

## Methylxanthine Toxicity

### CLINICAL SIGNS

#### Gastrointestinal and mild clinical signs:

- Restlessness
- Hyperactivity
- Panting
- Vomiting
- Diarrhoea
- PUPD
- Lethargy

#### Neurological:

- Hyperthermia
- Ataxia
- Tremors
- Seizures
- Coma

#### Cardiovascular:

- Tachycardia (+/- bradycardia if severe)
- Cardiac arrhythmias (eg VPCs)
- Hypertension (+/- hypotension if severe)
- Death (arrhythmias and respiratory failure)

### DIAGNOSTICS

- PCV/TS
- Blood Gas
- ECG
- NIBP
- Pulse oximetry
- USG
- +/- MBA (evaluate concurrent pancreatitis)
- +/- U/S (evaluate concurrent pancreatitis)
- +/- Radiographs (if concerned of aspiration)
- +/- In house urine drug testing
- +/- External laboratory analysis

### HISTORY

- Known ingestion of methylxanthine-containing products, owner finding packaging or wrappers empty, potential access to methylxanthine-containing products prior to development of above clinical signs
- Access to chocolate, coffee, asthma medications, stimulant (anti-fatigue) medications, cocoa bean hulls (garden mulch)
- Rule out access to other stimulatory drugs or toxins (e.g amphetamines, mycotoxins).

### PATHOPHYSIOLOGY

Theobromine is the predominant methylxanthine in the cocoa bean, along with caffeine in lower concentrations. Caffeine is also present in the coffee bean (and its by-products), and in fatigue-combating medications.

Chocolate of all kinds are readily available and highly palatable, attracting animals to the product. All animals can be affected by methylxanthine toxicosis, however dogs are most commonly affected due to their indiscretionate eating habits and easy access to an owner's foods or medications.

Methylxanthines act through inhibition of cellular phosphodiesterase, increasing intra-cellular cyclic adenosine non-phosphate, enhancing the release of catecholamines epinephrine and norepinephrine. Methylxanthines are competitive antagonists of cellular adenosine receptors and cause an increased entry of calcium into and inhibit

Guidelines:

Class 1 (C1) – *Definitely perform* (good evidence)

Class 2 (C2) – *Consider performing* (some evidence)

Class 3 (C3) – *Do not perform* (unsound evidence and/or deleterious)

calcium sequestration by the sarcoplasmic reticulum, increasing muscle contraction. The overall clinical picture is due to the neurological and cardiac stimulatory effects, along with gastrointestinal signs from local irritation.

They are readily absorbed from the gut, however the absorption and gastric emptying can be slowed from the fat composition of most chocolate products. Clinical signs generally occur within 6-12 hours of ingestion, but may be seen within 1-4 hours dependent on dose and type consumed. The half-life of theobromine is 17.5hrs and caffeine 4.5hrs. Theobromine's extended half-life is attributable to its enterohepatic re-circulation (returning to the circulating bloodstream via the portal vein after uptake in the ileum). There is also potential for prolonged clinical signs due to reabsorption through the urinary bladder. Metabolism occurs primarily by the liver and the majority excreted via the kidneys.

When calculating exposures, the combined total of theobromine and caffeine are determined to establish a total dose of methylxanthine ingested. When it is a mixed product (e.g. trail mix), or the dose consumed is unknown, always calculate based on worst-case scenario.

Mild clinical signs (e.g. V+/D+) : 20-40mg/kg

Severe clinical signs (e.g. tremors, arrhythmias): 40-50mg/kg

Life-threatening clinical signs (e.g. seizures, death): >60mg/kg

*Lethal dose (LD50) of caffeine 140mg/kg (110-200mg/kg) and theobromine 250-500mg/kg (100-500mg/kg) (D).  
Lethal Dose of caffeine 80-150mg/kg (C).*

Quick reference to determine significance of ingested dose, VIN Chocolate Toxicity Calculator:

<https://www.vin.com/members/cms/project/defaultadv1.aspx?pld=618&id=7131881>

## DIAGNOSTICS

### PCV/TS

- Evaluate hydration status

### Blood Gas

- Hyperlactataemia possible in shock or ictal/post-ictal presentation
- Electrolyte derangements possible due to vomiting and diarrhoea
- Hypokalaemia possible late in course of toxicity (from emesis and diuresis)
- Hypoglycaemia possible secondary to increased muscle activity

