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PET POISON HELPLINE®

Healing Heartbreak: A Case-Based Discussion About Cardiovascular Toxicity

July 13, 2021

Katie Peterson, DVM, DACVECC, DABT
Emergency and Critical Care Specialist
Pet Poison Helpline

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What is Pet Poison Helpline?

Email us for more information:
info@petpoisonhelpline.com

PET POISON HELPLINE®

- **24/7 animal poison control center**
- **Veterinary & human expertise**
  - 30+ DVMs, 100+ CVTs
    - DABVT, DABT
    - DACVECC
    - DACVIM
  - 10 PharmDs
  - 2 MDs
- **Case fee of $59 includes:**
  - Unlimited consultation
  - Fax or email of case report
- **Educational Center**
  - Free webinars (archived)
  - Wheel of Vomit
  - Textbook
  - Newsletters for vet professionals
  - Free resources for clinics
    - Videos
    - Electronic material
    - Clings
    - Social media graphics

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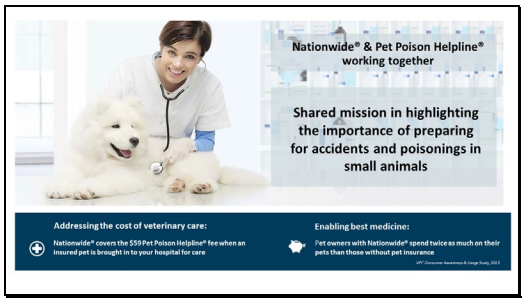

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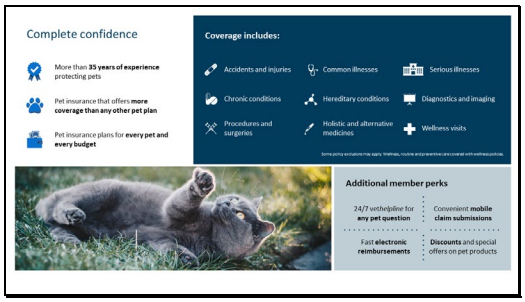

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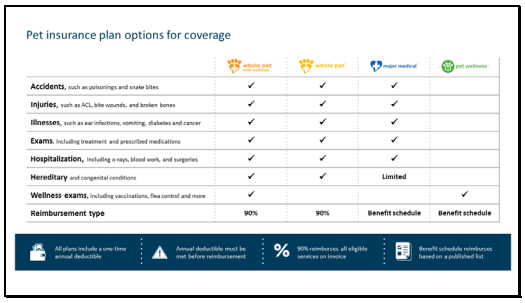

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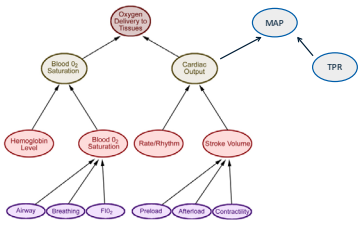
How to approach cardiac toxicity cases



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Case 1: Albuterol Toxicity

Oliver
- 5 year old
- MN
- Rottweiler
- 115lbs (52.2kg)

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Albuterol Toxicity: Oliver

- 1-2 hours prior bit into albuterol inhaler (90mcg albuterol/puff with 200 actuations)
- Heavy breathing at home
- Signs at DVM: tachycardia (HR 180), BP_{sys} 100mmHg, injected mm, slight agitation, dehydration, overweight
- Initial blood work: Hct 46.8, K 2.47, lactate 6.4

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Albuterol toxicity

- Mechanism of action: beta-2 agonist
  - Lungs: bronchodilation
  - Heart: increased contractility and increased heart rate
  - Blood vessels: relaxation/decreased blood pressure
  - CNS: increased sympathetic tone
  - Dogs often bite into inhalers
    - Large doses even when used
    - Oral lesions
    - Can also ingest vials for nebulization, tablets, syrup
    - Other β-2 agonists: levalbuterol, formoterol, salbutamol
    - May be combined with other medications

