Mushroom Toxicities

KEY POINTS:

1. If GI signs present more than 6-8hrs post ingestion suspect amatoxins (hepatic), gyrometrin (neurologic) or orellanine (renal)
2. There are 4 phases of amanita toxicity although not all cases will present clearly with all phases
3. Silibinins (milk thistle) reduce the uptake of amanitins into hepatocytes

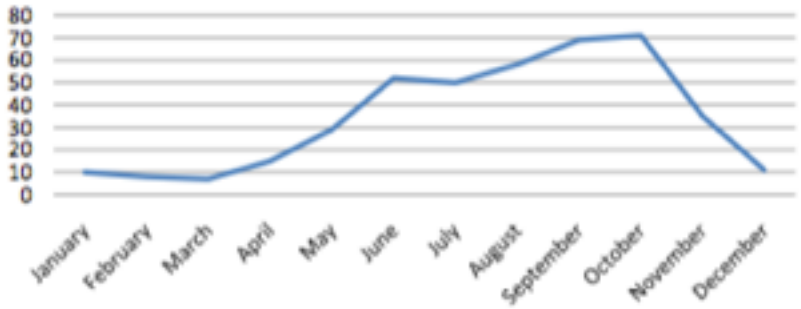

Fig. 1. ASPCA APCC average number of reported mushroom exposure cases by month (January 1, 2006–January 1, 2011).

Hepatotoxic mushrooms

Amanita phalloides. (*Courtesy of* Dr R. Michael Davis, UC Davis.)

- Contain cyclopeptides
- Amanita phalloides (death cap) is most toxic but other genre also contain the toxin (+ a. ocreata)
  - Located on West Coast from California to British Columbia, and East from Maryland to Maine
  - Most abundant n warm, wet years and appear in late summer and fall
  - Smooth, yellowish-green to yellowish-brown cap with white ring around upper stem, and white cup at base of stem
- Amanitins are the hepatotoxins responsible for most poisonings
- LD50 for methyl-*γ*-amanitin is 0.5mg/kg
  - In general main amanita spp. contain 1.5 to 2.3mg of amanitans per gram of mushroom dry weight; one mushroom can easily contain a lethal dose for animals or humans
- Inhibit RNA polymerase II; shut down transcription and so decreasing protein synthesis
  - Cells with high metabolic rate (hepatocytes, crypt cells, proximal convoluted tubules) are most prone to toxicity
  - Also cause hepatocyte apoptosis and amanitin-induced insulin release
- Do not undergo metabolism and are excreted unchanged in urine with small amount (7%) in bile
- Detectable in serum and urine before clinical signs and lab changes present

    - Concentrations do not correlate with severity or outcome
    - Can also test gastric content, liver, kidney or the mushroom itself
- Half life in dogs is 25-50mins

4 phases of toxicity:
- *Latent period* (6-12hr) post ingestion with NO clinical signs
- *Second phase:* GI signs (vomiting, diarrhea, pain, lethargy, anorexia) at 6-24hr post ingestion
    - After this phase severe hypoglycaemia may result due to glycogen breakdown
    - 50% of dogs with lethal doses may die secondary to this 1-2d post exposure
- *Third phase*: False recovery, lasts 12 to 24hrs
- *Fulminant liver failure:* Begins 36 to 48hrs after exposure (but sooner in puppies or with ingestion of large doses)
    - Coagulopathy, encephalopathy, renal failure
    - Histopath shows massive hepatocellular necrosis with collapse of hepatic cords, and acute tubular necrosis

- No specific treatments; mortality rate is 'high'
- Activated charcoal, with repeated doses for 24hrs post exposure
    - Enterohepatic recirculation is unlikely to be effective after 24hrs
- Dextrose, vitamin K, blood products, IV fluids (for volume replacement)
- **Silibinins (milk thistle) reduce the uptake of amanitins into hepatocytes**
    - **There is a product approved for amanita treatment in humans in Europe**
    - **Administered 50mg/kg IV at 5 and 24hr post exposure**
- **Penicillin G 1000mg/kg IV 5hr post ingestion may reduce uptake into the hepatocytes (efficacy is unknown)**
- Non-specific hepatoprotectants e.g. N-Acetylcysteine, SAMe (efficacy unknown)

Neurotoxic Mushrooms

Hydrazines
- Found in false morels (Gyromitra spp) which are thoroughout North America
- Toxin is present at 0.12-0.16 % fresh weight, toxic dose in children 10-30mg/kg
    - Data is unavailable for animals, only reported once in a dog
    - Vomited 2-3hrs after chewing on msushrome
    - lethargic then comatose 6hr post ingestion, death 30mins later
- Vomiting occurs secondary to direct irritation 6-12hr post exposure in people
- Toxin is hydrolysed then ultimately results in decreased GABA and decreased glutamic acid concentrations
- Seizures may develops
- Additional metabolites may cause hemolysis, liver failure and kidney failure
- No test for the toxin itself; primarily diagnozed by identifying mushroom
- Treatment is supportive
    - **Pyridoxine (B6) may be helpful in alleviating neurologic symptoms (75-150mg/kg IV)**

