A Year in Review: What’s New in the Veterinary Toxicology Literature

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Carol McConnell, DVM, MBA
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- Pre-existing conditions
- Boarding
- Grooming
- Tax
- Waste
Outline

• Literature Review:
  – Carprofen
  – Cocaine
  – Emesis in cats
  – Marijuana
  – Metaldehyde and iron toxicosis
  – Methionine
  – Tea Tree Oil
  – Walnuts (black walnut)
  – Xylitol

Carprofen

• Compare the effectiveness of activated charcoal alone versus the combination of emesis and activated charcoal in preventing carprofen absorption
• 6 dogs, 15mg/kg carprofen
  – At 30 mins: AC administered (2g/kg)
  – At 30 mins: Emesis + AC administered (2g/kg)
  – Control group
• Both AC and emesis + AC significantly reduced AUC and $T_{1/2}$
• AC (NOT emesis+AC) significantly reduced $T_{max}$

Pharmacokinetics

Carprofen

- Compare the effectiveness of activated charcoal, activated charcoal + sorbitol, and multi-dose activated charcoal in preventing carprofen absorption
- 8 dogs, 120mg/kg Carprofen + AC, ACS, MD
  - AC, ACS, and MD significantly reduced AUC
  - AC and MD (NOT ACS) significantly reduced Cmax
  - There were no differences in AUC or Cmax among the AC, ACS, and MD groups
  - MD significantly reduced T1/2 when compared to the control group.
  - T1/2 did not differ significantly among AC, ACS, and the control group
  - Tmax was not affected by any treatment

Cocaine

- Characterize the incidence, signalment, presenting complaint, history, clinical signs, diagnostic test results, complications, treatment, length of hospitalization, and outcome of dogs presenting with presumptive cocaine toxicity
- 19 dogs with + urine drug screen (March 2004 to March 2012)
  - Neurological abnormalities = all dogs
    - Mydriasis (11/19 [58%])
    - Hyperexcitability/hyperesthesia (10/19 [53%])
    - Ataxia (8/19 [42%])
    - Focal or generalized muscle tremors (8/19 [42%])
    - Reduced mental awareness (6/19 [32%])
    - Seizures (5/19 [26%])
  - Other signs included weakness (7/19 [37%]), vomiting (6/19 [32%]), and lethargy (3/19 [16%])
- CV signs:
  - Tachycardia (10/19 [53%])
  - Hypertension (4/19 [21%])
  - Hyperthermia (5/19 [26%])
- Blood work: hyperglycemia (4/19 [21%]) dogs and hyperlactatemia (9/19 [47%])
Cocaine

- Treatment:
  - None (3/19 dogs)
  - 16/19 hospitalized (median 15hrs (range 10-30hrs)
  - All dogs received IV fluid therapy
  - 9/16 received benzodiazepines (seizure vs sedation)
    - 2/3 refractory to benzodiazepines (Phenobarbital vs propofol)
  - 4 dogs received acepromazine for sedation when benzodiazepines were ineffective
- Hypertension and tachycardia generally responded to sedatives; one case received esmolol CRI
- Prognosis for survival was good, with supportive care

Emesis Induction in Cats

### IM Dexmedetomidine and Xylazine Comparison

<table>
<thead>
<tr>
<th></th>
<th>47 cats</th>
<th>24/47 (51.1%) vomited successfully</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylazine</td>
<td>21 xylazine</td>
<td>9/21 (43%) successful</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>26 dexmedetomidine</td>
<td>15/26 (58%) successful</td>
</tr>
</tbody>
</table>

### Xylazine

- 10/21 (48%) < 0.44mg/kg
- 11/21 (52%) ≥ 0.44mg/kg

### Dexmedetomidine

- 13/26 (50%) > 10μg/kg
- 13/26 (50%) ≤ 10μg/kg

*Not significant (P=0.31)*

- Median dose of xylazine 0.43 mg/kg
- Range: 0.36 to 0.64 mg/kg

- Median dose of dexmedetomidine 7μg/kg
- Range: 0.96-10μg/kg

*Not significant (P=0.53)*

Mean ± SD dose of dexmedetomidine administered was 11 ± 3 μg/kg

Emesis Induction in Cats

- 7 cats (22%)
  - IM in 4 cats (median dose of 7.0μg/kg (range 7-10μg/kg)
  - IV in 3 cats (median dose of 3.5μg/kg (range 0.96-10μg/kg)

- 7 cats (22%)
  - Xylazine: 25 (58%) cats, median dose 0.44 mg/kg; range 0.4-0.5 mg/kg
  - Dexmedetomidine: 16 (37%) cats, median dose 3μg/kg (range 0.96-10μg/kg)