### ECG

- Evaluate if arrhythmias are present or develop
- Monitor treatment of arrhythmias

### Non-invasive Blood Pressure (NIBP)

- Hypertension or hypotension presence, or development during course of intoxication
- If severely neurological, potential monitoring for Cushing's Reflex (hypertension in presence of bradycardia)

### Pulse oximetry

Guidelines:

Class 1 (C1) – *Definitely perform* (good evidence)

Class 2 (C2) – *Consider performing* (some evidence)

Class 3 (C3) – *Do not perform* (unsound evidence and/or deleterious)

- Presence of hypoxia and requirement of oxygen therapy in severely affected/neurological patients
- Easy continual monitor of heart rate if no ECG attached to patient (if arrhythmia present, may not read accurately)

***Urine Specific Gravity (USG)***

- Iso-hyposthenuria due to diuretic effect of methylxanthines

***+/- Biochemistry (evaluate concurrent pancreatitis)***

- If high content ingested with delayed presentation, consider running to determine if evidence of concurrent pancreatitis

***+/- U/S (evaluate concurrent pancreatitis)***

- As above
- If decontamination was unsuccessful can be used to determine if ball of chocolate in stomach (rarely can occur requiring surgical removal)

***+/- Radiographs (if concerned of aspiration)***

- If presenting with signs of vomiting or seizure already and concerned of aspiration (e.g hypoxia, harsh lung sounds)

***+/- In house recreational/street urine drug test***

- To rule out differentials if access to chocolate not confirmed

***+/- External Laboratory***

- Methylxanthines may be detectable in serum or plasma up to 3-4 days post-ingestion
- No in house test able to detect

## TREATMENT

### INITIAL MANAGEMENT

**Asymptomatic patient (outpatient treatment):**

To be considered when: recent ingestion and asymptomatic; ingestion of mild but potentially toxic dose (e.g. gastrointestinal signs range - approx. 15-30mg/kg); when owner declines further hospitalisation

- Emesis: Apomorphine tab into buccal mucosa or conjunctival sac
  - Up to 6hrs post-ingestion in stable patient (gastric emptying can be delayed)
  - If time of ingestion unknown in stable patient
  - NOT in unstable, neurological patient
  - Reverse once reached bile coloured vomitus
  - Reversal: Metoclopramide 0.5mg/kg SC
- Activated Charcoal: to bind any remaining toxin within GIT
  - Carbasorb (contains sorbitol – recommended cathartic to include): 5ml/kg PO q8
    - Preferentially let the dog lick up, or syringe into dogs mouth (avoiding aspiration)
    - If needs to be fed with chicken, as it is a non-specific binding agent, the presence of chicken is theoretically reducing its effectiveness

Guidelines:

Class 1 (C1) – *Definitely perform* (good evidence)

Class 2 (C2) – *Consider performing* (some evidence)

Class 3 (C3) – *Do not perform* (unsound evidence and/or deleterious)

- If dog licks up easily, consider sending home with pre-made syringe for O to feed in a bowl, **DO NOT INSTRUCT TO SYRINGE FEED**
  - Charcoal powder: 1-4g/kg q8 into 1g/5ml water
    - Used for subsequent doses, as cathartic is not indicated after first dose

#### Asymptomatic patient (inpatient treatment):

- As above initial decontamination
- +/- Gastric Lavage:
  - If lethal dose ingested but emesis induction unsuccessful or not indicated (laryngeal paralysis, brachycephalic, history of aspiration pneumonia)
    - Anaesthesia with ET tube (cuff inflated), pass lubricated stomach tube in lateral recumbency, flush with warm water solution, re-position patient to ensure all contents removed, **when pulling out tube ensure end is kinked**, it is not recommended to infuse with activated charcoal due to risk of aspiration
- Anti-nausea therapy: if signs of vomiting or nausea on presentation or during hospitalization
  - Maropitant: 1mg/kg SC or IV q24
  - Ondansetron 0.2-0.5mg/kg IV q8
  - Metoclopramide CRI: 2mg/kg/day
- Intravenous fluid therapy:
  - To assist rehydration, cardiovascular system, optimize GFR to permit diuresis
  - Dependent on animals requirement, if diuresis required without rehydration consider 1-1.5% x Maintenance of a balance solution
  - Supplement for any electrolyte derangements (e.g. hypokalaemia)
- Urinary Catheterisation:
  - Consider for patients with high or lethal dose ingestion, delayed presentation to clinic, ineffective decontamination, clinical signs present already
  - Reduces reabsorption through bladder mucosa, which prolongs clinical signs
  - Place in conscious (+/- sedation) males, or anaesthetised females