Isoxazoles
- Isotonic acid and muscimol
- Found in Amianita panthera and amanita muscaria
    - Widespread but most common in pacific northwest
    - clinical signs seen in people at 6mg of muscimol or 30-60mg of isotonic acid
    - concentrations are 6mg/kg and 100mg/kg in mushroom respectively

    - so one mushroom can contain a lethal dose???
- Poorly documented in dogs but have seen death in puppies after ingestion of single mushroom
- Muscimol increases membrane permeability to anions causing a hyperpolarization and then decreased excitability
- Also acts on GABBA receptors causing depression
- Clinical signs
    - disorientation, opisthotonus, paresis, seizures, miosis, vestibular signs, resp depression, coma (rare), (euphoria, hallucinations in humans)
    - in humans signs occur within 1/2 to 2 hrs of ingestion and full recovery occurs within 2 days
- Diagnostic tests unavailable
- Care with drugs that act as GABA agonists (pheno, diazepam) as can further aggravate CNS and resp depression

Psilocin and Psilocybin
- Psilocybe, Panaeolus, Conocybe and Gymnopilus genres
- Northwest and southwest US
- Toxin concentrations are variable (1.2-16.8mg/kg dry weight)
    - 10-20mg result in hallucinations
    - no data in animals
- Similar to serotonin -> activates CNS receptors
- Signs occur 1hr post ingestion and have resolved within 12hrs in people
- Dogs may become aggressive and ataxic, vocalize, have nystagmus, seizures, elevated body temp
- Can detect substances in the urine
- Generally mild and short acting so resolve without treatment or with supportive care

Muscarine-Containing Mushrooms
- Inocybe spp and clitocybe spp as well as others
- nondescript little brown mushrooms (but variable)
- Some fruit year round
- Thermostable muscarinic receptor agents that binds to ACh receptors
    - Parasympathomimetic
    - Not degraded by acetylcholinesterase so stimulation is unregulated
    - Does not cross blood brain barrier
- Clinical signs can occur within 5-30mins, generally within 2hrs
    - **SLUDDE (Salivation, Lacrimation, Urination, Diarrhea, Dyspnea, Emesis)**
    - Dyspnea may be due to bronchconstriction and increased bronchial secretions
    - May also see bradycardia, miosis, hypotension and abdominal pain
    - Ddx OPs, carbamates, and mycotixins
        - With pesticides may also see nicotinic signs such as tremors and seizures
- Can detect toxin in urine or identify mushrooms to support diagnosis
- Treatment:
    - Decontamination including activated charcoal if asymptomatic
    - Atropine (competes with muscarine at receptors)
        - ASPCA recommends 0.04mg/kg - give 1/4 IV and remainder SQ or IM
        - Titrate upwards and repeat as needed
        - Signs typically resolve within 30mins with treatment, would persist for several hours without

Gastrointestinal Irritants

- Large number of genera with wide distribution and variable appearance
- Most toxins have not been identified
- Proposed mechanisms include hypersensitivity, idiosyncratic, enzyme deficiencies, and local irritation
- Clinical signs
  - Onset expected within 15mins to several hours of ingestion
  - Commonly include vomiting, diarrhea, abdominal discomfort +/- hematemesis, hematochezia, hypersalivation, lethargy
  - Secondary electrolyte and volume disturbances
  - **Onset is typically more delayed in hepatotoxic and nephrotoxic cases**
- Decontaminate if asymptomatic
- Supportive treatment as needed
- Severity varies but prognosis is good in most cases
  - Expect full recovery within hours to days

Nephrotoxic Mushrooms

- Cortinarius spp (webcap)
- Found throughout North America but reports of toxicity are rare (none reported in animals here)
- rusty/red-brown colour
- Orellanine; mechanism is unclear
  - Inhibit protein synthesis in renal tubular epithelium
  - Reduce cellular NADPH -> free radical damage
  - Lag time before clinical signs so suspect is metabolised to active form
- Cortinarins may also be involved
- Individual variation in susceptibility
- Clinical signs
  - GI signs within 72hrs
  - Renal failure within 3 to 20 days
    - May see Oliguria followed by diuresis and recovery, or chronic renal failure
    - Liver enzymes expected to remain normal
- Diagnosis
    - Nonspecific
    - Renal biopsies (human) reveal interstitial edema, interstitial nephritis and acute tubular necrosis
    - Can detect orellanine in samples up to 6 months post ingestion
    - Orellanine can also be found in human plasma
- Treatment
  - Generally opportunity for decontamination passes prior to presentation
  - supportive care for renal failure
  - Prognosis varies; generally worse with a shorter latent period

QUESTIONS:

1. Describe the four phases of Amanita toxicity
2. What is the mechanism for dyspnea in muscarine toxicity

ANSWERS:

1. latent period (6-12hrs), GI signs at 6-24hrs post ingestion (+/-hypoglycemia), false recovery (for 12-24hrs), fulminant liver failure (+/- renal damage)

2. bronchoconstriction and increased bronchial secretion