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Albuterol clinical signs

- Rapid onset of signs within 1-2 hours
- Signs persist 24-48 hours
- Clinical signs
  - Tachycardia – sinus tachycardia, arrhythmias
  - Blood pressure
    - Hypotension: MOA of drug, decreased cardiac output (CO) from tachycardia
    - Hypertension: increased CO, agitation, sympathetic stimulation
  - Hypokalemia and hypophosphatemia
  - Weakness/lethargy, agitation, vomiting, muscle tremors, seizures (rare)

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Treatment recommendations for Oliver

- Start with IV fluids
  - Fluid bolus
- +/- sedation
- Beta blocker for tachycardia
- Supplement KCl (or KPO_4) in fluids
  - Monitor K q 4-6 hours
  - Use standard charts for supplementation
  - Not more than 0.5 mEq/kg/hr

Calculating Potassium Amounts for Fluids

Serum K+ (mEq/L)	Maximum rate* (mL/kg/hr)	Total mEq KCl needed per 1 L
<2.0	6	80
2.1–2.5	8	60
2.6–3.0	12	40
3.1–3.5	18	28
3.6–5.0	25	20

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Initial treatment for Oliver

- IV fluids with 40 mEq/L KCl supplementation at 2X maintenance
- Acepromazine 0.03mg/kg IV
- Maropitant

- Dull, tachycardic HR 180-190, BP_{sys} 30-60 mmHg

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Questions

Why the tachycardia?
A. B_2 stimulation
B. Hypovolemia
C. Hypotension
D. Myocardial damage

Why the hypotension?
A. Decreased CO
B. Hypovolemia
C. B_2 stimulation
D. Acepromazine

All of the above!

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Albuterol discussion


- Tachycardia causes
  - Beta-2 agonist MOA
  - Hypotension
  - Hypovolemia
  - Myocardial damage
- Treat HR > 180
  - Decreased cardiac output (CO)
  - Decreased myocardial perfusion
- Hypotension causes
  - Beta-2 agonist MOA of albuterol
  - Acepromazine
  - Tachycardia with decreased CO
  - Hypovolemia
- Treat systolic < 90mmHg or mean < 60mmHg
  - Decreased perfusion/O_2 delivery

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Treatment for hypotension and tachycardia

- Fluids
  - No volume loss reported
  - Reportedly dehydrated (~5% = 2600ml)
  - "Shock dose" 90 ml/kg ~3100-4600 ml
    - 20-30 ml/kg bolus crystalloid 2X
    - +/- 5ml/kg colloid bolus
- Injectable beta blockers
  - Propranolol
  - Esmolol
- Vasopressors- norepinephrine, vasopressin, dopamine

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Reassessment (~60 min later)

- Over 4L crystalloids given (77 ml/kg) and 5ml/kg colloid bolus
- BP recheck 84-100 systolic
- HR 180-230
- Hct 24.4, TP 3.1, P 0.9, K 2.5, Lactate 7.6

- Why the persistently elevated HR and lactate? Now what?!?

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Albuterol discussion

- Hyperlactatemia
  - Production > use
  - Product of anaerobic metabolism
    - Decreased perfusion
  - $Beta_2$ agonist
    - Increased glycogenolysis, glycolysis
    - Increased lipolysis
- Treatment
  - Improve perfusion
  - Resolve with drug excretion

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Albuterol discussion

- Tachycardia
  - Albuterol MOA
  - Myocardial injury?
  - Attempting to maintain BP?
  - Fluid overload?
  - Persistent hypokalemia?
- Treatment
  - Beta blocker
  - Monitor ECG for arrhythmias
  - Frequent BP monitoring
  - Monitor RR and effort
  - K supplementation and recheck in 4-6 hours

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Oliver outcome

- Fluid overloaded with increased RR and evidence on CXR
  - Discontinued IV fluids
  - Furosemide bolus + CRI
  - K= 3.26, consider oral K supplementation
- Hypotension- resolved
- Tachycardia- improved with propranolol but…
- Developed ventricular arrhythmias with HR 170-180
  - Recommended lidocaine bolus and CRI
- No additional follow up but no news is good news?