#### Symptomatic Patients (inpatient treatment):

- As above except for emesis induction is contraindicated in clinically affected patients
  - Activated charcoal q8 for 2-3x doses (Theobromine half-life 17.5 hours) acceptable in stable, clinically affected patients (e.g gastrointestinal signs only, mild tachycardia)
- Gastroprotectants: to be considered to prevent mucosal irritation
  - Esomeprazole 1mg/kg IV q8-12
- Cardiac disturbances:
  - Ventricular arrhythmias: Lignocaine 1-2 mg/kg IV bolus followed by 25-75ug/kg/min CRI
  - Hypertension/supraventricular tachyarrhythmias: metoprolol 0.2mg/kg PO q12 (metoprolol is preferred over propranolol due to the potential of reduced methylxanthine clearance with propranolol; monitor for hypotension)
  - Bradycardia: IV atropine 0.02 - 0.04 mg/kg IV or IM

Guidelines:

Class 1 (C1) – *Definitely perform* (good evidence)

Class 2 (C2) – *Consider performing* (some evidence)

Class 3 (C3) – *Do not perform* (unsound evidence and/or deleterious)

- Hypotension: dobutamine CRI 1-20mcg/kg/min
- Neurological disturbances:
  - Seizures: 0.5-1mg/kg IV Diazepam PRN +/- phenobarbitone or midazolam +/- propofol CRI
  - Tremors: consider methocarbamol boluses 40-50mg/kg IV over 3-5mins PRN +/- CRI 10mg/kg/hr (do not exceed 330mg/kg/day)
  - Severe uncontrollable seizure activity or comatose state: intubation and IV anaesthesia, considering half-life of toxin (4.5hrs for caffeine, 17.5 hours for theobromine)

## COSTS AND HOSPITALISATION

- Hospitalisation time to expect: typically 12-24hrs (can be up greater than 72hrs in severely affected animals due to theobromine half-life)
- Costs whilst hospitalized: Initial \$1000-\$2000 (depending on treatment), \$300-600/12hrs stable, \$500-800/12hrs unstable (conscious), ~\$3000/24hrs intubated

## PROGNOSIS AND RISK FACTORS

- Risk factors:
  - Young animals (natural curiosity)
  - Small breed dogs (higher risk of consuming large dose)
  - Brachycephalic breeds (risk of aspiration secondarily or respiratory compromise is greater)
  - Patients with prior episodes of acute or chronic pancreatitis (at a greater risk of pancreatitis concurrently developing)
  - Animals already on propranolol or steroids may have reduced clearance of methyxanthines
- Good to great prognosis in early and aggressive treatment for asymptomatic cases
- Good prognosis in early and aggressive treatment of mild-moderate asymptomatic cases
- 50:50 if aspiration occurs secondarily (lower if charcoal aspiration)
- Poor-guarded prognosis if cluster seizing on presentation or in a comatose state

## REFERENCES

1. Baldwin, K., & Ecc, V. T. S. (2008). Management of Chocolate Intoxication.
2. Pittenger, S. (2002). Chocolate Intoxication. *HCVMA Newsletter*, (February), 8–9.
3. Volmer, P. A., Toxicology, D., & Rosendale, M. E. (2002). STANDARDS of CARE Visit us at [www.VetLearn.com](http://www.VetLearn.com) EMERGENCY AND CRITICAL CARE MEDICINE ® M ANAGEMENT OF DIAGNOSTIC, 4(July), 1–5.

\*Use of any of this material is not for retail or public disclosure. It is intended for personal use and knowledge only

Author(s): Ella Yarsley

Reviewed:

Date:

Guidelines:

Class 1 (C1) – *Definitely perform* (good evidence)

Class 2 (C2) – *Consider performing* (some evidence)

Class 3 (C3) – *Do not perform* (unsound evidence and/or deleterious)