- 7 cats (22%)
  - Hydrogen peroxide (1.5-2.0 mL/kg)
  - No emesis


Emesis Induction in Cats

- 24/43 (56%) cats vomited
  - 11/25 (44%) Xylazine
  - 13/16 (81%) Dexmedetomidine
- Compared with xylazine, dexmedetomidine was significantly more likely to result in emesis (P = 0.018)
- Emesis was successfully induced in 7 of 7 (100%) with IM dexmedetomidine and in 6 of 9 (67%) with IV dexmedetomidine
- IM vs IV efficacy was not significantly different (P=0.212)

Marijuana

- Retrospective case series:
  - Jan 1, 2005 to Oct 1, 2010
- 125 dogs: known or suspected marijuana exposure
- Purpose of the study:
  - Determine if there was a correlation between the increasing number of medical marijuana licenses and marijuana toxicity in dogs
  - Also to report on the utility of a UDST to diagnose marijuana ingestion in dogs


Marijuana

- Clinical signs:
  - Ataxia (88%)
  - Mentally dull/obtunded/disoriented (53%)
  - Mydriatic pupils (48%)
  - Urinary incontinence (47%)
  - Hyperesthesia (47%)
  - Tremors, shaking, or twitching (30%)
  - Vomiting (27%)
- Combined marijuana and chocolate toxicity occurred in 21% of dogs
- Over half (58%) of the dogs were treated as outpatients
- 2 dogs died
Marijuana

• Group 1: positive UDST, and known marijuana ingestion, known exposure in their environment, and highly suspected by the clinician or owner
• Group 2: negative UDST and known marijuana ingestion
• Group 3: not tested with a UDST, but had a known marijuana ingestion

• Groups 1–3 combined: total number of marijuana toxicosis cases increased 4-fold from 2005 to 2010 (correlation coefficient 0.959 (P = 0.002)) when compared to the rise in medical marijuana registered card holders.

Marijuana

• Why? Six dogs (known THC ingestion) and a negative UDST...
• The limit of detection of the THC is 50 ng/mL
• False negatives may be seen with testing too recently after exposure
• In addition to 11-OH-Δ9-THC, dogs also metabolize THC to 8-OH-Δ9-THC with additional β-oxidation
This may contribute false negatives when using the human UDST

Metaldehyde and Iron phosphate

• A pesticide incident database from the NPIC was searched between October 1, 2000, and September 30, 2011
• 50 Metaldehyde products and 28 Iron phosphate products registered by EPA
• Purpose of the study: Report metaldehyde and iron phosphate exposures in animals, characterize iron phosphate exposure incidents in dogs for which signs compatible with iron toxicosis
• Decreased incidence in metaldehyde since 2006
• 1,500 reported exposures to molluscicides containing metaldehyde (n = 1,285) or iron phosphate (n = 215)
• 35 deaths associated with metaldehyde, none with iron phosphate

Iron Toxicosis

- MOA: Iron intake $\rightarrow$ GI epithelium absorption $\rightarrow$ bound to ferritin $\rightarrow$ in the circulation it is carried on transferrin; when these iron binding proteins are saturated $\rightarrow$ TOXICOSIS
- Iron excretion - GI tract via epithelial cell sloughing OR blood loss
- Iron $\rightarrow$ free radicals $\rightarrow$ tissue damage (GI, vascular, liver, heart)

- Clinical signs:
  - STAGE 1: (0–6hrs) Damage to the gastric mucosa, depression, abdominal pain, vomiting and diarrhea (+/- blood)
  - STAGE 2: (6–24hrs) Apparent recovery
  - STAGE 3: (12–96hrs) GI signs return, weakness, shock, GI hemorrhage, tachycardia, cardiovascular collapse, coagulation disorders, and possibly death
  - STAGE 4: (2–6wks) Repair of GI injury $\rightarrow$ fibrosis (not as commonly as stages 1–3)

Metaldehyde and Iron Phosphate

- Subset evaluation: 56 reports involving 61 dogs with suspected iron toxicosis
  - 31/56 (55%) reports involving 34 dogs - exposure occurred after the molluscicide product was applied to a surface
  - 11 (20%) reports involving 12 dogs – exposure to stored product

- Vomiting: most common clinical sign (40/56 [71%] reports involving 43 dogs)
- Diarrhea (24/56 [43%] and hemochezia (n=4)
- Lethargy (14/56 [25%] reports involving 15 dogs)
- Combinations (of above signs) in 21 (38%) reports involving 21 dogs

Methionine

- Descriptive study: Signalment, clinical findings, onset of signs, outcome, and prognosis
- Retrospective: January 2001 to December 2012
- 1,197 calls: 1,525 animals with potential methionine intoxication