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Lessons learned

- Avoid acepromazine with albuterol toxicity
- Judicious use of fluids
- Beta blockers almost always needed
- Delayed cardiac arrhythmias common with severe cases
- Prognosis generally good but can be complicated cases

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Case 2: Diltiazem toxicity

Teddy Bear
- 2 year old
- MN
- Mixed breed dog
- 9.9lbs (4.5kg)

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Diltiazem toxicity: Teddy Bear

- ~ 7 hours prior, ingested 240mg diltiazem XR (53.3 mg/kg)
- Lethargic at home
- Vitals at clinic: T 95° F, HR 20, RR 20, pale mm, CRT 3 sec

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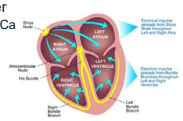
Diltiazem

- Mechanism of Action: Ca^{2+} channel blocker
  - Inhibits transmembrane influx of extracellular Ca
    - SA and AV node
    - Myocardium
    - Vascular smooth muscle
- Used therapeutically
  - Hypertension
  - Tachyarrhythmias - SVT, ventricular fibrillation
  - Diltiazem therapeutic dose orally: XR 3-5 mg/kg q12



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Calcium channel blockers

Compound	Family/class	Vasodilation	Cardiac contractility	SA nodal suppression (automaticity)	AV nodal conduction (contractility)
Diltiazem	Benzothiazepine	+++	++	+++++	++++
Verapamil	Phenylalkylamine	++++	++++	+++++	+++++
Nifedipine	Dihydropyridine	+++++	+	+	0
Amlodipine	Dihydropyridine	+++++	+	+	0

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Diltiazem toxicity

- Narrow margin of safety
  - >2x therapeutic dose may result in toxicity
  - LD_{50} = 50mg/kg
- Clinical signs
  - Cardiovascular signs: Bradycardia, decreased contractility, hypotension
  - Vomiting
  - CNS depression, seizures
  - Possible hypocalcemia and hypo or hyperkalemia
  - Hyperglycemia
  - Decreased perfusion organ injury (GI tract, kidneys, heart)
- Immediate vs extended release
  - Onset of signs, treatment and persistence of signs

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Treatment recommendations for Teddy Bear

- Activated charcoal if stable
- IV fluids
  - No evidence of dehydration or volume loss
  - Bolus may improve HR if due to decompensated shock
  - Improve stroke volume
  - Bolus 20-30 ml/kg 2X +/- colloid bolus
  - Risk of fluid overload due to decreased CO
- Baseline blood work: kidney values, iCa, K

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Treatment recommendations

- Atropine
  - Vagolytic
- Calcium gluconate bolus + CRI
  - Positive inotrope
  - Increases Ca availability for transport
  - Use even if iCa is normal
- IV lipids
  - Beneficial for lipid soluble drugs
    - Diltiazem LogP 2.7 to 3.0, LogD 1.9 at pH 7.4
    - Highly protein bound
  - May provide myocardial energy source
  - May need several doses to response

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Teddy Bear reassessment (~3 hours)

- Baseline blood work iCa 1.2, BG 426, BUN 36
- Treatment so far
  - IV fluids – crystalloids 25ml/hr (5.5 ml/kg/hr)
  - Atropine 0.02mg/kg IV and Ca gluconate bolus 10 mg/kg IV
  - No response- started Ca CRI and repeat atropine
  - Catheter SQ
  - Replace IVC and restart Ca CRI
  - Discontinue LRS and start Vetstarch
  - Start IV lipids – bolus + initial CRI
  - Active warming
- Current vitals: T: 96°F, HR 30, BP $_{sys}$ 40 mmHg

- Patient not responding to standard care…now what?!?

