had previous self limiting episodes of weakness in past couple of years but today is lethargic and weak.
- PE – tachyarrhythmia (>250), weak, poor pulse quality, pale oral mm
- Blood work - normal

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**Ventricular tachycardia**
Cardiac and non cardiac causes

- **Primary Cardiac**
  - Cardiomyopathy
  - Endocarditis
  - Myocarditis
  - Inherited channelopathies
  - Advanced valvular or congenital heart disease
  - Cardiac neoplasia or ischemia

- **Primary Non-cardiac**
  - Sepsis
  - Hypoxia
  - Trauma
  - GDV
  - Splenic neoplasia
  - Shock
  - Pancreatitis
  - IMHA
  - Uremia
  - Pheochromocytoma

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**All Cause Canine Chronic Heart Failure**

**Furosemide**
**ACE-inhibitor**
**Pimobendan**

- Amlodipine
- Sildenafil
- Nitroglycerin
- Nitroprusside
- Hydrochlorothiazide
- Spironolactone
- Diltiazem
- Sorbital
- Lidocaine
- Sedation
- Oxygen

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**Arrhythmic Right Ventricular Cardiomyopathy**
(ARVC, Boxer Cardiomyopathy)

- Autosomal dominant inheritance
- Ventricular arrhythmias – common
- Syncope is typical presenting sign
- Increase risk for sudden cardiac death
- Some progress to CHF/DCM
**ACUTE Treatment of V-tach**

- Lidocaine 2 mg/kg IV bolus up to 8 mg/kg
- Lidocaine CRI 30 - 80 mcg/kg/min

Adverse Effects: Nausea, Sedation, Seizures, AV block

**THERAPEUTIC RANGE**

[Graph showing lidocaine concentration over time with half-life (T1/2) of 1 hr]

**SOTALOL** (Betapace, Generic)

- Potassium channel blocker and non-selective beta-blocker
- Prolongs action potential duration (A+V)
- Primary indication is for chronic tx of severe ventricular tachyarrhythmias in Boxers and other breeds
- Also useful in SV arrhythmias
- Adverse effects - worsening of CHF, bradycardia, QT prolongation, Torsades de pointes, sudden death (Proarrhythmia)

**Heart rate and rhythm**

- Tachyarrhythmias – more common with dilated cardiomyopathies and end-stage mitral valve disease.
  - Rapid atrial fibrillation (>220/min)
    - Diltiazem 0.5 – 1.5 mg/kg PO q 8 hr
    - Calcium Channel Blocker –
      - Slows HR and AV Nodal Conduction
    - Side effects: Bradycardia, hypotension

**SVT (300/min) in 2 yo Lab in HF**

25 mm/s

**Atrial Fib (220/min) in 5 yo Grt Dane in HF**

50 mm/s

**Beta Blockers**

- Atenolol, Metoprolol
  - Beta adrenergic receptor blocker
  - Decreases HR and Contractility
  - Various Indications:
    - Adjunctive anti-arrhythmic
    - SVT or VT
    - Anti-ischemic
    - HCM and severe PS or SAS
  - Adverse effects: worsening of CHF (edema), bradycardia, hypotension, syncope