- Dosage ranged from 3.9 to 23,462 mg/kg
- Sources: Lawn saver products
  - Other sources (not included in this study) multivitamins, joint care supplements & SAMe
- Females (55%), males (44%)
Methionine

- Vomiting: occurred mean 2.8hrs (5mins - 9hrs)
- Ataxia: occurred mean 6.8hrs (1hr - 18hrs)
- Resolution of signs (92%) w/in 18hrs – 24hrs, all by 48hrs
- 33% each: at home care, outpatient DVM, hospitalized DVM care
- No fatalities
- Treatment
  - Decontamination (emesis w/in 2-4hrs)
  - IVF therapy, GI supportive therapy, safe housing
  - Correction of electrolyte and acid/base abnormalities

<table>
<thead>
<tr>
<th>Sign</th>
<th>Affected dogs</th>
<th>% affected dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>623</td>
<td>31.6</td>
</tr>
<tr>
<td>Ataxia</td>
<td>386</td>
<td>19.6</td>
</tr>
<tr>
<td>Lethargy</td>
<td>94</td>
<td>4.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63</td>
<td>3.2</td>
</tr>
<tr>
<td>Abnormal posture</td>
<td>53</td>
<td>2.7</td>
</tr>
<tr>
<td>Weakness</td>
<td>46</td>
<td>2.4</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>40</td>
<td>2.0</td>
</tr>
<tr>
<td>Disorientation</td>
<td>28</td>
<td>1.4</td>
</tr>
<tr>
<td>Hypermetria</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Vocalization</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Tremors</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Acidosis (9 cases), hypokalemia (8 cases), and hyperglycemia (7 cases)

Tea Tree Oil

- Retrospective study: Review of toxicosis from the use of 100% TTO in dogs and cats, focusing on clinical signs (onset time, types, frequency, duration, and severity) epidemiological information, and treatment
- Australian tree tea oil or melaleuca oil: Obtained by steam distillation of the freshly harvested leaves of Melaleuca alternifolia tree leaves
  - Rapidly absorbed orally or via skin due to lipophilic nature
  - >100 components, terpenes predominate (50-60%)
  - Marketed as an antiseptic, fungicide, and skin care agent
- 337 dogs / 106 cats, Jan 2002 to Jan 2012
- Major 31 (7%), moderate 248 (50%), mild 161 (36%)
- Intentionally applied 89%, accidental exposure 2%, unknown 9%
  - Cutaneous (50%), cutaneous & oral (30%), oral (15%), aural (3.6%), IV (1%)

Tea Tree Oil

**Dogs**
- Major 18 (5%)
- Moderate 215 (64%)
- Mild 102 (30%)
  - 2 dogs died
- Clinical signs:
  - Lethargy 18 (43%)
  - Paresis/hind limb weakness 150 (45%)
  - Ataxia 144 (43%)
  - Tremors 34 (10%)
  - Vomiting 20 (6%)
  - Coma 15 (5%)
  - Skin 3 (4%)
  - Increased liver enzymes (2%)

**Cats**
- Major 13 (12%)
- Moderate 33 (31%)
- Mild 59 (56%)
  - No deaths reported
- Clinical Signs:
  - Drooling 47 (44%)
  - Ataxia 24 (23%)
  - Lethargy 21 (20%)
  - Coma 17 (16%)
  - Tremors 10 (9%)
  - Hypothermia 8 (8%)
  - Skin 2 (2%)

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Tea Tree Oil

**Treatment:**
- Decontamination: bathing with dish soap, e-collar to prevent grooming (cats), single dose of AC/C
- **NO EMESIS = concern for terpenes (high viscosity molecule) and aspiration risk**
- General supportive care (heat, positional, respiratory, CV, etc)
- Tremors = methocarbamol vs diazepam
- Hepatoprotectants = SAMe, Denamarin, Milk Thistle, etc

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Walnut (black walnut tree)

**Purpose of the study:** Identify clinical signs associated with oral exposure to black walnut tree (Juglans nigra) wood, nuts, or nut hulls in dogs
- Compare clinical syndromes between wood ingestion and walnuts or nut hulls
- 93 dogs, Nov 2001 and Dec 2012
- 28 (30%) dogs: wood (50%) or wood shavings (50%)
- Most commonly reported in January, February, and April (12/28 cases)
- Primarily eastern North America
- Time to onset 0.17-19hrs
- The most commonly reported clinical signs for this group of dogs included lethargy or subdued behavior (41 [50%]), generalized hind limb weakness (13 [46%]), vomiting (13 [46%]), stiffness (8 [29%]), ataxia (7 [23%]), and tremors or fasciculations (7 [25%])
- The duration of clinical signs ranged from 1 to 33.25 hours (mean ± SD, 14.4 ± 2 hrs)
- 20/28 hospitalization: IV methocarbamol, anti-emetic