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Question: Patient not responding to standard care…now what?!?

A. Continue current therapy
B. Start high dose insulin and dextrose
C. Recommend euthanasia
D. Refer for pacemaker
E. A and B

A and B

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Diltiazem advanced treatment

- Recommendation for Teddy Bear
  - Continue warming
  - Recheck blood work – increase Ca gluconate CRI
  - Continue IV lipid emulsion
    - Recheck serum for lipemia q 2-4 hours
    - Repeat bolus dosing if serum clear
    - Discontinue after 24 hours if no response to treatment

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Diltiazem advanced treatment

- High dose insulin and dextrose (1U/kg bolus + CRI + dextrose CRI, titrate up to effect)
  - Requires central line placement and frequent BG and K monitoring
  - Positive inotrope, increased cardiac output
  - Carbohydrate energy source
  - Increased myocardial Ca
- Recommendation for Teddy Bear
  - Place central line and start HDI-dextrose
  - What about just a dextrose CRI? Short acting or long acting insulin?

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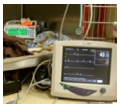
Diltiazem advanced treatment



- Glucagon
  - Positive inotrope and chronotrope
  - Can be difficult to obtain and expensive
- Vasopressors
  - May not improve outcome
  - Dopamine, epinephrine, dobutamine, norepinephrine, vasopressin
- Temporary pacemaker

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Teddy Bear outcome

- Started on high-dose insulin and dextrose CRI
  - After 2 hours and increasing to 3U/kg/hr HR improved to 72! BP stabilized
  - Weaned insulin over ~12 hours
  - Dextrose supplementation for ~24 hours
- Discharged ~3 days after exposure

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Lessons learned

- If not responsive to treatment, check IV catheter
- Lipids have several beneficial properties for some cardiac medications
- While labor intensive, HDI-dextrose can be life saving
- Toxicity can be severe but survival is possible

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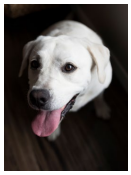
Case 3: Pimobendan toxicity

- Belle: 8 year old, FS Labrador retriever, 59.4lbs (27kg)
- Bo: 5 year old, MN, Mix breed 11lbs (5kg)
- Dog on pimobendan won't readily eat it so not in clinic



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Pimobendan toxicity: Belle and Bo

- 1-3 hours ago, ingested up to 42, 5mg Pimobendan
  - Belle 8.3 mg/kg
  - Bo 49.6 mg/kg
- Asymptomatic at home
- At the clinic: Belle HR 200, anxious; Bo asymptomatic
- Emesis performed: Belle produced material resembling pills
- What treatments need to be done for Belle? Bo?

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Pimobendan

- Mechanism of action: Inodilator
  - Positive inotropy
    - Inhibition of phosphodiesterase III (PDE-III)
    - Increase intracellular calcium sensitivity
  - Vasodilation
    - Inhibition of PDE-III causes both venous and arterial dilation
- Therapeutic dose 0.5 mg/kg/day

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Pimobendan

- Wide margin of safety
  - Doses >2 mg/kg considered toxic
- Onset of signs 1-2 hours
- CS persist 12-24 hours
- Clinical signs
  - GI signs (vomiting, diarrhea, anorexia)
  - Hypotension and reflex tachycardia
  - Arrhythmias

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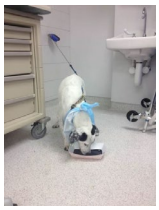
Pimobendan treatment for Bo

- Antiemetic
- 1 dose AC with sorbitol
- Monitoring in the clinic for 4 hours
- SQ fluids to go home
- Monitor for GI upset, pale gums, depression



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Pimobendan treatment for Belle

- ECG and BP on presentation
- Antiemetic
- 1 dose of AC with sorbitol
- IV fluids +/- bolus if BP low or normal
- Sedative as needed
- Address tachycardia if persistent with normal BP and sedative
- Baseline blood work-chemistry, electrolytes, PCV/TP

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Belle update (7 hours later)

- Administered 0.2 mg/kg butorphanol IV
- Currently:
  - Anxious
  - HR 200, increasing ventricular arrhythmias and episodes of V-tach
  - BP normal
- On IV fluids at 2X maintenance

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Question: What are the next steps for Belle?

