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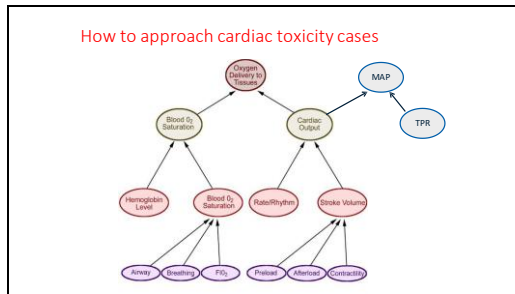
Healing heartbreak: a case-based discussion about cardiovascular toxicity

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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_{syst} 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 KPO₄) in fluids
 - Monitor K q 4-6 hours
 - Use standard charts for supplementation
 - Not more than 0.5 mEq/kg/hr

Serum K ⁺ (mEq/L)	Maximum rate* (mEq/kg/hr)	Total mEq KCl needed per 1 L
<2.0	6	60
2.1-2.5	8	80
2.6-3.0	12	120
3.1-3.5	18	180
3.6-5.0	25	250

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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?	Why the hypotension?
A. B ₂ stimulation	A. Decreased CO
B. Hypovolemia	B. Hypovolemia
C. Hypotension	C. B ₂ stimulation
D. Myocardial damage	D. Acepromazine

All of the above!

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Albuterol



- 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/O₂ 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
 - Beta₂ 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



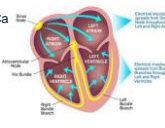
- Vitals at clinic: T 95° F, HR 20, RR 20, pale mm, CRT 3 sec

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Diltiazem

- Mechanism of Action: Ca²⁺ 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
 - LD₅₀ = 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
 - Diliazem 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

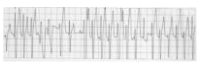
Anti-arrhythmic

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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)



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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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Thanks for attending!

Questions?