Walnut (black walnut tree)

- 65/93 (70%) cases: walnuts or hulls
- Commonly in September (n = 11), October (16), and December (8)
- Clinical signs in 40 of 65 (62%) cases
- Time to onset observed (n = 37 dogs) ranged from 0.02 to 192 hrs
- Most commonly reported clinical signs: vomiting (31 of 65 [48%], lethargy/subdued behavior (6 [9%]), diarrhea (5 [8%]) and anorexia (4 [6%])
- 15/65 (23%) developed neurological signs: lethargy, disorientation, tremors or fasciculations, ataxia, seizures, and generalized or hind limb weakness
- 17/65 (26%) dogs in this group were treated at a veterinary hospital
- IV or SC fluid administration (n = 6) and antiemetics (2)

Walnut (black walnut tree)

- Frequency of neurologic or musculoskeletal signs in each group
  - Wood 26/28 [93%]
  - Nuts and hulls 15/65 [23%]
- These signs were significantly (P < 0.001) more common in dogs that ingested wood compared to nuts and hulls
- The relative risk of developing neurologic or musculoskeletal signs after ingestion of black walnut wood in dogs was 4.02 times that for dogs that consumed nuts or nut hulls

Xylitol

- Clinical signs in 39 dogs (20%)
  - 24 did not have clinical signs in hospital
  - 9 were not hospitalized
  - 6 continued to have clinical signs in hospital (4/6 vomiting)
- 153/192 dogs = asymptomatic at presentation, 2 developed CS (vomiting)
- Diarrhea (1), partial seizure (1)
- Dogs that developed clinical signs ingested a significantly (P = 0.02) higher estimated dose of xylitol (0.49 g/kg; range 0.12–2.13 g/kg) than those that were asymptomatic (0.30 g/kg; range 0.03–3.64 g/kg)

Estimated xylitol dose was based on 0.5 g/piece or 1 g/piece
### Xylitol

#### Blood glucose information for 192 dogs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine</td>
<td>56.3</td>
</tr>
<tr>
<td>IVF</td>
<td>43.8</td>
</tr>
<tr>
<td>AC*</td>
<td>27.6</td>
</tr>
<tr>
<td>Hepatoprotectants</td>
<td>25.5</td>
</tr>
<tr>
<td>Dextrose</td>
<td>21.3</td>
</tr>
<tr>
<td>H2O2</td>
<td>14.1</td>
</tr>
<tr>
<td>Gastroprotectants</td>
<td>10.4</td>
</tr>
<tr>
<td>Anti-emetics</td>
<td>4.7</td>
</tr>
</tbody>
</table>

* The median duration of hospitalization was 18 hours (n = 122; range 1-70 hours)
* All dogs survived to discharge
* 158 were known to be alive at 28 days

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#### Blood glucose information in 30 hypoglycemic dogs (BG <60mg/dL)

<table>
<thead>
<tr>
<th>Initial BG (mg/dL)</th>
<th>Duration of BG</th>
<th>Time to lowest BG</th>
<th>Lowest BG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>55.5</td>
<td>3.0hrs</td>
<td>0.5hrs</td>
</tr>
<tr>
<td>Range</td>
<td>15-117</td>
<td>1-27hrs</td>
<td>0-30hrs</td>
</tr>
<tr>
<td># dogs evaluated</td>
<td>30</td>
<td>28</td>
<td>30</td>
</tr>
</tbody>
</table>

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#### Blood glucose information in 192 dogs

<table>
<thead>
<tr>
<th>Initial BG (mg/dL)</th>
<th>Duration of BG</th>
<th>Time to lowest BG</th>
<th>Lowest BG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>86</td>
<td>0 hrs</td>
<td>2hrs</td>
</tr>
<tr>
<td>Range</td>
<td>15-185</td>
<td>0-27hrs</td>
<td>0-58hrs</td>
</tr>
<tr>
<td># dogs evaluated</td>
<td>178</td>
<td>138</td>
<td>139</td>
</tr>
</tbody>
</table>

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* A majority of dogs (n = 137, 71.3%) had a serum biochemistry profile performed. The most common biochemical abnormality was an increase above the upper end of the reference interval for ALT and/or tBR (n = 30; 21.9%)
* Most dogs had a mild increase in ALT (200 U/L, n = 12), though 4 dogs had an ALT > 800 U/L
* RECHECK: Six dogs had increased liver values, though all values had decreased from hospitalization and all dogs were clinically normal on recheck

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Cope RB. A Screening study of xylitol binding in vitro to activated charcoal. Vet Hum Toxicol. 2004; 46(6); 336-7
When in doubt, call 800-213-6680

- Something you’re not familiar or comfortable with
- Odd clinical signs
- Animals with preexisting disease

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