A. Heavy sedation
B. Fluid boluses up to shock dose
C. Anti-arrhythmics
D. Turn off the ECG

Anti-arrhythmic

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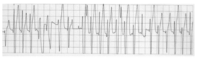
Belle treatment recommendations



- Tachycardia causes
  - MOA of pimobendan
  - Anxiety
  - Myocardial damage and secondary arrhythmia
  - Maintaining BP
- When to treat ventricular arrhythmia?
  - HR > 180
  - Ventricular tachycardia both intermittent or sustained
  - Affecting perfusion
  - R on T
  - Multi-form VPCs

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Belle treatment recommendations

- Fluids- judicious use
- Further sedation/anxiolytic
- Antiarrhythmic therapy
  - Beta blockers
  - Lidocaine
  - Procainamide
  - Mexiletine
  - Sotalol
- IV lipids (LogP 1.81, LogD -1.91)[A1]

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Follow up on Bo and Belle

- Bo- remained asymptomatic, no further treatment needed
- Belle
  - Moderate liver enzyme elevations (ALT 474, AST 210)
  - Arrhythmias responded to lidocaine CRI and switched to oral sotalol
  - Discharged ~24 hours after presentation with normal HR on sotalol
  - Plan to recheck ECG/HR and liver enzymes in 1 week

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Lessons learned

- Dogs will readily ingest this medication
- Rapid onset of signs--easy to identify culprit if multiple pets
- Toxicity can be challenging to treat, be aware if patient has underlying heart disease or failure
- May see other organ toxicity with perfusion abnormalities

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PET POISON HELPLINE®

Thanks for attending!

Questions?

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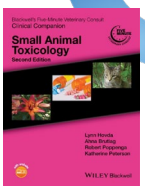
Blackwell's Five-Minute Veterinary Consult Clinical Companion:

Small Animal Toxicology

2nd Edition

Drs. Lynn Hovda, Ahna Brutlag, Robert Poppenga, Katherine Peterson

- Provides concise, bulleted information focused on the most important facts needed when treating a poisoned cat or dog
- Carefully organized for ease of use in an emergency, with important toxicants arranged alphabetically within categories
- Details clinically relevant information on the most common toxicants encountered by small animals
- Presents a wealth of color photographs to aid in plant identification
- Includes 14 new topics to this edition covering cyclosporine A, sleep aids, tacrolimus, bath salts, synthetic marijuana, poisonous lizards, imidacloprid, spring bulbs, and sodium monofluoroacetate



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- **Recorded and Available On-Demand:**
  - Decontamination: So Much More Than Vomiting!
- **Recorded and Available On-Demand:**
  - Ensuring Your Financial Wellbeing as a Veterinary Professional"
- **Recorded and Available On-Demand:**
  - The Caring Veterinary Medical Professional: Understanding the Grief Process
- **August 19th**
  - Couple-Care: Relationship First Aid for Veterinary Medical Professionals
- **October 5th**
  - Heavy Metal Toxins: Where They are Lurking May Surprise You
- **November 9th**
  - Seize the Day: Toxin Differentials in the Acutely Neurological Patient

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Thank you for attending!

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2. **I attended the webinar but wasn't the person who logged in. Can I still get interactive CE credit?**
   Yes. Send your name and email address to info@petpoisonhelpline.com by 1pm central time on Nov. 19, 2019 (strict deadline).
3. **Can I watch the recorded webinar online for CE credit?**
   Yes. You can receive non-interactive CE credit. Go to the "For Vets" page on our website, www.petpoisonhelpline.com for more info.

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